Original Article

The Impacts of Preoperative Chemoradiotherapy in Locally Advanced Rectal Cancer; Single-center Retrospective Analysis

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Key Words
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Purpose. Preoperative chemoradiotherapy has become the standard treatment for locally advanced rectal cancer. It can reduce tumor size and recurrence, increase the tumor resection rate, enhance the rates of sphincter-preservation procedures, and may improve the probability of curative tumor resection with fewer side effects. This study aimed to evaluate the three-year disease-free and overall survival of patients with rectal cancer who underwent preoperative chemoradiation.

Method. Between January 2007 and December 2020, 50 patients with locally advanced rectal cancer who underwent preoperative radiotherapy and chemotherapy before surgery were included in the study. The clinicopathological and surgical data were retrospectively analyzed.

Results. In our study, most patients were men (78%). The mean age of the patients was 58.46 years. All patients who underwent radical surgery had R0 resection, with all negative circumferential margins. Fifteen patients (30%) achieved a complete pathological response with no local recurrence. Overall, 98% of the patients had neoadjuvant rectal scores of < 16. Three-year disease-free survival and overall survival showed no significant difference between cN0 and cN+ group.

Conclusion. In treating locally advanced rectal cancer, neoadjuvant chemoradiotherapy has led to significant advances in local control for patients with positive lymph nodes, with less acute toxicity and an increased probability of curative tumor resection.

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Colorectal cancer is a public health issue worldwide and is the third most common cancer, with more than 1.9 million incidents of colorectal cancer recorded in 2020.[1] Multimodal treatment strategies, including neoadjuvant chemotherapy and radiotherapy before total mesorectal excision, have been applied to patients with locally advanced rectal cancer.[2-4] In many studies, preoperative chemoradiotherapy for locally advanced rectal cancer showed markedly improved local control compared with that of surgery alone. Thus, preoperative chemoradiotherapy is considered the optimal therapeutic regimen.[2] Preoperative chemoradiotherapy may be associated with less acute toxicity and greater rates of sphincter-preservation procedures and may increase the probability of curative tumor resection when compared with that of surgery alone.[5] Furthermore, tumor downstaging using preoperative chemoradiotherapy may lead to a

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complete clinical or pathological response.[6]

The primary objective of our study was to evaluate the three-year disease-free survival and overall survival of patients with rectal cancer who underwent preoperative chemoradiation treatment.

Material and Methods

Study design and patients

This retrospective study included patients with locally advanced rectal cancer who underwent preoperative radiotherapy followed by chemotherapy at the Department of Colorectal Surgery, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University and College of Medicine, Kaohsiung, Taiwan, between January 2007 and December 2020. The inclusion criteria were as follows: (1) pathologically confirmed rectal adenocarcinoma, (2) tumor located ≤ 10 cm from the anal verge, (3) clinical stage T3-4 or N+ or clinical T2 ultra-low rectal cancer, (4) preoperative radiotherapy followed by chemotherapy before surgery.

This retrospective study involved human participants in accordance with the ethical standards of the institutional and national research committee and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All data were recorded in the hospital database and were used for research purposes only.

Data on clinical and pathological variables, such as age, sex, tumor grade, clinical staging, type of surgery, pathologic staging, and toxicity profiles of radiotherapy were collected. Staging was determined using the 8th edition of the American Joint Committee on Cancer guidelines for tumor, node, and metastasis classifications.

Treatments protocols

The treatment protocols for all patients were discussed at the multidisciplinary team meeting.

Radiotherapy and chemotherapy

All enrolled patients received radiotherapy followed by chemotherapy before surgery. Radiotherapy options were either long or short. Patients who received long-course radiotherapy comprised a total of 50.4 Gy in 28 fractions over five weeks and three days. Chemotherapy options varied with the development of chemotherapy regimens. Weekly 5-FU + leucovorin infusion for 12 weeks was the most commonly used in the early '90s. Biweekly 5-FU/LV with Oxaliplatin was more commonly used in the 2000s,[7] which were also administrated for eight to 12 weeks. Surgery will be arranged 2-12 weeks after chemoradiotherapy for long-course radiotherapy. On the other hand, short-course radiotherapy comprised a total of 25 Gy in five fractions administered over five consecutive days, followed by 8-12 weeks of chemotherapy before surgery. Another alternative chemotherapy option for older patients with high comorbidities is oral chemotherapy with tegafur/leucovorin (UFT 300 mg/m^2/day daily and leucovorin 30-90 mg/day, day 1-28 every five weeks).

