Clinical outcome of neoadjuvant chemoradiation in rectal cancer treatment

Weerapat Suwanthanma, MD*, Saowanee Kitdomrat, MD, Chakrapan Euanorasetr, MD

Abstract
To determine the clinical and pathological outcome of locally advanced rectal cancer patients treated with neoadjuvant chemoradiation (chemoradiotherapy [CRT]) followed by curative surgery and to identify predictive factors of pathological complete response (pCR).

Locally advanced rectal cancer patients undergoing CRT followed by curative surgery from January 2012 to December 2017 were included. Patient’s demographic data, pretreatment tumor characteristics, type of CRT regimens, type of surgery, postoperative complications, pathological reports and follow up records were analyzed. Univariate and multivariate analyses were applied to identify predictive factors for pCR. Five-year disease free and overall survival were estimated by Kaplan–Meier method and compared between pCR and non-pCR groups.

A total of 85 patients were analyzed. Eighteen patients (21.1%) achieved pCR. The sphincter-saving surgery rate was 57.6%. After univariate analyses, tumor length >4 cm ($P = .007$) and positive lymph nodes ($P = .040$) were significantly associated with decreased rate of pCR. Complete clinical response was significantly associated with higher rate of pCR ($P = .015$). Multivariate analyses demonstrated that tumor length >4 cm ($P = .010$) was significantly associated with decreased rate of pCR. After a median follow-up of 65 months (IQR 34–79), the calculated 5-year overall survival and disease-free survival rates were 81.4% and 69.7%, respectively. Patients who achieved pCR tend to had longer 5-year disease-free survival ($P = .355$) and overall survival ($P = .361$) than those who did not.

Tumor length >4 cm was associated with decreased rate of pCR in locally advanced rectal cancer who had CRT followed by surgery. Longer waiting time or more intense adjuvant treatment may be considered to improved pCR and oncological outcomes.

Abbreviations: 3D-CRT = three-dimension conformal radiotherapy, 5-FU = 5-fluorouracil, APR = abdominoperineal resection, cCR = clinical complete response, CEA = carcinoembryonic antigen, CI = confidence interval, CRT = chemoradiotherapy, CT = computerized tomography, DFS = disease free survival, Gy = Gray, IQR = interquartile range, LAR = low anterior resection, LV = leucovorin, MRI = magnetic resonance imaging, N downstaging = node downstaging, OR = odds ratio, OS = overall survival, pCR = pathological complete response, T downstaging = tumor downstaging, TME = total mesorectal excision, UltraLAR = ultra low anterior resection, XELOX = Xeloda+Oxaliplatin chemotherapy regimen, ypT = pathological tumor stage after neoadjuvant chemoradiation.

Keywords: neoadjuvant chemoradiation, pathological complete response, rectal cancer

1. Introduction
Multimodality treatment with preoperative concurrent chemoradiotherapy (CRT) followed by total mesorectal excision (TME) were used as standard treatment for locally advanced mid and low rectal cancer to improved oncological outcomes in term of local recurrence and overall survival. Further regression of tumor after CRT increases the possibility for local control and sphincter preservation. Previous studies showed that 15% to 27% of patients following CRT and rectal surgery would get the maximum benefit and had a pathological complete response (pCR). The patients who achieved pCR experienced more favorable oncological outcome compared with patients who not achieved. However, there were some patients who did not response well after CRT and did not get benefit from these treatments. Therefore, it would be better if there were some methods to predict the response CRT before starting the treatment.

Few studies have reported some conflicting result of clinical predictive factors for pCR, including tumor size, nodal stage, and pretreatment carcinoembryonic antigen (CEA) level. Tumor length, as measured by computerized tomography scan or magnetic resonance imaging, is one of the routine clinical parameters collected in management of rectal cancer. Data on tumor length as a predictive factor of pCR were previously mentioned in esophageal cancer after treatment with neoadjuvant chemoradiotherapy. However, previous studies on tumor...
length as a predictive factor for pCR in rectal cancer are scarce and inconsistent.\textsuperscript{[18–20]} The lack of consistency may be attributable to the limited number of studies and small number of patients who achieved pCR. Therefore, there was no consensus on whether tumor length should be used as one of the clinically feasible predictive factors for pCR.

