J Med Sci J Med Sci 2014;34(5):201-206
DOI: 10.4103/1011-4564.143643


ORIGINAL ARTICLE

# Efficacy of Modified Neoadjuvant Chemoradiotherapy in Locally Advanced Rectal Cancer: A Single Institution Experience in Taiwan

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**Background:** Neoadjuvant chemoradiotherapy (NCRT) followed by total mesorectal excision is now recommended for patients with locally advanced rectal cancer (LARC). This retrospective study was aimed to analyze the treatment efficacy in LARC patients in a single institute. **Materials and Methods:** Rectal cancer patients with clinically T3, T4, or nodal positive (N1-2) diseases who received either NCRT or adjuvant chemoradiotherapy (ACRT) were retrospectively enrolled between 2007 and 2011. The treatment outcome and clinical characteristics of study population were compared. **Results:** There were 176 patients been enrolled with a mean age of 63.1 years. Totally, 123 (69.9%) patients received NCRT and 53 (30.1%) patients received ACRT, respectively. The median duration of follow-up was 43.3 months in NCRT group and 47.6 months in ACRT group. There was no significant difference about overall survival (OS), progression-free survival (PFS), and local relapse-free survival (LRFS) between two treatment groups. However, NCRT achieved pathological complete remission (pCR) of 27.6%. In addition, the patients with pathologically downstage after NCRT (the responders) had significantly better PFS ($P < 0.0001$), local RFS ($P = 0.0468$), and OS ($P = 0.0045$), compared with non-responder after NCRT. Oxaliplatin-based NCRT did not significantly increase treatment response, OS and PFS, compared with other regimens in our analysis ($P = 0.29$). **Conclusions:** In our cohort, NCRT achieved high pCR rate than those reported in previous literature. Although there was no significant improvement of OS, PFS, and LRFS in NCRT group, there was a significant improvement of LRFS, OS, and PFS in those responders after NCRT.

Key words: Neoadjuvant chemoradiotherapy, adjuvant chemoradiotherapy, rectal cancer, treatment outcome

## INTRODUCTION

Colorectal cancer is the third leading cause of cancer death in Taiwan.[1] Locally advanced rectal cancer (LARC, stage T3-4 and/or N1-2) has high local recurrence risk due to the absence of surrounding serosa. The surgical difficulties in obtaining wide free margins at resection also increase the possibility for recurrence. Herein, the treatment plan for LARC includes neoadjuvant chemoradiotherapy (NCRT) or adjuvant chemoradiotherapy (ACRT). Sauer *et al*. compared NCRT to ACRT in the treatment of clinical stage II/III rectal cancer. The results of this study found that NCRT group was associated with significant reduction in local recurrence, but no difference in overall survival (OS).[2] Because mesorectum is a potential metastatic site for rectal cancer, total mesorectal excision (TME) has become the standard surgical intervention in LARC patients, which involves sharp dissection of rectosacral fascia, excision of rectum, and mesorectum at the level of the levators.[3-5] Therefore, the current standard treatment for LARC is NCRT followed by TME.[6] By the previous study results, NCRT can improve treatment outcome and minimize toxicities by reducing tumor size, increasing tumor mobility and histopathologic downstaging.[7,8] However, one possible study design defect is NCRT group may be over-treated of early stage lesions which did not require adjuvant therapy.[2,9]

The purpose of this retrospective analysis was to assess and evaluate OS, progression-free survival (PFS), and local relapse-free survival (LRFS) in patients undergoing NCRT

Received: April 7, 2014; Revised: June 23, 2014; Accepted: July 15, 2014
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and ACRT in LARC in current clinical setting. The clinical parameters that may predict or affect treatment outcomes were also identified.

