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Original Article

Predictive Factors of Pathologic Complete Response after Preoperative Chemoradiation in Rectal Cancer

Thitipong Setthalikhit, MD[*], Chairat Supsamutchai, MD[†], Chumpon Wilasrusmee, MD[†], Tharin Thampongsa, MD[†], Jakrapan Jirasiritham, MD[†], Jirat Teerapradith, MD[†], Pattawia Choikrua, MD[†]

[*]*Department of Surgery, Surin Hospital, Surin, Thailand*
[†]*Division of General Surgery, Department of Surgery Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand*

Abstract

Background: Some rectal cancer patients may present with locally advanced disease requiring preoperative concurrent chemoradiation (CCRT) before radical surgery. But there is uncertainty as to what constitute predictors for pathologic complete response (pCR) after preoperative CCRT.

Objectives: To identify potential predictors of pCR after preoperative CCRT in rectal cancer.

Materials and Methods: A single-center retrospective cohort study of locally advanced rectal cancer patients who underwent preoperative CCRT followed by radical surgery at a tertiary care hospital between 1 January 2011 and 31 December 2017 was performed. Patients were categorized as having pCR or non-pCR. There were two chemotherapy regimens, 5-fluorouracil-based or Oxaliplatin-based regimens, in the present study. The radiotherapy dose to the pelvis was 50.4 Gy.

Result: A total of 145 patients were included; 25 (17%) patients in the pCR group, 120 (83%) in the non-pCR group. On univariable analysis, pretreatment tumor length less than 5 cm seen on computed tomography (CT) scan (p=0.018) and total harvested lymph nodes less than 12 nodes (p=0.02) were significantly associated with pCR, while initial carcinoembryonic antigen concentration of less than 5.0 ng/dL (p=0.078), clinical stage T2 (p=0.151), and circumferential tumor involvement (p=0.209) were marginally significant. On multivariable analysis, only pretreatment tumor length (p=0.0039), and total lymph nodes harvested (p=0.036) were significantly associated with pCR.

Conclusion: Our study showed that the pretreatment tumor length < 5 cm as seen on CT scan and total lymph nodes harvested < 12 are predictors of pCR after preoperative CCRT in patients with rectal cancer.

Keywords: Pathologic complete response, Preoperative chemoradiation, Locally advanced, Rectal cancer, Predictive factors

Introduction

Colorectal cancer is the third most deadly and fourth most commonly diagnosed cancer in the world.[1] In the last decade in Asia, the 5-year overall survival rate has remained at 60%.[2] Approximately 30% of cancers occur in the rectal area and are associated with worse clinical outcomes. A significant number of rectal cancers present with locally-advanced disease and benefit from neoadjuvant therapy prior to surgery.[3-5] The European Society of Medical Oncology (ESMO) recommends neoadjuvant therapy in locally advanced disease, lymph node involvement on imaging and where the adequacy of TME surgery is in question.[6]

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Correspondence address: *Chairat Supsamutchai, MD, Division of General Surgery, Department of Surgery Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand; E-mail: pogeneral2007@hotmail.com*

Pathological stage of tumor (pT-stage), number of pathologic lymph nodes (pN-stage), lymphovascular invasion, histopathologic grade, circumferential tumor margin, and tumor regression grade after preoperative neoadjuvant therapy are associated survival outcomes after treatment.[7-9]

Tumor regression grade is a measure of response of a tumor to preoperative concurrent chemoradiation therapy (CCRT). The regression grade ranges from pathologic complete response (pCR), partial response, stable disease, to disease progression.[10] Maas et al. has performed a meta-analysis of long-term outcomes of patients with pCR after preoperative CCRT for rectal cancer and found that pCR patients have better 5-year disease-free survival than other pathological response grades.[11]

Several studies have reported that pCR after preoperative CCRT is a good predictive factor for disease-free survival and overall survival. Therefore, pCR might be a helpful predictive factor in planning the treatment of patients after CCRT. The objective of this study is to identify factors associated with pCR after preoperative CCRT of rectal cancer in tertiary care center in Thailand.