In our study, we conducted a retrospective cohort to determine clinical outcome and identify rate and clinical predictive factors associated with pCR after CRT in the patients with locally advanced rectal cancer at our tertiary referral center. We further examine if the tumor length and its appropriate cut-point, measured preoperatively, can adequately predict pCR.

2. Materials and methods

2.1. Patients

All 476 rectal cancer patients were identified in the tumor registry of Ramathibodi Hospital from January 2012 to December 2017. Eighty-five primary rectal adenocarcinoma patients treated with CRT followed by curative intent rectal resection with total mesorectal excision who met the following criteria were included in our study: histopathologically confirmed adenocarcinoma, age \(\geq 18\) years old, distal extent of tumor <15 cm above the anal verge, clinical stage of T3/4 or positive lymph nodes. Patients who refused surgery, who had evidence of distant metastasis, who did not receive CRT, who had R2 resection and who had incompleteness of data were excluded (Fig. 1).

2.2. Treatment

All patients received Three-dimension conformal radiotherapy (3D-CRT). The delivered target dose of protocol was 45 Gy to the rectal tumor with a boost of 5.4 Gy limited to the mesorectum. A median radiation dose of 50.4 Gy (range, 46–54 Gy) over a mean duration of 5.6 weeks was given. 3 patients (5.5%) also received an additional boost restricted to the tumor, receiving up to a total of 54 Gy. In majority of patients, concurrent 5-fluorouracil (5-FU)-based therapy was administered either as a bolus infusion 5FU+leucovorin (LV) during the initial 5 weeks of radiotherapy or as a continuous intravenous infusion throughout the

We collected all available baseline clinical characteristics before CRT: age, gender, preoperative biopsy results. Initial tumor stage was assessed before CRT by Computerized Tomography (CT) of chest and whole abdomen, Magnetic Resonance Imaging (MRI) of pelvis. All patients were evaluated with a physical examination, colonoscopy or flexible sigmoidoscopy. Tumor height and length were estimated by rectal examination and endoscopy, and the tumor thickness and tumor length were measured with CT and MRI. CEA levels were determined before, after the completion of CRT and after the operation.

The study was reviewed and approved by ethical committee on human rights related to research involving subjects (ID 08-58-46). The requirement for informed consent was waived because of retrospective study design.

Figure 1. Study flow diagram. pCR= pathological complete response, R2=gross residual disease.
radiotherapy. In few patients, XELOX regimens or Xeloda were used. Evaluation of clinical response was performed using one of these or in combination of digital rectal examination, flexible sigmoidoscopy, CT scan or pelvic MRI which was determined by the multidisciplinary team. After proper waiting time from last dose of radiation, all patients in the study underwent curative intent resection either low anterior resection (LAR), ultraLAR or abdominoperineal resection (APR) with TME by our colorectal surgeons. All available data of clinical and surgical outcomes and complications were collected.

2.3. Pathologic staging

The grade of the tumor was assessed from the initial tumor biopsy and grouped into 1 of 3 categories: high, moderate, poor, and unidentified differentiation. The maximum tumor size measured by the maximum size of viable residual tumor cells in centimeters was documented. pCR was defined as the absence of viable tumor cells in the rectal wall and in any of the resected lymph nodes. The presence of acellular mucin at the previous tumor site or in lymph nodes was not considered as residual viable cancer cells. Patients with microscopic residual disease, defined as only a few clusters of viable malignant residual cells in the specimen (<1 mm), were in non-complete pathological response group. All pathological result of patients was collected and reported according to the eighth edition from the American Joint Committee on Cancer.

2.4. Statistical analyses

Statistical analysis was performed by using STATA (Version 14; Stata Corp LP). Analysis of patient characteristics data were compared between 2 groups (pCR and non-pCR) using the Student’s t test or Mann–Whitney for continuous variables, and Chi-square or Fisher’s exact test for categorical variables. Univariate and multivariate analyses were performed by using the logistic regression model, Odd ratios (OR) and 95% confidence intervals (CI) were calculated to identify predictors for pCR. Disease-free survival (DFS) and overall survival (OS) were estimated using the Kaplan–Meier method and differences between survival curves were determined by using the log-rank test. A P-value <.05 was considered statistically significant.