## MATERIALS AND METHODS

### Patients and study design

The medical records of patients with clinical stage T3-T4N0 or N1-2 rectal cancer who received either NCRT or ACRT between 2007 and 2009 were retrospectively analyzed. The disease stage was classified according to the TNM system, AJCC 7th edition. The Cancer Registry Group, Tri-Service General Hospital, approved the study. The clinical data retrieved from medical records included: Age, sex, local recurrence, curative resection (R0 resection), preoperative clinical stage, postoperative pathological stage, chemotherapy regimen, progression time, and survival. Preoperative staging was performed with abdominal and pelvic computed tomography (CT). Endoscopic ultrasound was optional.

### Treatment

The chemotherapeutic regimens used concurrently with preoperative RT employed oral UFUR (tegafur 100 mg and uracil 224 mg), intravenous high dose 5-fluorouracil (HDFL, 1500-2600 mg/m²/day) plus leucovorin (200-300 mg/m²/day), or oxaliplatin containing regimen (50 mg/m²/day, FOLFOX-like), concurrently with RT for 9-10 cycles. Radiation dose was fixed at a total dose of 4500 cGy divided equally over 5 weeks followed by 540 cGy/3 fraction boost at the tumor bed. Because the interval between RT and surgery was around 6-8 weeks, the preoperative chemotherapy was continued after the completion of RT and stopped 2 weeks before, they underwent surgery. The ACRT groups underwent upfront surgery and received the post-operative chemoradiotherapy as their pathological stage indicated. Radiation dose in ACRT group also had fixed total dose of 4500 cGy divided equally over 5 weeks followed by 900 cGy/5 fraction boost at the tumor bed. Patients in NCRT group were divided further into two subgroups by their treatment response. Those who were pathologically down-staged were defined as a responder, and those with stable or progressive disease were defined as non-responder.

### Follow-up

Patients were followed every 3 months for 2 years and every 6 months between 3 and 5 years and annually thereafter. Evaluation included serum carcinoembryonic antigen (CEA) level, abdominal CT, and colonoscopy as indicated. Recurrence was diagnosed on the basis of clinical imaging findings and/or elevated CEA levels. Pathologic confirmation was obtained in selected cases.

### Statistical analysis

Overall survival was defined from the time of diagnosis to death from any cause. PFS was defined from the start of treatment to the date of documented clinical progression or to the patient's death. LRFS was defined as patient survival since the start of the treatment till evidence of local recurrent of disease.[10] Pathological regression grade was evaluated by the scoring system of Dworak *et al*.[11] All analyses were performed using SPSS, version 19.0, software for Windows (SPSS, Inc.). The significance level was 5% for all analyses. Student's *t*-test and Chi-square test were used to compare the baseline characteristics of each group. Log-rank test and Kaplan-Meier plots were used to analyze PFS and OS. Log-rank test and Kaplan-Meier plots were used to analyze each groups' PFS, LRFS, and OS. Cox proportional hazards were calculated to evaluate the hazard effect on PFS, OS by each variable, including age, gender, clinical/pathological stage, grade, lymphovascular invasion (LVSI), regression score, chemotherapy regimen, and the modality of operation.

## RESULTS

### Clinical features

A total of 176 patients (72 females, 104 males) was registered and analyzed. One hundred and twenty-three (69.9%) patients received NCRT and 53 (30.1%) patients underwent ACRT. The demographic characteristics of the patient population are summarized in Table 1. Patients in ACRT group were significantly older than NCRT group ($P = 0.018$), but gender was equally distributed ($P = 0.149$). Most patients in NCRT group could be down-staged after therapy. A high pathological complete remission (pCR) rate (27.6%) and fewer events of LVSI (7.8%, $P = 0.021$) were observed in the NCRT group. Nevertheless, surgical approach via lower anterior resection (LAR) was significantly higher in ACRT group ($P = 0.003$). Table 2 shows the treatment response for the various chemotherapeutic regimens in the neoadjuvant context. Mean response rate is 70.6%, and there was no significant difference among these different regimens [Table 2, $P = 0.29$]. There were also no significant differences in PFS and OS between neoadjuvant and upfront surgery groups [Figure 1a and b, $P = 0.9627$, $P = 0.9432$, separately]. LRFS was also similar between the two groups ($P = 0.87$). In subgroup analyses, patients who responded to NCRT (pathologically down-staged) were defined as responders, and had significantly longer PFS [$P < 0.0001$, Figure 2a] and better OS [$P = 0.0045$, Figure 2b] compared with those of non-responders. In addition, the LRFS benefits were found in responders [Figure 2c]. When different chemotherapy regimens were compared, the survival benefit among