Materials And Methods

After approval was obtained from the institutional review board, patients who were diagnosed with rectal cancer and received chemoradiation between January 2011 to December 2017 at Ramathibodi hospital, Bangkok were considered for inclusion in the study. All patients were pathologically confirmed to have rectal cancer by tissue biopsy and preoperatively staged with computed tomography (CT) scan or Magnetic Resonance Imaging (MRI). Patients who did not receive neoadjuvant chemoradiation therapy, who were lost in follow-up, had incomplete records, had distant organ metastasis and who did not undergo surgery were excluded as per the study flow diagram. Age, sex, performance status, smoking, initial hemoglobin (Hb) level (g/mL), carcinoembryonic antigen (CEA) level (ng/dL), distance of tumor from the anal verge, diagnostic variables, clinical T staging, preoperative thickness and length as seen on computerized tomography scan (CT scan), organ metastasis before treatment, histology, treatment course, and outcomes after treatment were collected and analyzed. This study was approved by Ramathibodi Research Ethics Committee, and it is registered at ClinicalTrials.gov (NCT04443985). A flow diagram of the study is given in Figure 1.

Total radiation dose, time interval from CCRT to surgery, and chemotherapy were also collected during and after treatment. After preoperative CCRT, all patients were re-evaluated by a multidisciplinary team. Type of operation chosen depended on the preference of the surgeon. Radical rectal surgery was performed using open or laparoscopic techniques with standard total mesorectal excision (TME). Histological examination was done by experienced pathologists. Pathological response to preoperative treatment was classified as pathologic complete response (pCR group) or non-pCR (i.e., partial response, stable disease, and disease progression). Cancer margin was classified as proximal, distal and circumferential. Lymph node status after surgery was defined as the number of positive lymph nodes as well as the total number of lymph nodes harvested.

The data was summarized as mean (standard deviation, SD) or medial (interquartile range, IQR) for quantitative variables, as appropriate. Categorical variables were summarized as counts and percentage. Univariable analysis was performed using logistic regression modeling. A *p*-value of less than 0.05 was considered significant. Multivariable analysis was performed via a multiple logistic regression model with all significant factors from the univariable analysis included. All odds ratios (ORs) were reported along with 95% confidence intervals (95% CI). Data was analyzed using STATA V.14 (Stata Corp, Lakeway Drive, College Station, Texas USA).

Result

We included 145 patients who were treated with preoperative CCRT followed by oncologic rectal surgery in our hospital from January 2011 to December 2017 (figure 1). The mean age of the patients was 60.0 years (SD, 10.7 years). Most patients were male (68%) and had stage III adenocarcinoma with moderate differentiation (79%). The median follow-up time was 36 months, with a maximum follow up of 83 months.

The median of initial CEA level was 3.9 ng/dL (IQR, 2.3 to 9.4 ng/dL). The clinical T-stage was T2 in five patients (4%), T3 and T4 in 140 patients (96%). Almost all patients (97%) received radiotherapy doses greater than 50.4 Gy. The 5-FU-based chemotherapy regimen (5-Fluorouracil plus leucovorin) was the most common used, in 96 patients (66%).