3. Results

3.1. Clinical, disease and CRT characteristics

A total of 85 patients were included. The mean age was 59 years (range, 24–84 years). Clinical data, disease variables and CRT characteristics are presented in Table 1. For comparing of pCR and non-pCR groups, no statistically difference was found in gender, location of tumor, type of preoperative biopsies, clinical N stage, chemotherapy regimens, waiting time to surgery and CEA level before and after CRT. Our patients were predominantly male (68.9%). pCR groups were significantly older (P=.049). The mean pretreatment tumor length among pCR groups was significantly shorter compared with non-pCR groups (3.8 cm vs 5.4 cm). When using 4 cm of pretreatment tumor length as a cut-point, there was significant difference of pCR rate between pretreatment tumor length ≤4 and >4 cm group (P=.006). Most patient (83.5%) had pretreatment clinical T3 stage. There were 53 patients (62.4%) who had clinical N staging positive from imaging.

Majority of chemotherapy given in both groups was 5-FU+LV regimen (81.2%). The overall mean interval time between radiation and surgery was 67.8 days (range, 27–186 days). pCR group patients had longer waiting time to surgery but this difference did not reach statistically significance. However, in the small subgroup of patients with longer waiting time >11 weeks, 5 from 10 (50%) of them achieved pCR.

3.2. Clinical response, surgical outcomes and complications

Table 2 gives results of clinical response, surgical outcome and postoperative complications. Type of operations and complications were similar between both groups. Nearly half of patients (45.8%) were assessed for clinical response, mainly from the patients treated since the year 2015 to 2017. Response of CRT seen by endoscopy, partial or complete, had significant association with pCR (P=.001). The complete clinical response subgroup had achieved higher rate of pCR (5 from 6 patients, 83.3%) compared to partial clinical response subgroup (2 from 29 patients, 6.9%).

All patients underwent oncologic surgery with TME techniques. Of the 85 cases, 41 (48.2%) underwent LAR, 8 (9.4%) proceeded with ultraLAR and 36 (42.4%) had either APR or LAR with end colostomy. Of the 63 cases who had LAR, 50 (77.7%) of them had anastomosis while 14 (22.3%) of them the anastomoses were abandoned due to poor sphincter function or oncological reason. The overall sphincter-saving surgery rate was 57.6%.

There was no mortality within 30 days after surgery. The overall complications rate was 18.8%. Six (7.1%) patients developed superficial surgical site infection. Three (3.4%) patients had presacral collection which subsequently required percutaneous drainage for resolution. One (1.8%) patient had anastomosis stricture. In 22 patients who had APR, 5 (22.7%) of them had perineal wound infection and 1 patient had postoperative urinary retention.

3.3. Pathological outcome

Pathological data was available for 85 patients (Table 2). Of these, 18 (21.1%) patients achieved pCR. Histologic types of cancer, margin status, N (node) downstaging, number of lymph nodes harvested, lymphovascular invasion and perineural invasion were similar between both groups. Of all patients who had residual tumor, tumor histology mainly was moderately differentiated histology (71.6%).

Overall N downstaging rate was 35.3% which was lower compared to T (tumor) downstaging (70.6%). Total number of lymph nodes harvested was not difference in pCR (11.1 nodes) and non-pCR (14.9) groups (P=.496). Of the pathologic variables, T downstaging and positive lymph nodes status were correlated with pCR.

3.4. Oncological and survival outcome

Table 3 summarizes the oncological outcome. The mean follow-up time was 65 months (IQR 34–79). At the time of survival analysis, 15 patients (17.6%) had died. Two patients died from non-rectal cancer related causes (1 from angiosarcoma of spleen and another from bleeding neurofibromatosis at back). Overall recurrence rate was 30.6%. Most common site of recurrence was...
lung (34.6%). More local recurrence was occurred in non-pCR group (9.1%), but this difference did not reach statistically significance. The calculated 5-year overall survival (OS) and DFS rates were 81.4% and 69.7%, respectively. The Kaplan–Meier method revealed that the number of patients who achieved pCR tend to had higher DFS and OS rates than those who did not, even without statistically significant (\(P=0.355\) and \(P=0.361\), respectively; Figs. 2 and 3).

