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Clinical predictive factors associated with pathologic complete response in locally advanced rectal cancer

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ABSTRACT

Objective: In this study, our aim was to identify the main predictive factors associated with pathologic complete response (pCR) to neoadjuvantchemoradiotherapy (nCRT) in patients with locally advanced rectal cancer.
Methods: The patients who had locally advanced rectal cancer and underwent a long-course nCRT, followed by curative surgery between January 2009 and December 2015 at two-center were included. The clinical factors associated with pCR or non-pCR were analyzed by Logistic regression.
Results: Two hundred and three patients were included in this study. Forty-six patients (22.7%) had pCR and 157 patients (77.3%) had non-pCR. In the univariate analysis, no smoking history, clinically negative lymp node (cN-), well-differentiated tumor, tumor size of ≤5 cm, pre-nCRT CEA level of ≤5 (ng/mL) and median interval to surgery>8 week were associated with an increased rate of pCR. No smoking history [odds ratio (OR) = 3.382, P = .008], endoscopic tumor size of ≤5 [OR = 2.608, P = .03], cN- [OR = 3.800, P = *.002*], well-differentiated tumor [OR = 3.566, P = *.002*], median interval to surgery of >8 week [OR = 2.981, P = .014], and pre-nCRT CEA level of ≤5 (ng/mL) [OR = 3.067, P = .008] were determined to be independent predictive factors of pCR with logistic regression model analysis.
Conclusion: No smoking history, cN-, tumor size of ≤5 cm, well-differentiated tumor, pre-nCRT CEA level of ≤5 (ng/mL) and median interval to surgery of >8 weeks were independent clinical predictors for pCR in rectal cancer patients treated with long course of nCRT. This factors may help clinicians predict the prognosis of patients and develop proper treatment approach.

1. Introduction

Today, neoadjuvant chemoradiotherapy (nCRT) has become the standard option in the therapy of patients with locally advanced rectal cancer. nCRT also has higher rates of sphincter sparing surgery with lower local recurrence incidents.[1–4] The results regarding surgery and prognosis varies depend on the response to nCRT. Meta-analyses reported better prolonged clinical outcomes in patients with pathological complete response (pCR) after nCRT, in comparison with the patients without pathologic complete response (non-pCR).[5]

In patients with rectal cancer, it is known that up to 15–20% of pCR is obtained after neoadjuvant chemoradiotherapy, however some patients only respond partially or some develop resistance to chemoradiotherapy.[6] Therefore in some cases, chemoradiotherapy is performed for the patients who will not benefit as desired. It would be provide a great advantage if there were some methods to predict the response of patients before chemoradiation protocol. For this reason, pCR that associated with better outcomes has been drawn a great interest. In previous studies, factors such as tumor size, carcinoembryogenic antigen (CEA) levels have been reported to be of predictive value to pCR follow in nCRT.[7–9] However, there is still a lack of consensus on the predictive factors of pCR.

We aimed to determine the clinical factors and treatment

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parameters predictive of pCR after nCRT in the patients with locally advanced rectal cancer.

2. Material and methods

Two hundred and seventy-nine patients with locally advanced rectal cancer who had nCRT between January 2009 and December 2015 in two-center were evaluated retrospectively. Patients were recruited in the study according to the following criteria: 1- Pathologically proven rectal adenocarcinoma, 2- Localized tumor within the first 15 cm from anal verge, 3- Clinical stage both II or III, 4- Patients without distant metastasis, 5-Curative surgery following nCRT. Patients who did not have surgery following neo-adjuvant treatment or patients who were lost to follow up were excluded (n = 76). Besides, patients with a second primary malignancy, patients with hereditary colon cancer or patients who had endoscopic surgery were excluded from the study.

All patients were histopathologically diagnosed with adenocarcinoma. Pelvic magnetic resonance imaging, abdominopelvic computerized tomography, transrectal ultrasonography, or various combinations of these options were used for the clinical staging before nCRT. Surgery specimen and lymph nodes without viable tumor cells were defined as pCR and those with viable cells were defined as non-pCR, respectively.

Radiotherapy was performed to primary tumor site and perirectal metastatic lymph nodes in 42–54 Gy dose range, as 1.8–2 Gy fractions, five days a week for 30–35 days. Patients had one out of two different chemotherapy regimens simultaneously with radiotherapy: 225 mg/m^2/day of 5-Fluorouracyl (5 days a week) was introduced through central venous catheter with a pomp; 825 mg/m^2 oral capecitabine (2 times a day) was performed the whole week during the radiotherapy period. All patients had total mesorectal excision as the surgical procedure. Adjuvant FOLFOX chemotherapy (folinic acid, 5-flurouracyl, oxaliplatin) regimen was introduced in 3–6th weeks following the surgery.

Sex, age, body mass index (BMI), ECOG (Eastern Cooperative Oncology Group) performance score at the time of diagnosis, smoking history, clinical TNM staging, tumor differentiation, the distance between the tumor and the anal verge, endoscopic appearance of the tumor, endoscopic size of the tumor, chemotherapy regimen given with radiotherapy, radiotherapy dosage, interval between the radiotherapy and the surgery, carbohydrate antigen 19-9 (CA 19-9) and CEA levels before the therapy were reported. Moreover, hemoglobin level, trombocyte count, neutrophile/lymphocyte ratio (NLR), thrombocyte/lymphocyte ratio (PLR), lactate dehydrogenase and albumin levels before the nCRT were evaluated. For the NLR and PLR cut-off values were <3 and < 160 as the previous studies suggested, respectively.[10,11]

Rectum was defined as the 0 to 15th cm segment from the anal verge; inferior rectum as the 0–4.99 cm from the anal inlet, midrectum as 5 cm–9.99 cm portion, superior rectum as 10th to 15th cm portion.

