Pathological and Oncologic Outcomes of Consolidation Chemotherapy in Locally Advanced Rectal Cancer after Neoadjuvant Chemoradiation

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ABSTRACT

Objective: The current standard of care for locally advanced rectal cancer is associated with multimodality therapy. Neoadjuvant chemoradiation significantly decreased the locoregional recurrence rate and improved survival. However, distant metastasis develops rather than local recurrence, which becomes the leading cause of death. This study aimed to evaluate the oncological outcomes of total neoadjuvant therapy (TNT) in locally advanced rectal cancer.

Materials and Methods: This retrospective study recruited 18 patients diagnosed with locally advanced rectal adenocarcinoma (cT3-4 or cN1-2), treated with consolidation TNT. The primary endpoint was pathological complete response (pCR). The secondary endpoint included postoperative outcomes, local recurrences, and distant metastases.

Results: The pathologic complete response was observed in 27.8% of consolidation therapy cases and 25% of induction therapy cases. Downstaging of the T-category was achieved in 10 (55.6%) patients, and downstaging of the N-category was achieved in 14 (77.8%) patients. Only one patient who achieved pCR developed distant metastasis, whereas all patients with pathological stage III developed distant metastasis.

Conclusion: TNT is a promising approach for patients with locally advanced rectal cancer. This strategy improved complete pathologic response rates in TNT, and pCR was found to be associated with fewer local recurrences and greater disease-free survival.

Keywords: Consolidation chemotherapy; total neoadjuvant therapy; rectal cancer; pathologic complete response
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INTRODUCTION

In Thailand, colorectal cancer is the third most common cancer in men and the fourth in women,[1] with an estimated of over 10,000 new cases annually. Rectal cancer accounts for 40%–52% of all colorectal adenocarcinoma.[2] The current standard of care for locally advanced rectal cancer is associated with multimodality therapy, consisting of neoadjuvant chemoradiotherapy (CRT) that included either preoperative long-course CRT or short-course radiotherapy, followed by surgical resection with total mesorectal excision and adjuvant chemotherapy.[3]

Neoadjuvant chemoradiation significantly decreased the locoregional recurrence rate and improved survival.[4,5] Nevertheless, distant metastasis occurs rather than local recurrence, which becomes the leading cause of death.[6] A systemic spread was presumed to be caused by clinically undetectable micrometastases in a distant area.

Total neoadjuvant therapy (TNT) is an alternative treatment option to provide systemic therapy for patients

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with locally advanced rectal cancer and aims to reduce distant metastases. TNT refers to the administration of CRT plus chemotherapy followed by surgery, including induction and consolidation chemotherapy.[7] Moreover, a previous study showed that TNT achieved improved local control and reduced the duration of a diverting ileostomy.[8]

The benefits of this therapeutic strategy are increased downstaging, improved resectability by the downsizing of the tumors, potentially decreased sphincter-preservation rate, and reducing a significantly higher rate of pathological complete response (pCR).[9,10] Early systemic therapy allows for chemosensitivity assessment and eliminates micrometastatic disease before surgery, which would lead to better survival. This study aimed to evaluate the oncological outcomes of consolidation chemotherapy in poor responders after neoadjuvant chemoradiation.

MATERIALS AND METHODS

Patient populations

This single-center retrospective cohort study recruited 22 patients with locally advanced rectal adenocarcinoma who were treated with TNT and underwent elective surgery during the period from January 2012 to December 2020 at the Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand. Consolidation chemotherapy was completed by 18 patients, whereas 4 patients received induction chemotherapy.

The inclusion criteria were as follows: age 18 years or older at the time of diagnosis, received consolidation TNT, histologically proven rectal adenocarcinoma located up to 10 cm from the anal verge, locally advanced stage of T3/T4, or node-positive disease confirmed by computed tomography (CT) and/or magnetic resonance imaging (MRI) of the chest, abdomen, and pelvis. Patients who received palliative treatment, refused CRT, had a previous history of cancer, and received pelvic radiotherapy or systemic chemotherapy were excluded. Ethical approval for this study was obtained from Institutional Review Board, Faculty of Medicine Siriraj Hospital, Mahidol University (COA no. Si 600/2022).