Surgery

After complete neoadjuvant treatments, colonoscopy and abdominal computed tomography (CT) were performed to re-evaluate the tumor stage, and the restaging discussion was managed at the multidisciplinary team meeting. Surgeries included low anterior resection, abdominal perineal resection, Hartmann's procedure. The selection of laparotomy, laparoscopy, or protective stoma creation was based on the surgeon's preference and judgment.

Assessment

All patients underwent complete staging with a physical examination, digital rectal examination, colonoscopy, and computed tomography before treatment initiation. Chest and abdominal CT were performed to assess the tumor and rule out distant organ metastasis. Pelvic magnetic resonance imaging was performed to evaluate tumor and lymph node conditions. After neoadjuvant treatment, a restaging examination involving physical examination, colonoscopy, and CT or magnetic resonance imaging was performed

before discussion at a multidisciplinary team meeting. Staging was conducted according to the 8th edition of the American Joint Committee on Cancer guidelines for tumor, node, and metastasis classification. Pathological complete response was defined as no tumor at the primary lesion site on the specimen, according to pathology reports. The neoadjuvant rectal (NAR) score was calculated to assess tumor response as follows: $NAR = [5pN – 3(cT – pT) + 12]^2/9.61$.[8] Tumor downstaging was categorized as increased, decreased, or unchanged, according to the difference between the clinical and pathological stages. Postoperative complications were defined as any morbidity within 30 days of surgery. The Clavien-Dindo classification was used as a reference to grade surgical complications.

Statistical analysis

Survival curves were generated using the Kaplan-Meier method. The index date of survival analysis was the day the patient started RT. All statistical analyses were performed using the Statistical Package for Social Sciences, version 24 (IBM Corp., New York, NY, USA) and GraphPad Prism version 9 (GraphPad Software Inc., San Diego, CA, USA). Differences were considered statistically significant at a two-sided p-value < 0.05.

Results

Patient characteristics

A total of 50 patients were enrolled in this study. Patients were mostly men (78%) with a mean age of 58.46 ± 9.54 years. All patients were diagnosed with rectal cancer at clinical stage T3-4 or N+. The clinical stage, Eastern Cooperative Oncology Group Performance Status, pretreatment carcinoembryonic antigen levels, and tumor histology grades are summarized in Table 1.

Pathology findings after treatments

A total of 50 patients underwent surgery for rectal cancer. Forty-eight patients received radical surgery, with the exception of two who underwent local excision. All patients who underwent radical surgery had R0 resection, with all negative circumferential margins. Fifteen patients achieved a complete pathological response. Thirty-five patients (70%) had low NAR scores, and 14 patients (28%) had intermediate NAR

Table 1. Patient characteristics

	n = 50
Age at diagnosis (years)	58.46 ± 9.54
Sex	
Male	39
Female	11
ECOG-PS score	
0	39
1	10
2	1
Clinical T stage	
T2	5
T3	35
T4a	7
T4b	3
Clinical N stage	
N0	15
N+	35
Tumor distance from the AV (cm)	
≤ 5	36
> 5	14
Pretreatment CEA (ng/ml)	
< 5.0	37
≥ 5.0	13
Clinical stage	
I	4
II	9
III	37
Neoadjuvant chemotherapy regimen	
5FU + LV	36
MFOLFOX6	11
UFUR	1
Histology grade	
Well	0
Moderate	49
Poor	1
RT type	
Short	11
Long	39
Post-operative adjuvant chemotherapy	
Yes	19
No	31

scores. More than 50% of the patients experienced tumor and nodal downstaging after preoperative chemoradiotherapy. All 4 patients are ultra-low rectal cancer cases with tumor lying 1-3 cm above anal verge. These patients received good results from pre-operative chemoradiotherapy with much regression of tumor size. One of these three even received pathological complete response. The details of the pathological findings are summarized in Table 2.