### 3.5. Predictive factors for pCR

Four clinical predictors of pCR (age, tumor length, clinical response, and nodal status) were selected into the evaluation system. The univariate analysis indicated that Tumor length >4 cm (OR, 0.228; 95%CI, 0.08–0.69; \(P=0.009\)) and positive lymph nodes status (OR, 0.197; 95%CI, 0.04–0.93; \(P=0.04\)) were significantly and negatively associated with pCR. In contrast to tumor length and positive lymph node status, complete clinical response (OR, 16.364; 95% CI, 1.72–155.36; \(P=0.015\)) was significantly correlated with increased pCR (Table 4).

The multivariate analysis revealed that only tumor length >4 cm (OR, 0.134; 95%CI, 0.03–0.59; \(P=0.008\)) was a significant predictor of decreased rate of pCR. Although it did not reach statistical significance, there was a trend for complete clinical response and node negative patients to achieve pCR (Table 5).

### 4. Discussion

This study described clinical, surgical and pathological factors associated with pathological response and oncological outcomes in 85 locally advanced rectal cancer treated with CRT followed by surgery over a 6-year period at the tertiary hospital in

#### Table 1

| Variables | Total (n=85) | Non-pCR (n=67) | pCR (n=18) | \(P\) |
|-----------|-------------|----------------|------------|------|
| Age (year), mean ± SD | 59.3 ± 10.9 | 58.1 ± 11.3 | 63.8 ± 8.4 | .049 |
| Gender, n (%) | | | | |
| Male | 56 (68.9) | 44 (65.7) | 12 (66.7) | .937 |
| Female | 29 (34.1) | 23 (34.3) | 6 (33.3) | |
| Location (cm from anal verge), mean ± SD | 5.6 ± 2.7 | 5.5 ± 2.8 | 5.9 ± 2.4 | .606 |
| Preoperative biopsy, n (%) | | | | |
| Well differentiation | 16 (18.8) | 15 (22.4) | 1 (5.6) | .457 |
| Moderately differentiation | 54 (63.5) | 41 (61.2) | 13 (72.2) | |
| Poorly differentiation | 8 (9.4) | 6 (8.9) | 2 (11.1) | |
| Unknown differentiation | 5 (5.9) | 3 (4.5) | 2 (11.1) | |
| Fragment of dysplastic cell | 1 (1.2) | 1 (1.5) | 0 | |
| Tuberculosis, high grade dysplasia | 1 (1.2) | 1 (1.5) | 0 | |
| Tumor length (cm), mean ± SD | 5.1 ± 2.3 | 5.4 ± 2.4 | 3.8 ± 1.0 | .000 |
| ≤ 3 cm | 14 (16.5) | 8 (11.9) | 6 (33.3) | .066 |
| > 3 cm | 71 (83.5) | 59 (88.1) | 12 (66.7) | |
| ≤ 4 cm | 33 (38.8) | 21 (31.3) | 12 (66.7) | .006 |
| > 4 cm | 52 (61.2) | 46 (68.7) | 6 (33.3) | |
| cT stage, n (%) | | | | |
| Stage 2 | 4 (4.7) | 1 (1.5) | 3 (16.7) | .028 |
| Stage 3 | 71 (83.5) | 57 (85.1) | 14 (77.8) | |
| Stage 4 | 10 (11.8) | 9 (13.4) | 1 (5.6) | |
| cN stage, n (%) | | | | |
| Negative | 32 (37.6) | 24 (35.8) | 8 (44.4) | .503 |
| Positive | 53 (62.4) | 43 (64.2) | 10 (55.6) | |
| Chemo regimens, n (%) | | | | |
| 5FU + LV | 69 (81.2) | 52 (77.6) | 17 (94.4) | .362 |
| Xeloda | 13 (15.3) | 12 (17.9) | 1 (5.6) | |
| XELOX | 3 (3.5) | 3 (4.5) | 0 | |
| Waiting time to surgery (day), mean ± SD | 67.8 ± 23.5 | 63.2 ± 20.6 | 74.1 ± 31.9 | .333 |
| ≤ 8 weeks | 22 (25.9) | 18 (26.9) | 4 (22.2) | .690 |
| > 8 weeks | 63 (74.1) | 49 (73.1) | 14 (77.8) | |
| ≤ 10 weeks | 61 (71.8) | 50 (74.6) | 11 (61.1) | .258 |
| > 10 weeks | 24 (28.2) | 17 (25.4) | 7 (38.9) | |
| ≤ 11 weeks | 70 (82.4) | 57 (85.1) | 13 (72.2) | .293 |
| > 11 weeks | 15 (17.6) | 10 (14.9) | 5 (27.8) | |
| PreCCEA, median (IQR) n = 78 | 7.7 (3.1, 22.3) | 8.5 (3.7, 22.3) | 3.5 (2.6, 22.9) | .250 |
| ≤ 5 ng/dL | 42 (51.0) | 23 (37.1) | 9 (56.3) | .165 |
| > 5 ng/dL | 46 (59.0) | 39 (62.9) | 7 (43.7) | |
| PostCCEA, median (IQR) n = 63 | 3.7 (2.3, 5.4) | 3.8 (2.3, 5.6) | 3.6 (2.6, 5.3) | .865 |
| ≤ 3 ng/dL | 25 (39.7) | 20 (41.7) | 5 (33.3) | .565 |
| > 3 ng/dL | 38 (60.3) | 28 (28.3) | 10 (66.7) | |
| Postoperative CEA, median (IQR) n = 83 | 2.0 (1.2, 3.0) | 2.0 (1.2, 2.8) | 2.2 (1.3, 3.6) | .654 |