Data collection

The data collected included patient demographics, age at diagnosis, sex, performance status, tumor size, and location. Preoperative clinical assessments included physical examination, colonoscopy, abdominal MRI, chest CT, and serum carcinoembryonic antigen measurement. The clinical stage was classified according to the American Joint Committee on Cancer (AJCC) 8th staging system.[11] Initial evaluation was performed by a surgeon, medical oncologist, and radiation oncologist, and the CRT regimen was selected at the discretion of the treating physician.

Clinical response was evaluated by digital rectal examination and endoscopy. Restaging MRI was performed 6–8 weeks after the completion of concurrent chemoradiation and TNT. The chemotherapy regimen, radiation dose, operative approach, surgical procedure, pathological staging, adverse reactions of chemoradiation, and postoperative complications were reviewed. The histology of surgical specimens was reviewed and confirmed by pathologists and was classified based on the modified Ryan scheme for the tumor regression score.[12] Patients were classified as complete responders (TRG0), near-complete responders (TRG1), partial responders (TRG2), and poor responders (TRG3).

The primary endpoint was pCR. pCR or ypT0N0 was defined as the absence of residual tumor cells in the surgical specimen. The secondary endpoints included postoperative outcomes, Clavien–Dindo classification of complications,[13] sphincter preservation, mortality, local recurrences, and distant metastases.

The study was performed with the approval of the Institutional Review Board, Faculty of Medicine Siriraj Hospital, Mahidol University (COA no. Si 517/2022), and the requirement for informed consent was waived.

Statistical analysis

All data were analyzed using IBM SPSS Statistics, version 26.0 (IBM Corp., Armonk, NY, USA). The descriptive analysis was performed. Quantitative variables with normal distribution were summarized as mean and standard deviation (SD), whereas non-normal variables were presented as median and interquartile range (IQR). Qualitative variables were reported as frequency and percentage. The pCR of each clinicopathological variable was evaluated by univariate and multivariate logistic regression analyses. A p-value < 0.05 was considered significant.

RESULTS

Patient characteristics

A total of 22 patients with locally advanced rectal cancer who received consolidation TNT were enrolled, and the baseline characteristics of the study population are shown in Table 1. The mean age of the patients at the initial diagnosis was 61.2 years, with a SD of 12.9 years (range, 34–81 years), and approximately 66.7% of the cases occurred in men. The median distance of the tumor from the anal verge was 5.0 cm (IQR 3–6), and 72.2% of tumors were located at the site 5 cm below the anal verge. The majority of cases were classified as clinical

TABLE 1. Demographic data (n = 22).

Characteristics	
Age (years), mean ± SD (range)	59.9 ± 11.5 (range 34–81)
Sex, n (%)	
Male	14 (63.6)
Female	8 (36.4)
ASA classification, n (%)	
ASA I	1 (4.6)
ASA II	18 (81.8)
ASA III	3 (13.6)
Body mass index(kg/m^2), mean ± SD	23.7 ± 2.7
Clinical T stage, n (%)	
cT1	1 (4.5)
cT2	0
cT3	17 (77.3)
cT4	4 (18.2)
Clinical N stage, n (%)	
cN0	2 (9.1)
cN1	18 (81.8)
cN2	2 (9.1)
AJCC clinical stage, n (%)	
Stage 2	2 (9.1)
Stage 3	20 (90.9)
Preoperative diversion	6 (27.3)
Raised preoperative CEA level*	14 (63.6)
Distance from anal verge, n (%)	
≤5 cm	15 (68.2)
5.1–10 cm	7 (31.8)
Total radiation dose (Gy), median (IQR)	50.4 (50.1–54)
Induction regimen, n (%)	4 (18.2)
Consolidation regimen, n (%)	18 (81.8)
Operation, n (%)	
LAR	4 (18.2)
TaTME	6 (27.3)
APR	12 (54.5)
Approach, n (%)	
Open	8 (36.4)
Laparoscopic	13 (59.1)
Robot	1 (4.5)

Abbreviations: ASA, American Society of Anesthesiologists physical status classification

* Serum carcinoembryonic antigen (CEA) levels >5 ng/mL are considered elevated.

T3 (88.9%) based on the AJCC. Approximately 88.9% were clinical node-positive cases. The nodal status was N1 in 14 (77.8%) and N2 in 2 (11.1%) patients.