Table 1. Patient characteristics

| Characteristics | NCRT ($n$ = 123), $n$ (%) | ACRT ($n$ = 53), $n$ (%) | $P$ |
|---|---|---|---|
| Age, years, mean (range) | 61.5±14.4 (26-95) | 66.9±13.1 (26-92) | 0.018 |
| Gender | | | |
| Male | 77 | 27 | 0.149 |
| Female | 46 | 26 | |
| Distance above anal verge (cm) | 7.6±3.9 | 12.6±5.1 | <0.0001 |
| Clinical stage by TNM | | | |
| cT2N0M0 | | 6 | 0.0038 |
| cT3N0M0 | 33 | 21 | |
| cT4N0M0 | 1 | | |
| cT1N1M0 | 1 | | |
| cT2N1M0 | 13 | 6 | |
| cT3N1M0 | 56 | 14 | |
| cT4N1M0 | 1 | | |
| cT2N2M0 | 1 | 2 | |
| cT3N2M0 | 14 | 4 | |
| cT4N2M0 | 3 | | |
| Stage I | | 6 | <0.0001 |
| Stage II | 34 | 21 | |
| Stage III | 89 | 26 | |
| Pathological stage by TNM (yp in NCRT group) | | | |
| pCR | 34 (27.6) | | <0.0001 |
| pI | 31 | 0 | |
| pII | 23 | 29 | |
| pIII | 26 | 24 | |
| pIV | 5 | 0 | |
| N/A | 4 | 0 | |
| Pathological grade | | | |
| Grade 0 | 32 | 0 | <0.0001 |
| Grade 1 | 8 | 3 | |
| Grade 2 | 70 | 46 | |
| Grade 3 | 6 | 4 | |
| N/A | 7 | 0 | |
| Regression grade | | | |
| Grade 1 | 8 | | |
| Grade 2 | 10 | | |
| Grade 3 | 42 | | |
| Grade 4 | 29 | | |
| N/A | 34 | | |
| Lymphovascular space involvement | 7 (7.8)<br>9 unknown | 9 (16.7)<br>1 unknown | 0.021 |
| Chemotherapy | | | |
| Nil | 0 | 9 | <0.0001 |
| HDFL | 70 | 5 | |
| UFUR | 30 | 20 | |
| FOLFOX-like | 22 | 11 | |
| Other | 1 | 8 | |
| Type of surgery | | | |
| LAR | 85 | 50 | 0.003 |
| APR | 27 | 2 | |
| Wide excision | 5 | 0 | |
| Other | 6 | 1 | |
| Median overall survival | Not reached | 67.9 months | 0.943 |
| Local relapse | 9 | 3 | 1.0 |
| Distant metastasis | 24 | 8 | 0.531 |

NCRT = neoadjuvant chemoradiotherapy; ACRT = adjuvant chemoradiotherapy; pCR = pathological complete remission; N/A = not applicable; HDFL = high dose 5-fluorouracil; UFUR = tegafur 100 mg and uracil 224 mg; FOLFOX = oxaliplatin containing regimen; LAR = lower anterior resection; APR = abdominoperineal resection, TNM = tumor node metastasis

Table 2. Effects of chemotherapy

| Chemoregimen | Down stage | Poor response | Response rate (%) | $P$ |
|---|---|---|---|---|
| HDFL | 49 | 18 | 73.1 | 0.29 |
| UFUR | 20 | 9 | 69 | |
| FOLFOX-like | 15 | 7 | 68.3 | |

HDFL = high dose 5-fluorouracil; UFUR = tegafur 100 mg and uracil 224 mg; FOLFOX = oxaliplatin-containing regimen

subgroups was not significantly different [Figure 3a and b]. By Cox-regression model for hazard evaluation [Table 3], only pathological staging determined PFS ($P < 0.004$) rather than OS ($P = 0.054$). All other clinical factors did not show clinical effects from our studies.

