Original Article

Predictive Factors for Complete Response Following Neoadjuvant Chemoradiotherapy for Rectal Cancer

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Key Words
Rectal cancer;
Pathological complete response;
Neoadjuvant chemoradiotherapy;
CEA;
NLR

Purpose. Accurate assessment of the potential pathological complete response following neoadjuvant concurrent chemoradiotherapy is important for the appropriate treatment of rectal cancer. However, the factors that predict response to neoadjuvant chemoradiotherapy are poorly defined. Therefore, this study aimed to analyze the predictive factors for developing pathological complete response after neoadjuvant chemoradiation for rectal cancer.

Methods. We reviewed 86 consecutive patients from January 2015 to December 2021, who underwent long-course neoadjuvant chemoradiotherapy at a single institution. Clinicopathological features were analyzed to identify predictive factors for pathological complete response in rectal cancer after neoadjuvant chemoradiation.

Results. The pathological complete response rate in rectal cancer after neoadjuvant chemoradiation was 15.1%. The patients were divided into pathological response and non-response groups. The two groups were evaluated for gender, age, tumor stage, tumor differentiation, tumor location, carcinoembryonic antigen level and neutrophil-lymphocyte ratio. We found that clinical stage, tumor size, pre-concurrent chemoradiotherapy neutrophil-lymphocyte ratio, and post-operative carcinoembryonic antigen level were trended significant associated with pathological complete response; however, after univariable evaluation, none of the clinicopathological factors predicted pathological complete response to neoadjuvant concurrent chemoradiotherapy for rectal cancer significantly.

Conclusions. We did not identify any clinicopathological factors that could predict pathological complete response after neoadjuvant concurrent chemoradiotherapy for rectal cancer. The clinical stage, tumor size, pre-concurrent chemoradiotherapy neutrophil-lymphocyte ratio, and post-op carcinoembryonic antigen levels were slightly associated with pathological complete response. The small sample size is a limitation of this study. Additional investigations are needed to identify the prognostic and predictive clinicopathological factors and biomarkers in these patients.

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Colorectal cancer (CRC) is the third commonest malignancy and the second leading cause of cancer-related deaths worldwide.[1] Rectal cancer accounts for 30-35% of CRC cases, and approximately 50% of

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rectal cancers are diagnosed at a locally advanced stage.[2] Advancements in the treatment of neoadjuvant concurrent chemoradiotherapy (CCRT),[3] followed by total mesorectal excision (TME), have improved outcomes significantly in recent decades. After neoadjuvant CCRT, approximately 10-30% of patients achieve a complete pathological response. Patients achieving pathological complete response (pCR) after neoadjuvant CCRT have a lower incidence of recurrence and more favorable long-term survival than those without pCR.[4,5] Therefore, the ability to predict the efficacy of neoadjuvant CCRT in patients with rectal cancer has clinical significance. Multiple predictive factors for pCR exist, including tumor size, nodal stage, pretreatment carcinoembryonic antigen (CEA) level, and tumor distance from the anal verge. Recent studies have shown that inflammation is closely associated with tumorigenesis, with a high neutrophil-to-lymphocyte ratio (NLR), increased neutrophil levels and decreased lymphocyte levels indicating poor prognostic factors in colorectal cancer.[6,7] This retrospective study aimed to evaluate the clinical factors, including NLR, that can predict pCR to neoadjuvant CCRT in rectal cancer.