Surgery and postoperative complications

All patients completed radiotherapy without delays or dose reductions. The median interval between the in last day of radiotherapy and surgery was 108 days (15.4 weeks). The most common toxicity was grade 1 diarrhea, followed by grade 1 dermatitis. No toxicity above grade 3 was observed.

Table 2. Post treatment pathology findings

	n = 50
T stage	
ypT0	18 (36%)
ypT1	4 (8%)
ypT2	8 (16%)
ypT3	15 (30%)
ypT4	5 (10%)
N stage	
ypN0	36 (72%)
ypN1	8 (16%)
ypN2	6 (12%)
Circumferential resection	
Negative	50 (100%)
Positive	0
Stage	
ypT0N0	15 (30%)
yp stage I	12 (24%)
yp stage II	11 (22%)
yp stage III	12 (24%)
NAR score	
Low (< 8)	35 (70%)
Intermediate (8-16)	14 (28%)
High (> 16)	1 (2%)
T-downstaging	
Decrease	33 (66%)
Not decrease	17 (34%)
N-downstaging	
Decrease	29 (58%)
Not decrease	19 (42%)

Most patients underwent radical surgery. Of these, forty-two patients underwent low anterior resection; six patients had abdominal perineal resection. Two patients with ultra-low rectal cancer underwent local excision. Approximately 84% of the patients who underwent low anterior resection received a protective stoma. No anastomotic leakage, postoperative urinary retention, or surgical site infections were observed in this study. However, one patient was diagnosed with a urethral injury and treated with percutaneous nephrostomy. Details of the operative characteristics and postoperative complications are summarized in Table 3.

Follow-up and medium-term survival

The median follow-up duration was 48.4 months. None of the patients experienced local recurrence. Fifteen patients (30%) had a pathological complete response, with no local recurrence; however, four pa-

Table 3. Operative characteristics and post-operative complications

	n = 50
Interval between RT and surgery, median (weeks)	15.4 (1-106)
Type of operation	
LAR	42
APR	6
Hartmann	0
Local excision	2
Surgical approach	
Laparotomy	13
Laparoscopy	33
Robotic surgery	2
Trans-anal only	2
Stoma creation	
Protective stoma	42
End colostomy	6
Post operative complication	
Anastomosis leakage	0
Urine retention	0
Urethra injury	1
Ileus	1
Surgical site infection	0
Clavien-Dindo grade	
I	0
II	1
III	1
IV	0

tients were diagnosed with distant metastasis during follow-up. The three-year overall survival was significantly lower among the advance cT-stage group; especially cT4 group. However, three-year disease-free survival and overall survival showed no significant difference between cN0 and cN+ group (Fig. 1).

Discussion

Previous studies have reported conflicting results regarding the role of preoperative chemoradiotherapy in patients with locally advanced rectal cancer.[9,10] Many European studies have shown that preoperative chemoradiotherapy reduces the rate of local recurrence and improves local control but has no impact on overall survival.[6,11] A few studies have stated that preoperative chemoradiotherapy is unnecessary and might be overtreatment for patients with stage I or II rectal cancer.[12,13] Retrospective studies have reported that preoperative chemoradiotherapy is essential for locally advanced rectal cancer. A previous study compared surgery alone and preoperative chemoradiotherapy in rectosigmoid junction cancer and found that preoperative chemoradiotherapy was associated with a 5% improvement in five-year overall survival.[14] Another study from Korea reported that patients with early T3 rectal cancer who were either treated with surgery alone or preoperative chemoradiotherapy showed a five-year local recurrence rate of 2% for both groups, and the five-year disease-free survival was not statistically different (87% in surgery alone versus 88% in preoperative chemoradiotherapy group).[15]

In our study, we found that there was no statistical difference in the three-year disease-free survival and overall survival in patients with rectal cancer having positive regional lymph nodes. Previously, we had included study patients with resectable stage IV disease, which may have different results. According to the American Cancer Society, the five-year relative sur-