## DISCUSSION

Several clinical trials have assessed the treatment response to NCRT in LARC and the pCR has ranged from 13.5% to 35%, with various combinations of chemotherapy and radiotherapy.[6,12,13] Different NCRT protocols were designed to maximize the treatment effect and most of which were 5-flurouracil (5-FU)-based regimens with or without oxaliplatin.[2,14] For LARC, the ACRT significantly improves both local control rate and OS as compared with surgery alone or postoperative irradiation, historically.[15,16] The German study showed NCRT was superior in terms of local control and there was no effect on OS between NCRT and ACRT groups.[8] In our

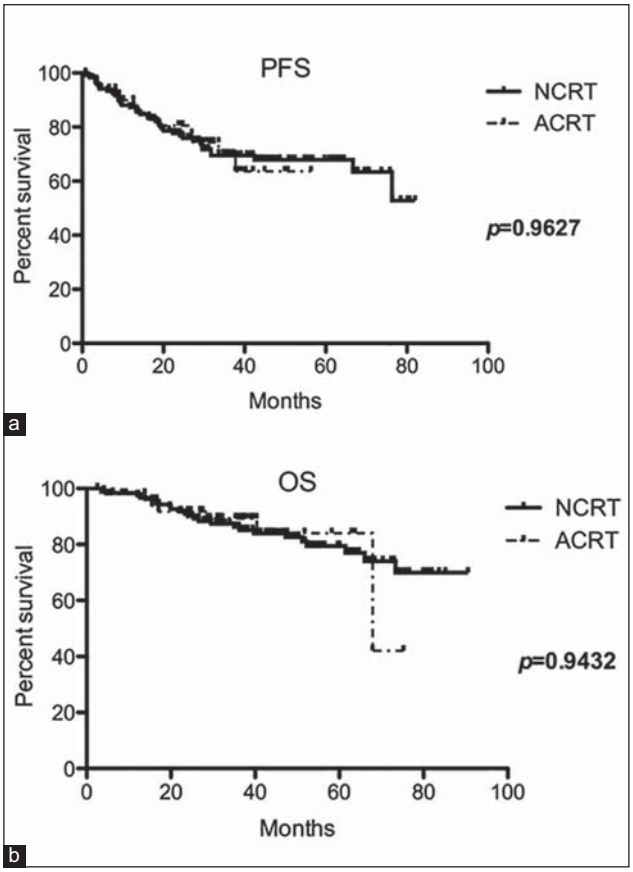


**Figure 1.** Progression-free survival and overall survival in patients with preoperative chemoradiotherapy versus adjuvant chemoradiotherapy. No significant differences were found (a: $P = 0.9627$; b: $P = 0.9432$, separately)

Table 3. Cox regression survival analysis of total group

| Variables | HR | 95% CI | *P* |
|---|---|---|---|
| Progression-free survival | | | |
| NCRT | 1.841 | 0.922-3.679 | 0.084 |
| Gender | 1.195 | 0.615-2.319 | 0.599 |
| Age | 1.001 | 0.980-1.023 | 0.908 |
| Pathological staging | 1.248 | 1.074-1.450 | 0.004 |
| Grade | 1.650 | 0.982-2.772 | 0.058 |
| LVSI | 1.558 | 0.717-3.384 | 0.263 |
| Overall survival | | | |
| NCRT | 1.779 | 0.723-4.378 | 0.210 |
| Gender | 1.101 | 0.481-2.522 | 0.820 |
| Age | 1.013 | 0.986-1.042 | 0.341 |
| Pathological staging | 1.193 | 0.997-1.428 | 0.054 |
| Grade | 1.927 | 0.972-3.821 | 0.060 |
| LVSI | 1.378 | 0.584-3.254 | 0.464 |