Methods

Patients

The data for this study were collected from the Cancer Registry Dataset of the Veteran General Kaohsiung Medical Center between January 1, 2015 and December 31, 2021. The electronic medical records and cancer registry datasets were retrospectively reviewed. All patients were regularly monitored after diagnosis until death or the last follow up. We identified 86 patients with rectal cancer who underwent neoadjuvant CCRT followed by TME in accordance with National Comprehensive Cancer Network (NCCN) guidelines in this study: histopathologically confirmed adenocarcinoma, age ≥ 18 years, distal extent of tumor < 15 cm above the anal verge, clinical stage of T3/4 or positive lymph nodes. The exclusion criteria were: previous cancer history, age < 18 years, clinical stage I or IV, incomplete patient data, and palliative care. All patients received long-course radiation therapy at dose of 45-50 Gray (Gy) in 25-28 fractions to the pelvis according to the NCCN recommendation. All patients received pre-operative chemotherapy in 6 courses of oral 5-FU/leucovorin, or intravenous FOLFOX regimens. Our Cancer Registry Dataset provided the following clinical pathological characteristics: age, gender, clinical stage, pathological stage, habit (smoking/betal nuts/drinking), tumor distance from the anal verge, pre CCRT CEA level, pre CCRT NLR, post CCRT CEA level, and post-operative CEA level. The pathological response was evaluated using one of these or combined with digital rectal examination, flexible sigmoidoscopy, computed tomography scan or pelvic magnetic resonance imaging, determined by a multidisciplinary team. Tumor regression grade (TRG) was determined using a standard 5-point scale as initially described by Dworak et al.,[8] with grades 3 and 4 counts as responses and grades 0 to 2 counts as non-responses. The NLR was determined by dividing the neutrophil count by the total lymphocyte count. The NLR values were determined based on the complete blood count obtained within 2 weeks of neoadjuvant CCRT. Patients with acute infections were excluded.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows (version 22.0; IBM Corp., Armonk, NY). Student's t-test for continuous variables and chi-square test (Fisher's exact test) for categorical variables were performed. Logistic regression was used to identify the predictors of tumor pathological response. Statistical significance was set at 0.05.

Results

We divided 86 patients, 13 and 73 patients into the response and non-response groups, respectively. The mean age of the patients was 63 years old (range: 42-83 years). There were predominantly male (72.1%) and female (27.9%) patients. Most patients had clinicopathological features, including moderated differ-

entiated tumor (91.9%), pretreatment clinical T3 stage (86%), pretreatment clinical stage III (84.9%), lymph nodes invasion (73.3%), tumor located over 5-9 cm above anal verge (59.3%), oral chemotherapy regimen UFUR + Folina (95.3%), MMR no loss tissue (96.5%), pre-CCRT, post CCRT, post-op CEA level < 5 ng/dL and pre-CCRT NLR < 3.5 were dominant (61.6%, 73.3%, 80.2%, 69.8%). Clinical N stage 0, 1, 2 (27.9% vs. 38.3% vs. 33.8%) and numbers of harvested lymph nodes < 14 or ≥ 14 (47.7% vs. 52.3%) were well balanced. The pCR rate in patients with rectal cancer after neoadjuvant chemoradiation was 15.1%. No differences were observed in gender, age, differentiation, clinical stage, tumor size, number of lymph nodes harvested, lymph node invasion, tumor location, mismatch repair protein expression, pre-CCRT CEA level, pre-CCRT NLR, post-CCRT CEA level or post-OP CEA level (Table 1).

In our study, clinical stage II and III ($p = 0.062$), pre-CCRT NLR between < 3.5 and ≥ 3.5 ($p = 0.073$), and post-op CEA level between < 5 and ≥ 5 ng/dL ($p = 0.061$) showed nearly significant difference. The pathological response groups have shorter mean pretreatment tumor length than the non-response groups (3.2 cm vs. 5.3 cm). When using 4 cm of pretreatment tumor length as a cut-point, there was a significant difference in pathological response rate between the pretreatment tumor length ≤ 4 and > 4 cm group ($p = 0.030$).

Six predictors of pathological response (clinical stage, tumor size, pre-CCRT CEA level, pre-CCRT NLR, post-CCRT CEA level, and post-OP CEA level) were selected for the evaluation. After logistic regression univariate analysis, no predictive factors were significance for pathological response (Table 2). Only post-operative CEA levels showed a nearly significant difference (OR, 0.153; 95% CI, 0.056～-1.235; $p = 0.072$).