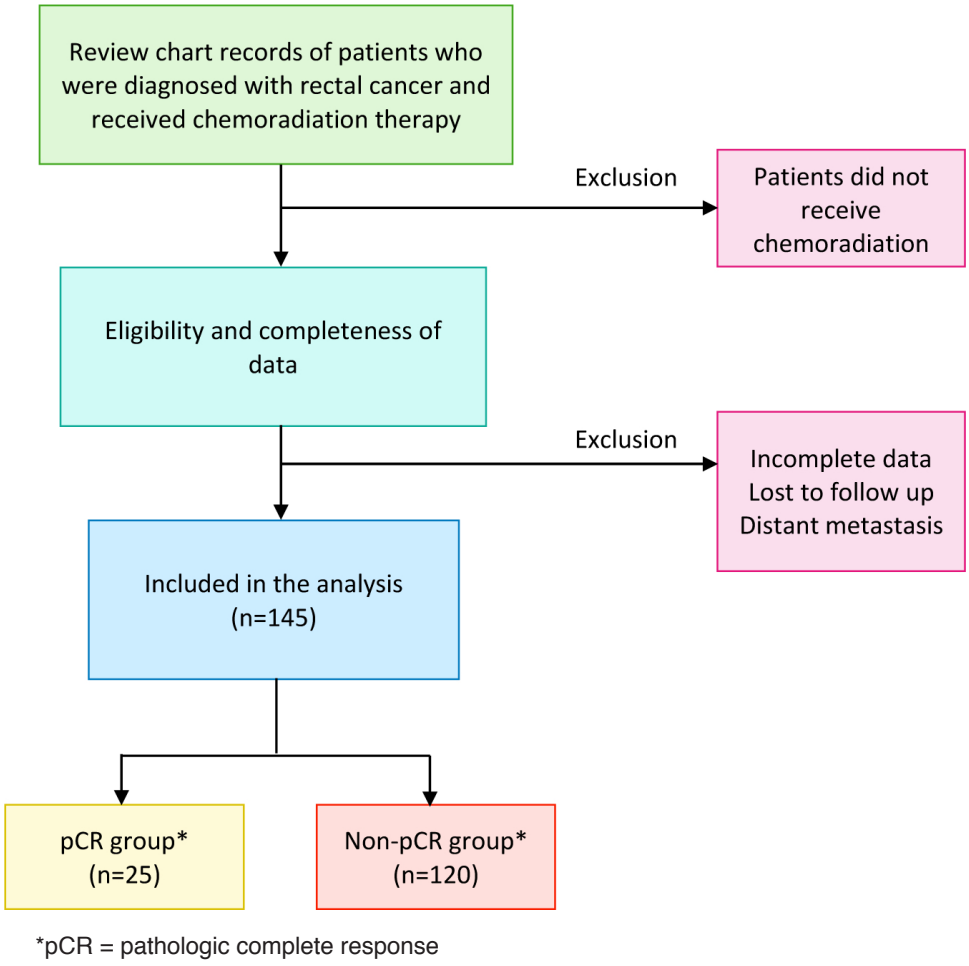

Figure 1 Study flow diagram

The median number of total lymph nodes harvested was 13 (IQR, 9 to 17). The median number of positive lymph nodes was 0 (IQR, 0 to 1). Pathologic complete response was seen in 25 patients (17%). Patient characteristics and treatment received are listed in **Table 1**, and pathological results are given in **Table 2**.

Table 3 shows the univariable analysis of predictive factors of pCR. Initial CEA levels less than 5.0 ng/dL was associated with a higher pCR rate than those of more than 5.0 ng/dL, but this was not statistically significant (21% vs 11%, $p = 0.141$). A preoperative tumor length of less than 5cm seen on CT scan was associated with a higher pCR rate than those of more than 5cm (22% vs 7%, $p = 0.033$), which was statisticall significant. Patients with total LN harvested less than 12 had a higher pCR rate than those with total LN harvested greater than 12 (26% vs 12%, $p = 0.028$), which was also statistically significant. Sex, age, performance status, smoking, initial Hb level, distance of tumor from anal verge, pathologic differentiation, clinical T-stage, preoperative thickness seen on CT scan, distant organ metastasis, chemotherapy regimen, total dose of radiotherapy, interval from CCRT to operation, pathological size, circumferential involvement, were not significantly associated with pCR.

Table 4 shows the result of the multivariable analysis. Pre-operative tumor length less than 5 cm as seen on CT scan (odds ratio (OR), 0.26; 95% confidence interval (CI), 0.07 to 0.93; $p = 0.039$), and total number of LN harvested less than 12 (OR, 0.38; 95% CI, 0.16 to 0.94, $p = 0.036$) was significantly associated with pCR.

Figure 2 shows the Kaplan-Meier survival curves for patients with pCR vs. those with non-pCR, with the latter also categorized as stages I to III. Patients with pCR had a higher survival rate than those with non pCR stage II at 60 months, but this was not statistically significant ($p = 0.210$), while the former patients had a statistically-significant higher survival rate than those with non pCR stage III ($p = 0.048$).