Total neoadjuvant therapy

Two cases (11.1%) were classified as clinical stages II, and 16 (88.9%) cases were classified as stage III at initial diagnosis. All patients received long-course radiotherapy, with a median radiation dose of 50.4 Gy (IQR 50–54). About two-thirds of the patients (72.2%) received preoperative radiotherapy with concurrent capecitabine, and 5 (27.8%) patients received concurrent 5-fluorouracil-based chemotherapy. A poor responder was defined as follows: threaten margin or positive circumferential margin (70.6%). After the completion of CRT, poor responders received either consolidation chemotherapy with capecitabine and oxaliplatin (CAPOX; 66.7%) or fluorouracil, leucovorin calcium, and oxaliplatin (FOLFOX; 33.3%) regimen. Induction chemotherapy was completed by 4 patients, who received chemotherapy with various regimens in the form of CAPOX, FOLFOX, or FOLFIRINOX. After completing the induction chemotherapy, concurrent CRT with capecitabine or FOLFOX was given.

Response to treatment

Therapeutic response was assessed by clinical examination, colonoscopy, MRI, and histopathology. Clinical response was evaluated after induction or consolidation chemotherapy, and restaging was performed 6–8 weeks after concurrent chemoradiation, in which the median time of restaging was 53 (IQR 45–59) days following the completion of radiation. Tumors were gradually downstaged after received TNT. Two patients had a clinical complete response (cCR), as shown in Fig 1.

Surgery

The standard surgical procedure for locally advanced rectal cancer is abdominoperineal resection (APR) and low anterior resection (LAR) with total mesorectal excision. All patients underwent curative surgical resection, and the mean time from completion radiation to operation was 251.6 ± 68.6 days. During the preoperative period, diverting loop colostomy was performed in 5 (27.8%) patients Moreover, 11 (61.1%), 2 (11.1%), and 5 (27.8%) patients underwent APR, LAR, and transanal total mesorectal excision, respectively.

None of the patients had 30-day postoperative mortality. Postoperative complications occurred in 2 (11.1%) patients, which were classified as Clavien–Dindo grade III complications. One of them developed colostomy necrosis and underwent resection and relocation of the stoma. Another patient had postoperative intra-abdominal hemorrhage, who underwent re-exploration for bleeding control.

The anal sphincter preservation rate was 38.9%, and protective ileostomy or colostomy was performed in all cases. However, the rate of permanent stoma after sphincter-saving surgery was 42.8%, which was associated with tumor recurrence. One patient developed a 1-cm liver nodule during preoperative restaging; thus, these

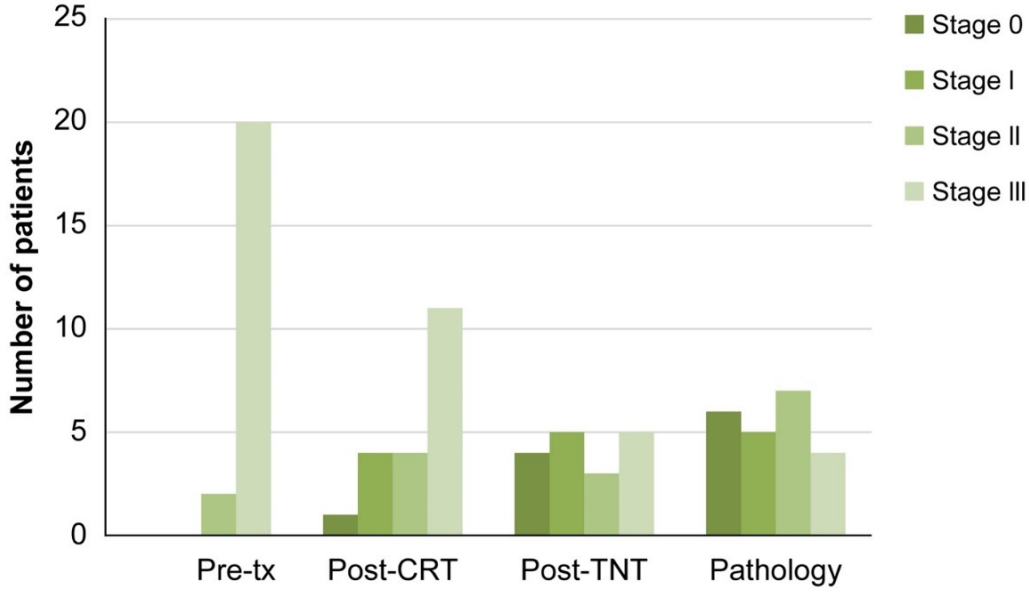

Fig 1. Response to treatment over time including pretreatment clinical stage (pre-tx), clinical response after chemoradiation completion (post-CRT; 54-day median time from radiation completion), clinical response after total neoadjuvant therapy completion (post-TNT), and pathological stage.

patients underwent hepatectomy. Laparoscopic and robotic-assisted surgery was performed in 11 (61.1%) and 1 (5.6%) patient, respectively.