Discussion

Neoadjuvant CCRT followed by TME, is the standard treatment for clinical stage II and III rectal cancer. Neoadjuvant CCRT can result in tumor regression, T- or N-downstaging, and improved local control. However, factors that predict patient response to neoadjuvant CCRT for rectal cancer have been poorly defined. Some studies have evaluated different clinical factors associated with complete response to preoperative CCRT for rectal cancer. Das et al., (2007a) identified circumferential tumor extent as the only factor significantly associated with pCR in a retrospective review of 562 patients.[9] Armstrong et al., (2015) found that lower pre-CCRT CEA levels and proximity to the anal verge were predictors of pCR after evaluating the clinical factors of 885 patients.[10] Setthalikhit et al., (2021) showed that a pre-CCRT tumor length of less than 5 cm, as seen on CT scan, and total lymph nodes harvested fewer than 12 during surgery were predictors of pCR in a retrospective review of 145 patients.[11] Our study evaluated multiple clinicopathological factors and biomarkers; however, none were significantly associated with the pathological response.

TNM system and clinical stage are closely associated with the prognosis of CRC. Some previous studies have assessed clinical stage as predictor for tumor response to neoadjuvant CCRT.[12,13] Our study showed that nearly significant difference between clinical stage II and III ($p = 0.062$), but no significant difference (OR = 0.81, 95% CI = 0.178-3.73, $p = 0.95$) in logistic regression univariable analysis. To the best of our knowledge, lower clinical stages are associated with better pathological response. The vary result may be due to most of our patients were used computed tomography scan alone, rather than combined with pelvic magnetic resonance imaging for clinical staging. Therefore, preoperative clinical diagnosis is less accurate than postoperative pathological diagnosis. Further studies should be conducted to confirm the authentic values of clinical stage as indicators of pCR.

The group of tumor length ≤ 4 and > 4 cm showed significant difference for pCR in chi-square test analysis ($p = 0.030$) but no significant difference in further logistic regression univariate analysis (OR = 0.262, 95% CI = 0.032-0.61, $p = 0.122$). By obtaining tumor length as preditctive factor for pCR in preoperative period, it gives the advantage to surgeons for making preoperative decision before treatment. For

Table 1. Clinical characteristics (n = 86)

Variables	Total (n = 86) (%)	Response (n = 13) (%)	Non-response (n = 73) (%)	*p*-value
Gender				0.673
Male	62 (72.1%)	10 (76.9%)	52 (71.2%)	
Female	24 (27.9%)	3 (23.1%)	21 (28.8%)	
Age	62.45 ± 10.581	64.62 ± 10.634	62.07 ± 10.528	0.953
Differentiation				0.124
Well	3 (3.5%)	2 (15.4%)	1 (1.4%)	
Moderate	79 (91.9%)	9 (69.2%)	70 (95.8%)	
Poor	4 (4.6%)	2 (15.4%)	2 (2.8%)	
Clinical T				0.375
2	5 (5.8%)	4 (30.8%)	1 (1.4%)	
3	74 (86%)	8 (61.5%)	66 (90.4%)	
4	7 (8.2%)	1 (7.7%)	6 (8.2%)	
Clinical N				0.835
0	24 (27.9%)	3 (23.1%)	21 (28.8%)	
1	33 (38.3%)	6 (46.1%)	27 (37%)	
2	29 (33.8%)	4 (30.8%)	25 (34.2%)	
Clinical stage				0.062
II	24 (27.9%)	3 (23.1%)	21 (28.8%)	
III	62 (72.1%)	10 (76.9%)	52 (71.2%)	
Tumor size				0.030
< 4 cm	36 (41.9%)	9 (69.2%)	27 (37%)	
≥ 4 cm	50 (58.1%)	4 (30.8%)	46 (63%)	
LN harvest number				0.629
< 14	41 (47.7%)	7 (53.9%)	34 (46.6%)	
≥ 14	45 (52.3%)	6 (46.1%)	39 (53.4%)	
LN invasion				0.746
No	63 (73.3%)	10 (76.9%)	53 (72.6%)	
Yes	23 (26.7%)	3 (23.1%)	20 (27.4%)	
Dist_AAV				0.546
< 5	18 (20.9%)	1 (7.7%)	17 (23.3%)	
5-9	51 (59.3%)	9 (69.2%)	42 (57.5%)	
10-15	17 (19.8%)	3 (23.1%)	14 (19.2%)	
Regimen				0.387
UFUR + Folina	82 (95.3%)	13 (100%)	69 (94.5%)	
FOLFOX	4 (4.7%)	0 (0%)	4 (5.5%)	
MMR				0.805
No loss	83 (96.5%)	13 (100%)	70 (95.8%)	
MSI low	2 (2.3%)	0 (0%)	2 (2.8%)	
MSI high	1 (1.2%)	0 (0%)	1 (1.4%)	
CEA_preCCRT				0.108
≥ 5 ng/dL	33 (38.4%)	2 (15.4%)	31 (42.5%)	
< 5 ng/dL	53 (61.6%)	11 (84.6%)	42 (57.5%)	
NLR_preCCRT				0.073
< 3.5	60 (69.8%)	10 (76.9%)	50 (68.5%)	
≥ 3.5	26 (30.2%)	3 (23.1%)	23 (31.5%)	
CEA_postCCRT				0.341
≥ 5 ng/dL	23 (26.7%)	2 (15.4%)	21 (28.8%)	
< 5 ng/dL	63 (73.3%)	11 (84.6%)	52 (71.2%)	
CEA_postOP				0.061
≥ 5 ng/dL	17 (19.8%)	2 (15.4%)	15 (20.5%)	
< 5 ng/dL	69 (80.2%)	11 (84.6%)	58 (79.5%)	