Table 1 Patient characteristics and preoperative treatment received

Characteristics	Number (n=145)
Age (mean ± SD)	60.0 ± 10.7
Age group, n (%)	
≤ 60 years	66 (45)
> 60 years	79 (55)
Sex, n (%)	
Male	98 (68)
Female	47 (32)
Performance status, n (%)	
ECOG 0	93 (64)
ECOG 1	52 (36)
Smoking, n (%)	
No	95 (65)
Yes	50 (35)
Initial Hb level, g/mL (median (IQR)	12.4 (11.0,13.6)
Initial Hb level, n (%)	
< 10 g/ml	18 (12)
≥ 10 g/ml	127 (88)
CEA level, ng/dL (median (IQR)	3.9 (2.3,9.4)
CEA level, n (%)	
≤ 5.0 ng/dL	85 (59)
> 5.0 ng/dL	60 (41)
Distance from anal verge, cm (median (IQR)	5 (4.0,7.5)
Distance from anal verge, n (%)	
Lower (< 4cm)	31 (21)
Middle (4cm-8cm)	90 (62)
Upper (> 8cm)	24 (17)
Differentiation, n (%)	
Well	16 (11)
Moderate	115 (79)
Poor	5 (4)
Mucinous	9 (6)
Group of differentiation, n (%)	
Well and Moderate	131 (90)
Poor and Mucinous	14 (10)
Clinical T stage, n (%)	
T2	5 (4)
T3 and T4	140 (96)
Pre-op thickness from CT, cm (median (IQR)	1.4 (1.0,1.9)
Pre-op thickness from CT, n (%)	
≤ 1 cm	110 (76)
> 1 cm	35 (24)
Pre-op length from CT, cm (median (IQR)	4.9 (3.8,6.1)
Pre-op length from CT, n (%)	
≤ 5 cm	100 (69)
> 5 cm	45 (31)
Chemotherapy regimen, n (%)	
5FU+LV	96 (66)
Oxaliplatin	7 (2)
Xeloda	32 (22)
Other	10 (7)
Total dose of radiotherapy, Gy (median (IQR)	50.4 (50.4,50.4)
Total dose of radiotherapy, n (%)	
< 50.4 Gy	4 (3)
≥ 50.4 Gy	141 (97)
Interval from CCRT to operation, wk (median, IQR)	9.0 (7.9,11.0)
Interval from CCRT to operation, n (%)	
< 7 wk	21 (15)
≥ 7 wk	124 (85)

Table 2 Pathological findings

Pathological Findings	Number (n=145)
Pathological tumor size, cm (median (IQR))	2 (1,3)
Pathological tumor size, n (%)	
≤ 5 cm (includes pCR)	140 (96)
> 5 cm	5 (4)
Circumferential involvement, % (median (IQR))	60 (40,80)
Circumferential involvement, n (%)	
< 100 %	117 (81)
100 %	28 (19)
Proximal margin, n (%)	
Negative	145 (100)
Positive	0
Distal margin, n (%)	
Negative	145 (100)
Positive	0
Circumferential margin, n (%)	
Negative	143 (99)
Positive	2 (1)
Total LN harvested (median (IQR))	13 (9,17)
Total LN harvested, n (%)	
< 12	58 (40)
≥ 12	87 (60)
Positive LN (median (IQR))	0 (0,1)

Table 3 Univariable analysis of predictors of pathologic complete response

Predictors	pCR n=25 n (%)	Non-pCR N=120 n (%)	OR (95% Conf.)	*p*-value
Age group, n (%)				
≤ 60 years	10 (40.0)	56 (46.7)	1	Reference
> 60 years	15 (60.0)	64 (53.3)	1.31	0.543
Sex, n (%)				
Male	16 (64.0)	82 (68.3)	1	Reference
Female	9 (36.0)	38 (31.7)	1.21	0.674
Performance status, n (%)				
ECOG 0	15 (60.0)	78 (65.0)	1	Reference
ECOG 1	10 (40.0)	42 (35.0)	1.23	0.636
Smoking, n (%)				
No	19 (76.0)	76 (63.3)	1	Reference
Yes	6 (24.0)	44 (36.7)	0.54	0.230
Initial Hb level, n (%)				
< 10 g/ml	4 (16.0)	14 (11.7)	1	Reference
≥ 10 g/ml	21 (84.0)	106 (88.3)	0.69	0.552
CEA level, n (%)				
≤ 5.0 ng/dL	18 (72.0)	67 (55.8)	1	Reference
> 5.0 ng/dL	7 (28.0)	53 (44.2)	0.49	0.141
Distance from anal verge, n (%)				
Lower (< 4cm)	5 (20.0)	26 (21.7)	1	Reference
Middle (4cm-8cm)	16 (64.0)	74 (61.7)	1.12	0.834
Upper (> 8cm)	4 (16.0)	20 (16.6)	1.04	0.957
Differentiation, n (%)				
Well	4 (16.0)	12 (10.0)	1	Reference
Moderate	20 (80.0)	95 (79.2)	0.63	0.464
Poor	1 (4.0)	4 (3.3)	0.74	0.819
Mucinous	0 (0.0)	9 (7.5)	-	-
Group of differentiation, n (%)				
Well and Moderate	24 (96.0)	107 (89.2)	1	Reference
Poor and Mucinous	1 (4.0)	13 (10.8)	0.34	0.314
Clinical T staging, n (%)				
T2	2 (8.0)	3 (2.5)	1	Reference
T3 and T4	23 (92.0)	117 (97.5)	0.29	0.194
Pre-op thickness from CT, n (%)				
≤ 1 cm	21 (84.0)	89 (74.2)	1	Reference
> 1 cm	4 (16.0)	31 (25.8)	0.54	0.301
Pre-op length on CT, n (%)				
≤ 5 cm	22 (88.0)	78 (65.0)	1	Reference
> 5 cm	3 (12.0)	42 (35.0)	0.25	**0.033**
Chemotherapy regimen, n (%)				
5FU+LV	16 (64.0)	80 (66.7)	1	Reference
Oxaliplatin	1 (4.0)	6 (5.0)	0.83	0.870
Xeloda	4 (16.0)	28 (23.3)	0.71	0.575
Other	4 (16.0)	6 (5.0)	3.33	0.086
Total dose of radiotherapy, n (%)				
< 50.4 Gy	1 (4.0)	3 (2.5)	1	Reference