cT = clinical tumor, PostCCEA = postchemoradiotherapy CEA, PreCCEA = prechemoradiotherapy CEA.

\(\text{CEA} = \text{clinical lymph node, IQR} = \text{interquartile range, pCR} = \text{pathological complete response}\)
Thailand. The overall pCR rate of 21.1% is comparable with previous studies. Our result demonstrated that tumor length ≥ 4cm was found to be predictive factor with decreased pCR on univariate and multivariate analyses.

Neoadjuvant chemoradiation (CRT) has been the standard of care for patients with locally advanced rectal cancer because it contributes high rate of local control and sphincter preservation which resulted from effect of tumor shrinkage. Patients who had CRT together with good rectal cancer surgery (TME) yield better oncological result by decrease local recurrence and increase DFS and OS. After complete CRT, patients were re-evaluated for possible clinical complete response (cCR), which defined as no gross tumor was seen in physical examination, endoscopy and post-CRT imaging. From flexible sigmoidoscopy, cCR was defined as area of scarring without gross tumor at the rectal mucosa. Patients who achieve cCR can selectively be candidates in watch and wait protocol.

### Table 2
Clinical response, surgical outcomes and pathological results.

| Variables                      | Total (n = 85) | Non-pCR (n = 67) | pCR (n = 18) | P  |
|-------------------------------|----------------|------------------|-------------|----|
| **Clinical Response, n (%)**  |                |                  |             |    |
| No                            | 1 (1.2)        | 1 (1.5)          | 0           |    |
| Not assessed                  | 47 (55.3)      | 36 (53.7)        | 11 (61.1)   |    |
| Partial clinical response     | 31 (36.5)      | 29 (43.3)        | 2 (11.1)    |    |
| Complete clinical response    | 6 (7.0)        | 1 (1.5)          | 5 (27.8)    |    |
| Operation, n (%)              |                |                  |             |    |
| LAR                           | 41 (48.2)      | 32 (47.8)        | 9 (50.0)    | .194 |
| ultraLAR                      | 8 (9.4)        | 4 (5.9)          | 4 (22.2)    |    |
| APR                           | 22 (25.9)      | 19 (28.4)        | 3 (16.7)    |    |
| LAR with end colostomy        | 14 (16.5)      | 12 (17.9)        | 2 (11.1)    |    |
| Complication, n (%)           |                |                  |             |    |
| No                            | 69 (81.2)      | 52 (77.6)        | 17 (94.4)   | .173 |
| Yes                           | 16 (18.8)      | 15 (22.4)        | 1 (5.6)     |    |
| SSI                           | 6 (7.1)        | 6 (9.0)          | 0           |    |
| SSI (perineal)                | 5 (5.9)        | 4 (5.9)          | 1 (5.6)     |    |
| Presacral collection          | 3 (3.4)        | 3 (4.5)          | 0           |    |
| Anastomotic stenosis          | 1 (1.2)        | 1 (1.5)          | 0           |    |
| Urine retention               | 1 (1.2)        | 1 (1.5)          | 0           |    |
| Specimen group, n (%)         |                |                  |             |    |
| Well differentiation          | 7 (8.2)        | 7 (10.5)         | –           |    |