LN= lymph node, Dis_AAV = tumor distance above anal verge, MMR = mismatch repair protein, MSI = microsatellite instability, preCCRT = neoadjuvant CCRT, NLR = N/L ratio.

Table 2. Univariate analyses on predicting factors for pathological response

Variables	Univariate analyses			
	Response (n = 13) (%)	Non-response (n = 73) (%)	OR (95% CI)	*p*-value
Clinical stage			0.81 (0.178~3.73)	0.95
II	3 (23.1%)	21 (28.8%)		
III	10 (76.9%)	52 (71.2%)		
Tumor size			0.262 (0.032~0.61)	0.122
< 4 cm	9 (69.2%)	27 (37%)		
≥ 4 cm	4 (30.8%)	46 (63%)		
CEA_preCCRT			0.812 (1.61~-2.049)	0.207
≥ 5	2 (15.4%)	31 (42.5%)		
< 5	11 (84.6%)	42 (57.5%)		
NLR_preCCRT			0.901 (0.691~-2.90)	0.233
< 3.5	10 (76.9%)	50 (68.5%)		
≥ 3.5	3 (23.1%)	23 (31.5%)		
CEA_postCCRT			0.418 (0.179~-2.81)	0.374
≥ 5	2 (15.4%)	21 (28.8%)		
< 5	11 (84.6%)	52 (71.2%)		
CEA_postOP			0.153 (0.056~-1.235)	0.072
≥ 5	2 (15.4%)	15 (20.5%)		
< 5	11 (84.6%)	58 (79.5%)		

preCCRT = neoadjuvant CCRT, NLR = N/L ratio.

locally advanced rectal cancer, intravenous FOLFOX is not standard regimen in neoadjuvant CCRT. Thus, for patients who had preoperative tumor length > 4 cm may require additional treatment in order to improve pCR rate and oncological outcome.

CEA is a tumor-associated antigen, with important clinical value in predicting the tumor response to surgery and as a prognostic marker for tumor regression or recurrence. Some studies have found that CEA levels are associated with response to CCRT. Yeo et al., (2013) showed that the CEA level before treatment was an important predictive factor for pCR in a cohort of 609 patients who received preoperative chemoradiotherapy.[14] Garland et al., (2014c) found that pretreatment serum CEA levels and decreased pre- to post-treatment serum CEA levels were independent risk factors for pCR.[15] In addition, several studies have reported different pre-CCRT CEA cut-off values for predicting pCR to neoadjuvant CCRT. According to Das et al., a pre-CCRT CEA level > 2.5 ng/mL is associated with a lower tumor downstaging rate, whereas the cut-off for predicting complete pathological response has been estimated to be 5, 5, 6, and 10 ng/mL, respectively in studies by Zeng et al., Wang et al., Yang et al., and Takagawa et al.[16-19]

Herein, the pre-CCRT, post-CCRT, and port-op CEA level cut-offs were set at a normal value of 5 ng/mL and showed no significant association with pCR. CEA levels may be affected by cigarette smoking, biliary disease, or metabolic syndrome. Low sensitivity of CEA levels in predicting response to CCRT might be due to other factors, such as tumor grade, location, stage, and patient characteristics, influencing the response to CCRT.