Table 3 Univariable analysis of predictors of pathologic complete response

Predictors	pCR n=25 n (%)	Non-pCR N=120 n (%)	OR (95% Conf.)	*p*-value
≥ 50.4 Gy	24 (96.0)	117 (97.5)	0.61	0.680
Interval from CCRT to operation, n (%)				
< 7 wk	3 (12.0)	18 (15.0)	1	Reference
≥ 7 wk	22 (88.0)	102 (85.0)	1.29	0.699
Pathological findings				
Pathological tumor size, n (%)				
≤ 5 cm (includes pCR)	25 (100.0)	115 (95.8)	-	-
> 5 cm	0 (0.0)	5 (4.2)		
Circumferential involvement, n (%)				
< 100 %	22 (88.0)	95 (79.2)	1	Reference
100 %	3 (12.0)	25 (20.8)	0.51	0.316
Proximal margin, n (%)				
Negative	25 (100.0)	120 (100.0)	-	-
Positive	0 (0.0)	0 (0.0)		
Distal margin, n (%)				
Negative	25 (100.0)	120 (100.0)	-	-
Positive	0 (0.0)	0 (0.0)		
Circumferential margin, n (%)				
Negative	25 (100.0)	118 (98.3)	-	-
Positive	0 (0.0)	2 (1.7)		
Total LN harvested, n (%)				
< 12	15 (60.0)	43 (35.8)	1	Reference
≥ 12	10 (40.0)	77 (64.2)	0.37	**0.028**

Table 4 Multivariable analysis of predictors of pathologic complete response

Predictors	Odds Ratio	95% CI	*p*-value
Pre-op length on CT < 5 cm	0.26	0.07 to 0.93	**0.039**
Total LNs harvested < 12	0.38	0.16 to 0.94	**0.036**

Discussion

Preoperative CCRT plays a major role in rectal cancer treatment, especially for locally advanced rectal cancer. CCRT can reduce tumor size, increase the tumor resection rate, and enable anus preservation. In addition, preoperative chemoradiotherapy may reduce the local recurrence rate.

CCRT may induce tumor regression resulting in pathologic complete response (pCR) in some patients. Previous studies reported pCR rates between 11% to 22%.[12-16] The present study found a pCR rate of 17% (25 of 145 patients). Pathologic complete response may be as important as TNM stage as a prognostic indicator for patient outcome after preoperative CCRT.[11] Predictors of pCR identified by previous studies included low levels of serum carcinoembrogenic antigen (CEA)[15,17-18], longer interval time after chemoradiation[12], serum albumin level[19] and certain gene expressions.[20-21]

Low serum CEA may not only predict pCR but is also a prognostic factor for oncologic outcomes. Park et al.[22] stated that preoperative CEA levels less than 5 ng/mL was a useful prognostic indicator of lower risk of systemic recurrence and higher survival in Stage III rectal cancer patients. Wu et al.[23] also demonstrated that