| Moderately differentiation    | 48 (56.5)      | 48 (71.6)        | –           |    |
| Poorly differentiation        | 3 (3.5)        | 3 (4.5)          | –           |    |
| Residual tumor, cannot classify | 8 (9.4)     | 8 (11.9)         | –           |    |
| Mucinous type                 | 1 (1.2)        | 1 (1.5)          | –           |    |
| Distal margin, mean±SD        | 2.9±2.1        | 2.9±2.2          | 2.9±1.5     | .991 |
| **T downstaging, n (%)**      |                |                  |             |    |
| No                            | 25 (29.4)      | 25 (37.3)        | 0           | .002 |
| Yes                           | 60 (70.6)      | 42 (62.7)        | 18 (100)    |    |
| **ypT stage, n (%)**          |                |                  |             |    |
| **Stage 0**                   | 19 (22.4)      | 1 (1.5)          | 18 (100)    | .000 |
| Stage 1                       | 1 (1.2)        | 1 (1.5)          | 0           |    |
| Stage 2                       | 22 (25.9)      | 22 (32.8)        | 0           |    |
| Stage 3                       | 43 (50.6)      | 43 (64.2)        | 0           |    |
| **N downstaging, n (%)**      |                |                  |             |    |
| No                            | 55 (64.7)      | 45 (67.2)        | 10 (55.6)   | .360 |
| Yes                           | 30 (35.3)      | 22 (32.8)        | 8 (44.4)    |    |
| **Nodal status, n (%)**       |                |                  |             |    |
| Negative                      | 57 (67.1)      | 41 (61.2)        | 16 (88.9)   | .026 |
| Positive                      | 28 (32.9)      | 26 (38.8)        | 2 (11.1)    |    |
| 1–3 lymph nodes               | 22 (27.8)      | 20 (29.9)        | 2 (100)     | .999 |
| >3 lymph nodes                | 6 (7.1)        | 6 (9.0)          | 0           |    |
| Number of lymph nodes harvested, mean±SD | 14.1±9.0 | 14.9±9.2 | 11.1±7.9 | .496 |
| **Angiolymphatic invasion, n (%)** n = 68 | | | |
| Absence                       | 49 (72.1)      | 39 (67.2)        | 10 (100)    | .052 |
| Presence                      | 19 (27.9)      | 19 (32.8)        | 0           |    |
| **Perineural invasion, n (%)** n = 68 | | | |
| Absence                       | 55 (80.9)      | 45 (77.6)        | 10 (100)    | .189 |
| Presence                      | 13 (19.1)      | 13 (22.4)        | 0           |    |

APR = abdominoperineal resection, LAR = low anterior resection, N = node, pCR = pathological complete response, SSI = surgical site infection, T = tumor, ultraLAR = ultra low anterior resection, ypT = pathological T stage after neoadjuvant chemoradiaion.
Waiting for the highest degree of tumor downstaging after CRT is of clinical relevance, as this will optimize the chance of an R0 resection and sphincter-saving surgery. Furthermore, after waiting for cCR, some subgroups of patients can also achieve pCR. pCR, defined by no residual tumor cell found in pathological specimens, is a crucial predictive factor associated with favorable oncological outcome, which was previously demonstrated in many studies.[9,23,24] The pCR rate in this study was 21.1%, which was comparable to other studies ranged between 10% and 26%.[9,25]