Treatment efficacy

The pCR was observed in 27.8% of the patients receiving consolidation therapy. The histopathological results are summarized in Table 2. The final pathology revealed ypT2N0 in 4 (22.2%), ypT3N0 in 7 (38.9%), and ypT3N1 in 2 (11.1%) patients. Downstaging of the T-category was achieved in 10 (55.6%) patients, and downstaging of the N-category was achieved in 14 (77.8%) patients, whereas stable disease was observed in 2 (11.1%) patients. The mean number of retrieved lymph nodes was 10.9 ± 6.9. The resection margins were 83.3% for the negative margin (R0) and 16.7% for the microscopic-positive margin (R1). Perineural invasion was present on histopathological assessment in 5 (27.8%) patients, and lymphovascular invasion was reported in 3 (16.7%) patients. Tumor regression was evaluated according to the modified Ryan scheme as TRG0 in 5 (27.8%) patients, TRG1 in 2 (11.1%), TRG2 in 3 (16.7%), and TRG3 in 5 (27.8%). The univariate analysis was used to assess the predictive value of variables for achieving pCR. Clinicopathological factors were not significantly associated with pCR including age, gender, comorbidities, body mass index, clinical stage, tumor location, positive circumferential resection margin (CRM), radiation dose, and chemotherapy type. The results of the analyses are summarized in Table 3.

Survival and recurrence

The mean follow-up time was 36.8 ± 15.8 (range, 16.3–72.1) months. Recurrence was recorded in 6 (33.3%) patients. The mean recurrent time was 23.1 ± 14.5 (range, 2.1–45.7) months. Locoregional recurrences of rectal cancer occur in 2 (11.1%) patients, and 4 (22.2%) patients developed distant metastases. The lung and liver were the most common sites of distant metastasis (Table 4).

DISCUSSION

Neoadjuvant CRT followed by total mesorectal excision remains a standard treatment for stage II and III rectal cancer. We found that TNT improved

TABLE 2. Pathological features.

	Total	Consolidation (N = 18)	Induction (N = 4)
Pathologic T stage, n (%)			
ypT0	6 (27.3)	5 (27.8)	1 (25)
ypT1	0	0	0
ypT2	5 (22.7)	4 (22.2)	1 (25)
ypT3	11 (50)	9 (50)	2 (50)
ypT4	0	0	0
Pathologic N stage, n (%)			
ypN0	18 (81.8)	16 (88.9)	2 (50)
ypN1	3 (13.6)	2 (11.1)	1 (25)
ypN2	1 (4.6)	0	1 (25)
Pathologic stage, n (%)			
Stage 0 (ypT0N0)	6 (27.3)	5 (27.8)	1 (25)
Stage 1 (T2N0)	5 (22.7)	4 (22.2)	1 (25)
Stage 2 (T3N0)	7 (31.8)	7 (38.9)	0
Stage 3 (T3N1/T3N2)	4 (18.2)	2 (11.1)	2 (50)
Pathologic response, n (%)			
TRG 0	6 (27.3)	5 (27.8)	1 (25)
TRG 1	2 (9.1)	2 (11.1)	0
TRG 2	4 (18.2)	3 (16.7)	1 (25)
TRG 3	6 (27.3)	5 (27.8)	1 (25)

Abbreviation: TRG, tumor regression grade.

TABLE 3. Univariate analysis of clinicopathological factors associated with pathological complete response.

Variable	Univariable analysis		
	OR	95% CI	*P*-value
Age	0.98	0.90–1.07	0.72
Sex	1.20	0.16–8.65	0.85
ASA classification	0.46	0.03–5.41	0.53
Body mass index	0.76	0.52–1.11	0.16
Distance from anal verge (≤5 cm, 5.1–10 cm.)	1.10	0.14–8.12	0.92
Preoperative diversion	2.27	0.20–24.88	0.50
Raised preop CEA	2.20	0.32–14.97	0.42
Clinical T stage	1.36	0.25–7.43	0.71
Clinical N stage	0.25	0.02–3.11	0.28
AJCC Clinical stage	0.61	0.09–4.03	0.61
TNT therapy (induction, consolidation)	1.15	0.09–13.87	0.91
Positive CRM	0.66	0.09–4.92	0.69
Concurrent chemoradiation	0.54	0.06–4.56	0.57
Total radiation dose	1.39	0.82–2.38	0.21
Consolidation chemotherapy	0.55	0.24–1.23	0.14

TABLE 4. Complications and recurrence.