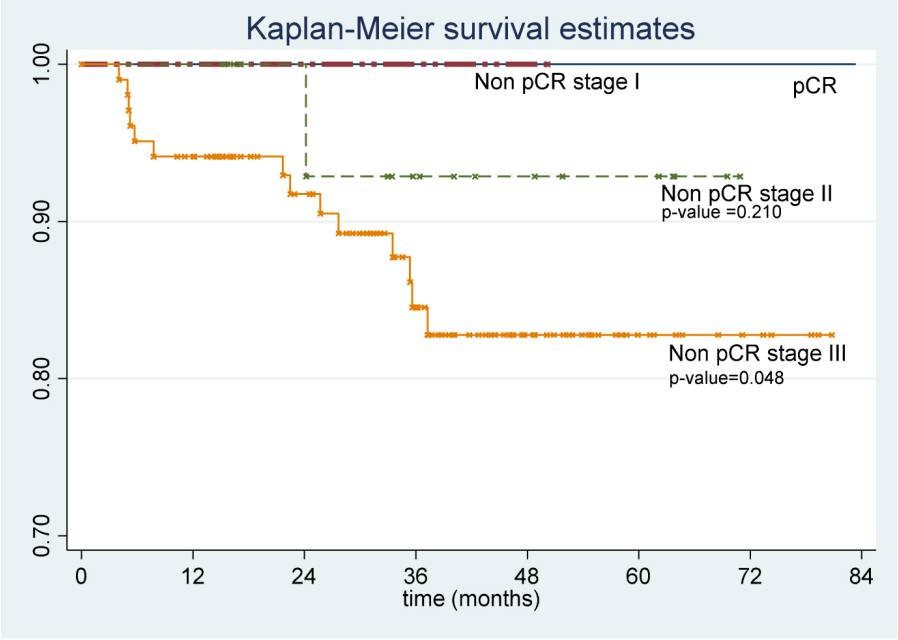

Figure 2 Kaplan-Meier survival curves for patients with and without pCR

local recurrence of rectal cancer had a significant correlation with high CEA levels. The monitoring of serum CEA is used to predict or detect the recurrence of rectal cancer.[24-26]

Other studies, e.g., that of Das et al.,[17] reported that a pretreatment CEA concentration of less than 2.5 ng/dL was significantly associated with pCR. Huh et al.[15] reported that the pretreatment CEA concentration (< 5 ng/mL vs. ≥ 5 ng/mL; OR, 2.66; 95% CI, 1.38 to 5.12; $p = 0.010$) was a significant predictor in their multivariable analysis. Furthermore, Restivo et al.[18] reported that lower pretreatment CEA concentrations ($p < 0.001$) and better differentiation ($p = 0.010$) were statistically significant in univariate analysis, and CEA < 5.0 ng/dL was independently associated with pCR in a multivariable analysis (OR, 9.32; 95% CI, 2.16 to 40.19; $p = 0.030$). However, in our study a pretreatment CEA concentration of less than 5 ng/dL was not associated with pCR.

The interval between completion of CCRT and surgery was reported to be a predictive factor of pCR in many studies. Choi et al.[12] stated such an an interval to be longer than 7 weeks, a result similar to that of Wolthuis et al.[27] There appears to be an association between intervals longer than 7 weeks after neoadjuvant chemoradiotherapy and pCR. A recent report in 2020 from Lichthardt et al.[28] found that a prolonged time interval of 8 weeks or more in patients with locally-advanced rectal cancer seems to be related to higher rates of pCR.

In the present study, patients with time interval from CCRT to operation of longer than 7 weeks had a slightly higher pCR rate when compared with others (18% vs 14%). However, this difference was not statistically significant ($p = 0.699$).

In the present study, we found that the pCR rate was higher in patients with pretreatment tumor length of less than 5 cm as seen on CT scan, and also higher when total lymph nodes harvested was fewer than 12. This result is similar to that of Garland et al.,[29] where smaller tumor size was also correlated with pCR. In a recent study from Brazil, Bustamante-Lopez et al.,[30] also reported that pCR was associated with less than 12 lymph nodes harvested, because chemoradiation caused the primary tumor and pathologic lymph nodes to regress. Thus, in these cases there is less chance for lymph nodes to be harvested when compared with patients without pCR or without neoadjuvant chemoradiation.

Other factors, such as circumferential involvement, macroscopic ulceration, and the distance from the anal verge to the tumor, have also been shown to be associated with pCR.[17,19-21,31] But these factors were not found to be significant in the present study, possibly due to the small sample size.

Limitations of the present study included a retrospective design, a single institution experience and

a small sample size. In the future, we hope that larger prospective studies will be conducted to confirm our results.

Conclusion

Pretreatment tumor length of less than 5 cm as seen on CT scan, and total lymph nodes harvested during surgery are predictors of pCR after preoperative CCRT in patients with rectal cancer. Clinical T stage, circumferential mass < 100%, tumor size, tumor location, tumor differentiation, and chemotherapy regimen were not associated with pCR in the present study.

Conflict Of Interest

No potential conflict of interest relevant to this article was reported.

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