NCRT = neoadjuvant chemoradiotherapy; LVSI = lymphovascular space involvement; CI = confidence interval; HR = hazard ratio

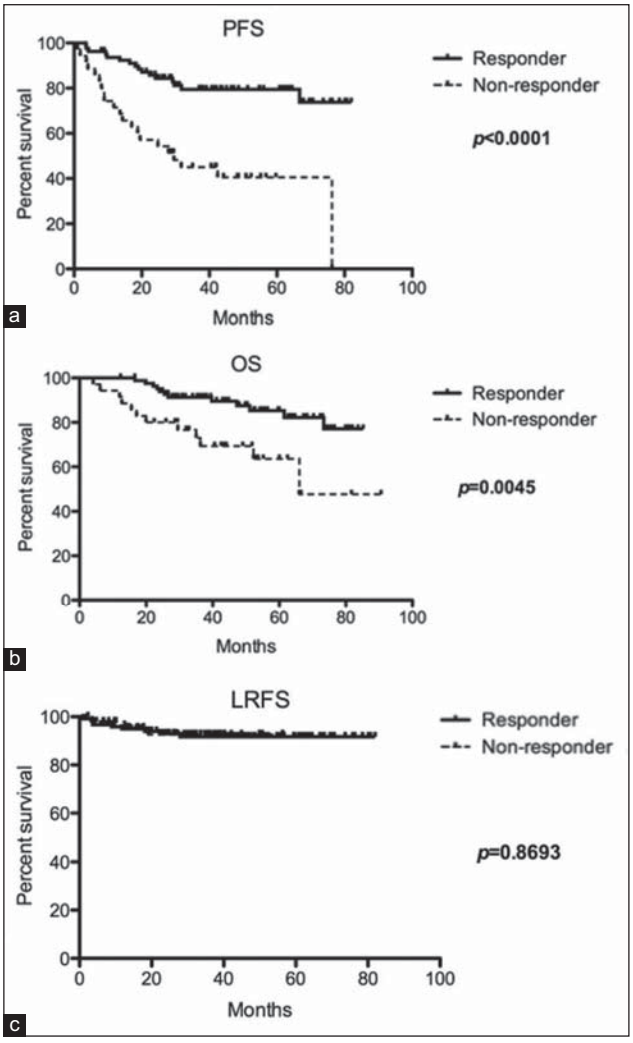


**Figure 2.** Progression-free survival and overall survival in patients who are down-staged (responders) versus non-responder. Significant differences were demonstrated (a: $P < 0.001$; b: $P = 0.045$, separately). The responders showed clinical benefit over the non-responders (c: $P = 0.046$)

study, the overall pCR rate was 27.6% for all patients, which is slightly higher than reported by previous clinical trials and total response rate was 74%.[17,18] In ACRT group, more patients underwent LAR than abdominoperineal resection (APR) under acceptable surgical risk due to lower abdominal pain after the operation and less complications, including bleeding, infection, and temporary difficulty with emptying the bladder.[19,20] The tumor location was significantly lower in NCRT compared with ACRT group ($P < 0.0001$), therefore, approximately one-fourth of them still needed to receive APR after treatment in NCRT group. There is no survival benefit in the NCRT group about PFS and OS, which was compatible with results of previous clinical trials.[2] In addition, LRFS rate was not different between the two groups ($P = 0.87$), which