There are numerous techniques to increase pCR rate. One of the most important predictors previously studied for increase pCR rate is waiting time interval after CRT to surgery. However, the strategy of increased waiting time to increase pCR requires a balance between allowing sufficient time for the maximal effects of CRT to be achieved and not allowing too much time so the tumor can repopulate. Lyon R90–01 trial, published in 1999 was the only randomized controlled trial to examine the time interval to surgery. In this study, a total of 210 patients with rectal cancer were randomized between surgery after a short (<2 weeks) and long (6–8 weeks) interval from the last day of CRT. Their result showed that the longer interval was associated with a significant higher patients group with ypT0–1 in resected specimens, but not pCR.[26] Moore et al reported in 2004 that trend toward increased pCR rates and downstaging with increased waiting time interval. However, sphincter preservation is not increased.[27] Large retrospective cohort study on this topic analyzed waiting time after CRT in 1593 patients; the pCR rate was highest in patients waiting 10 to 11 weeks interval.[28] One meta-analysis in 2013 including 13 trials, 3584 patients concluded that an interval longer than 6 to 8 weeks from the end of neoadjuvant CRT and surgery significantly improved pCR rate compared to shorter interval group around 6% (19.5% vs 13.5%).[29] Recently, a prospective randomized trial (GREC-CAR-6 Trial) reported that waiting interval more than 11 weeks after CRT did not increase pCR rate after surgery.[30] Due to these conflicting results, there was no specific waiting time period recommended in guidelines. The wide range of 8 to 12 weeks was suggested as an appropriate interval time after CRT.[31] In our study waiting time in pCR and non-pCR group was different (74

| Table 3 |
|---|
| Oncological outcomes. |
| Variables | Total (n=85) | Non-pCR (n=67) | pCR (n=18) | P |
| Follow up time (month), median (IQR) | 65 (34, 79) | 61 (31, 78) | 74 (64, 88) | .107 |
| Recurrence, n (%) |  |  |  |  |
| No | 59 (69.4) | 45 (67.2) | 14 (77.8) | .386 |
| Yes | 26 (30.6) | 22 (32.8) | 4 (22.2) | .560 |
| Liver | 5 (19.2) | 5 (22.7) | 0 |  |
| Lung | 9 (34.6) | 6 (27.3) | 3 (75.0) |  |
| Local recurrence | 2 (7.7) | 2 (9.1) | 0 |  |
| > 1 locations | 6 (23.1) | 5 (22.7) | 1 (25.0) |  |
| Unknown | 4 (15.4) | 5 (18.2) | 0 |  |
| Death, n (%) |  |  |  |  |
| No | 70 (82.4) | 54 (80.6) | 16 (88.9) | .509 |
| Yes | 15 (17.6) | 13 (19.4) | 2 (11.1) |  |
| Death from disease | 13 (15.3) | 11 (16.4) | 2 (11.1) |  |
| Death from other causes | 2 (2.4) | 2 (3.0) | 0 |  |

IQR = interquartile range, pCR = pathological complete response.

Figure 2. Five-year disease-free survival in patients with pCR vs those with non-pCR. pCR = pathological complete response.

Figure 3. Overall 5-year survival in patients with pCR vs those with non-pCR. pCR = pathological complete response.
The major advantage of tumor length as a predictor factor for pCR was supported by several studies. Ouyang et al. in 2021 reported that tumor length >4 cm was a significant predictor of pCR, with an odds ratio (OR) of 0.307 (95% confidence interval [CI] 0.09–0.98) for patients with tumor length >4 cm compared to those with tumor length ≤4 cm. Another study showed that tumor length >4 cm was significantly associated with decreased rate of pCR (OR = 0.197, 95% CI 0.04–0.93). These results suggest that tumor length >4 cm may be an early predictor of pCR and high sensitivity to total neoadjuvant therapy.

In our study, we observed that tumor length >4 cm was significantly associated with decreased rate of pCR. The OR for tumor length >4 cm was 0.582 (95% CI 0.39–0.96) compared to tumor length ≤4 cm. This suggests that patients with tumor length >4 cm may require additional treatment to improve pCR rate and oncological outcome.

We acknowledge several limitations of our study. First, the number of patients was relatively small and from a single institution, which could limit generalizability of results. Second, few previous studies reported tumor length as the predictor for pCR. However, these studies did not give the cut-off point of tumor length. The major limitation in our study is the lack of a standardized protocol for re-evaluation after CRT in our institution. Moreover, the overall rate of endoscopic assessment of clinical response during this period was only 16.36%.