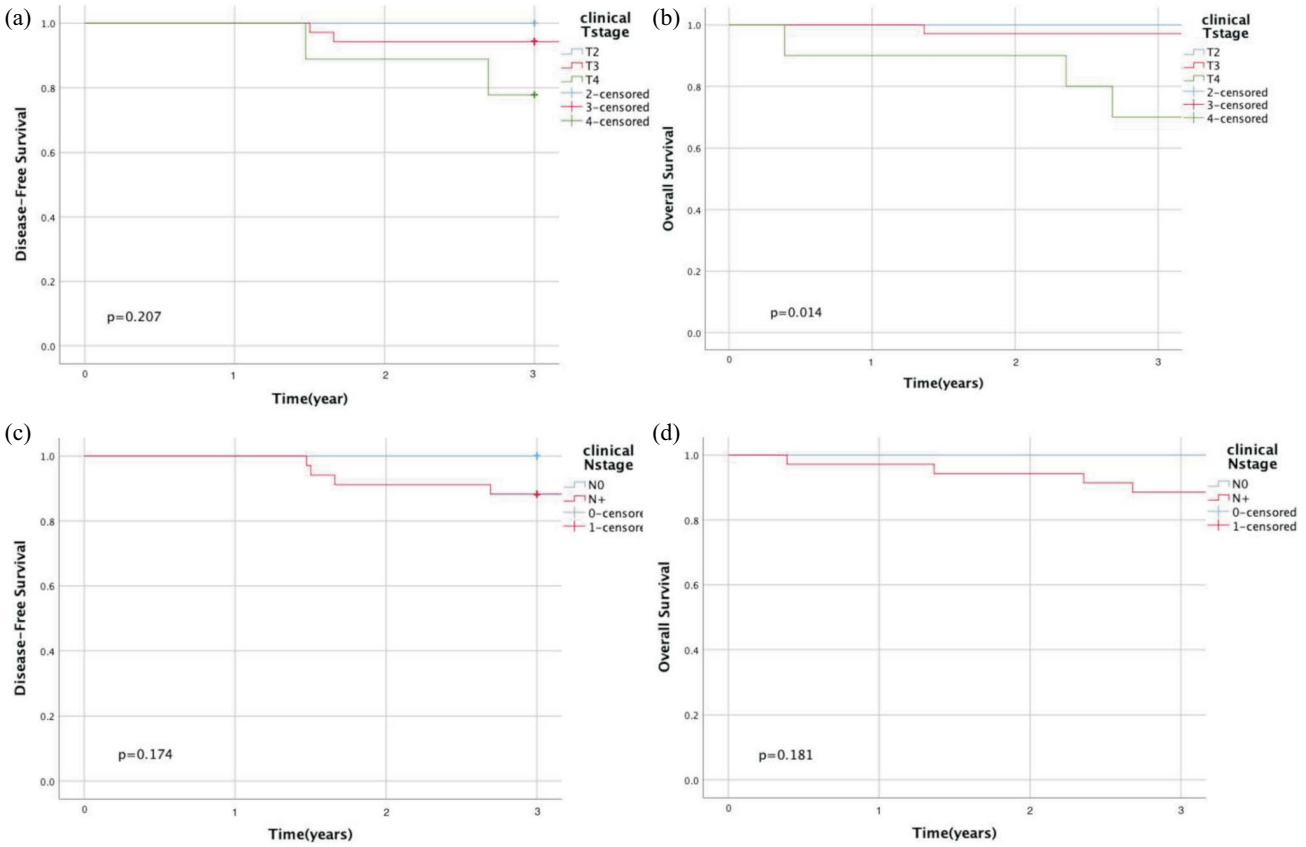

Fig. 1. Comparison of Kaplan-Meier survival curves between different T stage and N stage.