	Total	Consolidation (N = 18)	Induction (N = 4)
Mortality, n (%)	0	0	0
Major complication, n (%)	2 (9.1)	2 (11.1)	0
Recurrent, n (%)			
No recurrent	15 (68.2)	12 (66.7)	3 (75)
Local recurrent	2 (9.1)	2 (11.1)	0
Distant metastasis	5 (22.7)	4 (22.2)	1 (25)
Distant metastatic site, n (%)			
Lung	3 (37.5)	3 (16.7)	0
Liver	3 (37.5)	3 (16.7)	0
Pancreas	1 (12.5)	0	1 (25)
Brain	1 (12.5)	1 (5.6)	0

complete pathologic response rates. Previous studies have revealed that 15%–20% of the treated patients achieved pCR after conventional neoadjuvant chemoradiation therapy,[14,15] whereas our study revealed that 27.8% of patients who received TNT had higher pCR. A pCR is associated with fewer local recurrences (odds ratio (OR) 0.25; $p = 0.002$), distant metastases (OR 0.23; $p < 0.001$), and greater disease-free survival at 5 years (OR 4.33; $p < 0.001$) than standard therapy.[16,17] In a previous systematic review, the pooled 5-year DFS and 5-year OS rates were 65% and 74%, respectively.[18]

TNT improved pCR rates in both consolidation and upfront therapies. In our study, pCR was observed in 27.8% of the patients on consolidation therapy, which is comparable to the recent meta-analysis.[18,19] However, The OPRA trial demonstrated slightly higher pCR rates than our study which could be attributed to the lymph node staging.[20] Downstaging of the T-category was achieved in approximately half of our patients, whereas downstaging of the N-category was observed in more than two-thirds of the patients. Downsizing of rectal cancer in response to TNT can change a previously inoperable tumor to an operable tumor. Thus, consolidation chemotherapy should be an option in poor responders to neoadjuvant therapy.

Among five patients who achieved pCR, one developed distant lung and brain metastasis at 30.2 months, whereas among two patients with pathological stage III cancer who poor responders to TNT developed distant metastasis. Furthermore, 33.3% of the patients with microscopic residual tumor had distant metastasis at 2.1 months without local recurrence. Distant metastasis remains the major reason for treatment failure in TNT.

The cCR was evaluated by digital rectal examination, colonoscopy, and radiographic images. After the completion of CRT, two patients had cCR; however, all of them achieved a pCR. The disconcordance of the pCR and cCR is associated with the accuracy of the examinations and imaging findings.[21]

Our data showed that the mean time from the completion of radiation therapy to operation was 35.9 weeks. A prolonged interval between radiation to surgery may increase the risk of radiation-induced pelvic fibrosis but does not increase the surgical technical difficulty and complications.[21,22] In this study, there was no conversion to open surgery, and surgical complications (Clavien–Dindo grade III; 11.1%) were comparable to those in previous studies.[10] Therefore, laparoscopic surgery is feasible in long-waiting time cases after CRT.

We achieved a sphincter-preservation rate of 45.5% in low rectal cancers, especially in two-thirds of tumors located within 5 cm from the anal verge. The sphincter-preservation surgery improves the patient's quality of life and allows an early return to work. A previous study showed no difference in the proportion of sphincter-preserving surgery when compared with conventional therapy.[8]

This study has some limitations. First, this is a preliminary retrospective review with a small population, which presents potential selection bias. The randomization of the patients is ethically challenging, and some drug regimens were based on health insurance. Second, the follow-up time was short. Thus, more patients should be analyzed. A prospective randomized controlled trial with longer follow-up periods for survival analysis is warranted.

CONCLUSION

TNT is a promising approach for patients with locally advanced rectal cancer. This strategy improved complete pathologic response rates in both consolidation and upfront therapies, and pCR was found to be associated with fewer local recurrences and greater disease-free survival. However, distant metastasis remains the predominant cause of treatment failure. Long-term follow-up can provide estimates of the effectiveness of systemic therapy.

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