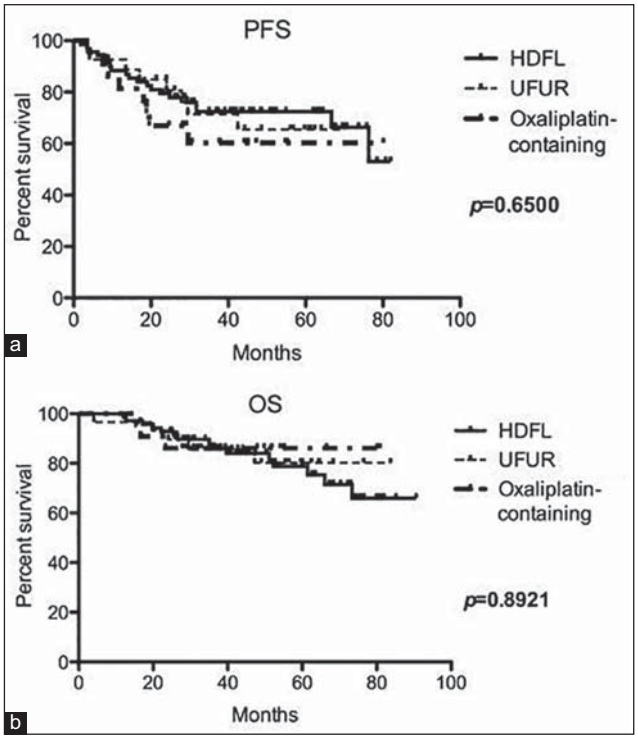


**Figure 3.** Progression-free survival and overall survival in patients who received various chemotherapy combinations. No significant differences were shown (median survival: Not reached in both analyses)

was not compatible with the previous literatures.[21] Longer follow-up time, and larger study population may be needed to prove the efficacy of NCRT.

Martijnse *et al*. conducted a prospective observational study of 504 rectum cancer patients with T3 or T4 lesions and compared the treatment effects of long course radiotherapy, 5-FU, and leucovorin, a combination of capecitabine and oxaliplatin (CORE), and capecitabine only.[22] They concluded that the CORE regimen resulted in the survival benefit compared with the other treatment groups. From our cohort, the overall response rate was similar among all chemotherapy groups (68.3-73.1%) and was not significantly different ($P$ = 0.29) between each other. We could not corroborate this result in our patients with T3 or T4 lesion, perhaps due to our relatively small sample size in the subgroup analysis.

Upon specific analysis of factors that could be associated with disease progression, including staging, LVSI, gender, age, and clinical response, we found none to be predictive of disease progression. Only treatment response and pathological staging could predict PFS, which was compatible with other cohorts.[22] The possible explanations were current modalities for staging rectal cancer had limitation, including abdominal CT, transanal ultrasound, and pelvic magnetic resonance imaging (MRI). Therefore, it was uneasy to confirm the clinical stage before operation, which might mask the clinical significance.

There are several limitations of this study. First, this is a retrospective study and patients did not receive uniform dosage of treatment in HDFL and FOLFOX-like groups. Second, the patient numbers are relatively small, and the results could not be interpreted by stratification. Third, transrectal ultrasound and pelvic MRI were not routinely done in our institute for staging rectal cancer before surgery, which might interfere the accuracy of our patients' clinical stages.

## CONCLUSION

Patients with LCRC who were treated with NCRT in our institute experienced good pathological responses. There were no significant differences in PFS and OS between NCRT and ACRT groups. However, subgroup analysis showed that treatment response of pathological down-staging predicted better PFS and LRFS. A larger randomized control trial is warranted to further validate our results.

## ACKNOWLEDGMENTS

The Cancer Registry Group, Tri-Service General Hospital, approved the study. The authors thank Chia-Ling Yu, who assisted with patient's survival data collection. The authors also thank Dr. Anthony J. Janckila and Dr. Vivek R. Sharma for critical review of the manuscript.

## DISCLOSURE

The authors declare that this study has no conflict of interest and financial support.

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