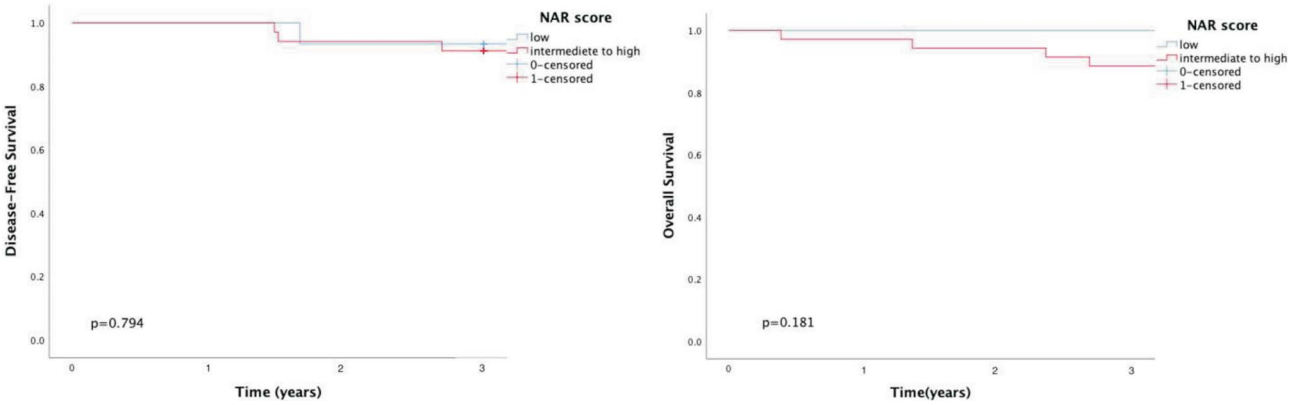

Fig. 2. Comparison of Kaplan-Meier survival curves between low NAR score and intermediate to high NAR score.

vival rate of patients with stage IV rectal cancer is 17%. However, some studies have shown that a combination of surgical resection for metastatic cancer and adjuvant chemotherapy may improve overall survival.[16] However, we excluded patients with stage IV rectal cancer due to the criteria does not meet.

In addition, we included the neoadjuvant rectal (NAR) score in our study because it is used for early determination of treatment response in many studies.[17] NAR score assigns categories to different parameters, which are then combined to give an overall predictive score. This score helps clinicians classify patients into risk groups (e.g., low, intermediate, high risk) for treatment response. In this study, three-year disease-free survival and overall survival showed no significant difference between low NAR score and intermediate to high NAR score (Fig. 2).

Our study has a few limitations. First, our study retrospectively collected data from a single center. Second, only data from our institution were collected; larger patient samples from multiple centers in a randomized controlled study may provide additional information.

Conclusion

In the treatment of locally advanced rectal cancer, the use of neoadjuvant chemoradiotherapy has led to significant advances in local control in patients with positive lymph nodes, with less acute toxicity and an increased probability of curative tumor resection. Preoperative chemoradiotherapy may increase the rate of sphincter preservation procedures; however, further investigation is needed.

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原　著

術前放化療對局部晚期直腸癌的影響：單一中心回顧性研究

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目的　術前放化療不僅可以減少腫瘤體積和減少復發，還可以提高腫瘤切除率、提高保肛手術率，並可能增加腫瘤根治性切除的可能性，且副作用較小。本篇研究指在是評估接受術前放化療的臨床效果。

方法　本研究為回溯性研究，從 2007 年 1 月至 2020 年 12 月期間，收集單一醫院 50 名接受術前放射及化學治療直腸癌患者，進行臨床病理和手術資料進行回顧性分析

結果　位病人中，大多數為男性。所有患者的平均年齡為 58.46 歲。所有病人接受根治性手術。其中有十五名患者達到病理完全反應。我們對治療後病人評估新輔助直腸評分，有 98% 的患者評分 < 16。cN- 及 cN+ 組的三年無疾病存活和總存活率有顯著差異。

結論　在局部晚期直腸癌的治療中，術前放化療的使用使 N+ 組患者的局部控制取得了顯著進展，且急性毒性較小，增加了腫瘤根治性切除的可能性。

關鍵詞　直腸惡性腫瘤、術前放化療。