Recent studies have suggested that immune cells, such as neutrophils, have a pro-tumor effect on the tumor microenvironment and can influence the environment throughout the stages of tumor progression. The secreted cytokines and chemokines mediate inflammatory cell recruitment, tumor growth, angiogenesis and adaptive immune response suppression.[20] In comparison, lymphocytic infiltration, predominantly by CD4+ or CD8+ T cells, in the primary tumor is recognized as an anti-tumor immune response, and prominent infiltration is associated with improved survival in CRC.[21,22] Thus, NLR, the ratio of neutrophils to lymphocytes, reflects the balance between pro- and anti-tumor immune activities. We hypothesized that host immune status, as

determined by NLR, could predict tumor response after preoperative neoadjuvant CCRT in rectal cancer.

Dudani et al., (2019) showed that NLR was not an independent predictor of pCR in patients who received pre-CCRT for rectal cancer.[23] Ke et al., (2020) identified the pre-CCRT NLR as an independent prognostic factor for patients with rectal cancer that could be used as a potential biomarker to identify high-risk patients for more intense treatment and care.[24] Chun-Ming Huang et al., (2021) demonstrate that high NLR (≥ 3.2) was a promising predictor of reduced OS and DFS in patients with rectal cancer who achieved a pCR to neoadjuvant CCRT.[25] In our study, the NLR was not significantly associated with pCR significantly. Although, NLR can be obtained simply from routine blood tests, no consensus exists regarding the NLR cut-off value. A cut-off value of 3 or 5 for NLR as a continuous variable has been studied in rectal cancer. In addition, studies have suggested that the NLR is closely related to cardiovascular or cerebrovascular disease.[26,27]

Limitations

The limitations of our study include the small sample size, single institute design, and retrospective design, which introduce the potential for unmeasured bias. Another limitation of our study is that the NLR is a marker of systemic inflammation and is easily influenced by certain circumstances, such as nutritional status, inflammatory diseases, metabolic diseases, and the administration of anti-inflammatory medicine.

Conclusion

We did not identified any clinical factors that could predict pCR after neoadjuvant CCRT for rectal cancer. Additional investigations are needed to identify the prognostic and predictive clinical factors or biomarkers for these patients.

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Conflicts of Interest

The authors have no conflicts of interest to disclose.

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原　著

直腸癌術前同步放化療後病理完全緩解反應的預測因素

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背景　為了準確評估直腸癌術前同步放化療後病理完全緩解的反應，對於直腸癌的後續治療非常重要。然而預測因素尚未明確。因此，本研究分析了直腸癌術前同步放化療後病理完全緩解反應的預測因素。

方法　我們從 2015 年 1 月至 2021 年 12 月審查 86 例來自同一機構接受直腸癌術前同步放化療的患者。我們分析了臨床病理學特徵，以確認直腸癌術前同步放化療後病理完全緩解反應的預測因素。

結果　直腸癌術前同步放化療後病理完全緩解率為 15.1%，患者分為病理緩解有反應組和無反應組。兩組在性別、年齡、腫瘤分期、腫瘤分化程度、腫瘤部位、癌胚胎抗原指數和嗜中性球淋巴球比值方面進行評估。我們的研究顯示，腫瘤臨床分期、腫瘤大小、術前同步放化療嗜中性球淋巴球比值和術後癌胚胎抗原指數有病理完全緩解的趨勢，但更進一步研究後發現沒有任何因素對預測直腸癌術前同步放化療後病理完全緩解具有顯著影響。

結論　我們沒有發現任何臨床病理因素可以預測直腸癌術前同步放化療後可否達到病理完全緩解。腫瘤臨床分期、腫瘤大小、術前同步放化療、嗜中性球淋巴球比值和術後癌胚胎抗原指數有些微預測病理完全緩解的趨勢。我們的研究可能樣本數太小。需要進行額外的研究來確定這些患者的預後狀況、預測性臨床病理因素或生物標誌物。

關鍵詞　直腸癌、病理完全緩解反應、癌胚胎抗原指數、嗜中性球淋巴球比值。