The findings of our study suggested that tumor length >4 cm was the only factor significantly associated with decreased rate of pCR on univariate analyses and multivariate analyses whereas others did not. This finding should be explored in future, large scale prospective studies as there may be implications for selection of appropriate treatment in these group of rectal cancer patients with tumor length longer than 4 cm such as longer waiting time or more intense neoadjuvant therapy to improve pCR rate and long-term oncological outcome.
Author contributions

Conceptualization: Weerapat Suwanthanma, Saowanee Kitudomrat, Chakrapan Euanorasetr.

Data curation: Weerapat Suwanthanma, Saowanee Kitudomrat.

Formal analysis: Weerapat Suwanthanma, Saowanee Kitudomrat.

Methodology: Saowanee Kitudomrat, Chakrapan Euanorasetr.

Project administration: Weerapat Suwanthanma, Saowanee Kitudomrat, Chakrapan Euanorasetr.

Resources: Weerapat Suwanthanma.

Supervision: Weerapat Suwanthanma.

Writing – original draft: Weerapat Suwanthanma, Saowanee Kitudomrat, Chakrapan Euanorasetr.

Writing – review & editing: Weerapat Suwanthanma, Saowanee Kitudomrat, Chakrapan Euanorasetr.

References

[1] Krook JE, Moertel CG, Gunderson LL, et al. Effective surgical adjuvant therapy for high risk rectal carcinoma. N Engl J Med 1991;324:709–15.
[2] Fisher B, Wolmark N, Rockette H, et al. Postoperative adjuvant chemotherapy or radiation therapy for rectal cancer: results from NSABP protocol R-01. J Natl Cancer Inst 1988;80:21–9.
[3] Heald RJ, Ryall RD. Recurrence and survival after total mesorectal excision for rectal cancer. Lancet 1986;1:479–82.
[4] MacFarlane JK, Ryall RD, Heald RJ. Mesorectal excision for rectal cancer. Lancet 1993;341:57–60.
[5] Havenaar K, Grossmann I, DeRuiter M, et al. Definition of total mesorectal excision, including the perineal phase: technical considerations. Dig Dis 2007;25:44–50.
[6] Pucciarelli S, Toppan P, Frison ML, et al. Complete pathologic response following preoperative chemoradiation therapy for middle to lower rectal cancer is not a prognostic factor for a better outcome. Dis Colon Rectum 2004;47:1798–807.
[7] Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 2004;351:1731–40.
[8] Wagnan R, Minsky BD, Cohen AM, et al. Sphincter preservation in rectal cancer with preoperative radiation therapy and coloanal anastomosis: long term follow-up. Int J Radiat Oncol Biol Phys 1999;42:51–7.
[9] Mass M, Nelemans PJ, Valentini V, et al. Long-term outcome in patients with a pathologic complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data. Lancet Oncol 2010;11:835–44.
[10] Janjua NA, Khoo VS, Abbruzzese J, et al. Tumor downstaging and sphincter preservation with preoperative chemoradiation in locally advanced rectal cancer: the M.D. Anderson Cancer Center experience. Int J Radiat Oncol Biol Phys 1999;44:1027–38.
[11] Rodel C, Martus P, Papadopoulos T, et al. Prognostic significance of tumor regression after preoperative chemoradiotherapy for rectal cancer. J Clin Oncol 2005;23:8688–96.
[12] Theodoropoulos G, Wise WE, Padmanabhan A, et al. T-level downstaging and complete pathologic response after preoperative chemoradiation for advanced rectal cancer result in decreased recurrence and improved disease-free survival. Dis Colon Rectum 2002;45:895–903.
[13] Garland ML, Vather R, Bunkley N, et al. Clinical tumor size and nodal status predict pathologic complete response following neoadjuvant chemoradiotherapy for rectal cancer. Int J Colorectal Dis 2014;29:301–7.
[14] Cuervo-Semedo L, Lambregts DMK, Maas M, et al. Rectal cancer: assessment of complete response to preoperative combined radiation therapy with chemotherapy—conventional MR volumetry versus diffusion-weighted MR imaging. Radiology 2011;260:734–43.
[15] Gash KJ, Basor O, Kiran RP. Factors associated with degree of tumour response to neo-adjuvant radiotherapy in rectal cancer and subsequent corresponding outcomes. Eur J Surg Oncol 2017;43:2032–9.