2.1. Statistical analysis

Statistical analyses were performed using *'Statistical Package for The Social Sciences'* version 18.0 for Windows (SPSS, Inc, Chicago, IL, USA). The variables were investigated according to the visual (histograms, probability plots) and analytical methods (Kolmogorov Simirnov/Shapiro-Wilk's test) to determine whether they are normally distributed or not. Data was presented as median and range, and categorical variables were presented as the frequency with percentages. Continuous variables were analyzed with the Mann-Whitney U tests. Categorical variables were analyzed using the Chi-square or Fisher exact test, when appropriate. Univariate and multivariate analyses (logistic regression and Cox proportional hazard ratio) were performed to identify factors that predict pCR.

3. Results

3.1. Clinicopathologic characteristics

Two hundred and three patients were evaluated in this study. The demographical features and tumor characteristics are shown in Table 1. The median age was 58 (range = 21–85) year and 135 of them were male (%66.5), 68 were female (33.5%). There were one or more comorbid diseases in 56% of the patients, and hypertension and diabetes mellitus were most frequent comorbidities. 49% patients had clinical stage 3 and 51% had clinical stage 2 disease. Moderately differentiated adenocarcinoma was the most common histopathological subtype (54%). The median distance from anal verge to the tumor was 6 cm (range = 1–15). The median endoscopic diameter of the tumor was 5 cm (range = 1–12) and most of them (66%) had ulcerovegetan appearance. The median radiation dose was 50 Gy (range = 42–54 Gy). Concomitant to radiotherapy, 20 patients (10%) were treated with oral capecitabine alone, and 183 (90%) patients were treated with 5-fluorouracil alone, respectively. Median interval between the chemoradiotherapy and surgery was 58 days (range = 19–120 days).

3.2. Pathologic and non-pathologic complete response

Pathological complete response achieved in 46 out of 203 patients (22.7%) whereas 157 patients (77.3%) did not achieved. Clinical and pathological variables were compared between non-pCR and the pCR group. Sex, age, BMI, ECOG performance score, the distance between the tumor and the anal verge, comorbidities, endoscopic appearance of the tumor, radiotherapy dose and the applied surgical procedure were similar between the pCR and non-PCR groups. Former or current smoker patients were higher in number in non-PCR group (p = .009). Well-differentiated adenocarcinoma was the most common histopathological subtype (50%) in pCR group, whereas in non-pCR group moderately differentiated adenocarcinoma was the most common subtype (62%). Clinical stage 2 and negative lymph nodes were more common in pCR group in comparison with non-pCR (p < .001). Median pretreatment CA 19-9 and CEA levels were reported to be lower in pCR patients and median CA 19-9 and CEA levels were within normal ranges in both groups (p = .003, p = .03, respectively). Median tumor size was larger in the non-pCR group (5 vs 5.2 cm). The median interval between completion of the nCRT and the surgery was longer in the pCR group (62.5 vs 54 days).

3.3. Univariate and multivariate logistic regression analysis

Patients were analyzed separately for categorical parameters for both univariate and multivariate logistic regression analysis. The distance between the tumor and the anal verge were categorized into 3 groups: superior (10–15 cm), middle (5–9.99 cm) and inferior (<5 cm). Since the median time interval between completion of nCRT and surgery was 58 days, 8 weeks was used as the median interval to surgery parameter for the analysis.

Broad univariate analysis was performed using approximately 22 parameters (Table 2). In the univariate analysis, No smoking history, clinically negative lymp node (cN-), well-differentiated tumor, tumor size of ≤5 cm, pre-nCRT CEA level of ≤5 (ng/mL) and median interval to surgery>8 week were associated with an increased rate of pCR.

Multivariate logistic regression analysis revealed that no smoking history (p = .008), cN- (p = .002), endoscopic tumor size of

Table 1
Clinicopathologic characteristics of patients.

Characteristics	pCR (%) n = 46	Non-pCR(%) n = 157	Total (%) n = 203	P value
Age (median, years)	57 (21–83)	58 (22–85)	58 (22–85)	.62
Gender				
Female	11 (23.9)	57 (36.3)	68 (33.5)	.11
Male	35 (76.1)	100 (63.7)	135 (66.5)	
Smoking	14 (30.4)	82 (52.2)	96 (47.3)	**.009**
ECOG				
0-1	44 (95.7)	138 (87.9)	182 (89.7)	.17
2	2 (4.3)	19 (12.1)	21 (10.3)	
Comorbidity				
Yes	28 (60.9)	85 (54.1)	113 (55.7)	.41
No	18 (39.1)	72 (45.9)	90 (44.3)	
cTNM classification				
II	34 (73.9)	70 (44.6)	104 (51.2)	<**.001**
III	12 (26.1)	87 (55.4)	99 (48.8)	
cN classification				
cN-	34 (73.9)	70 (44.6)	104 (51.2)	
cN+	12 (26.1)	87 (55.4)	99 (48.8)	<**.001**
Tumor differentiation				
Well	23 (50.0)	37 (23.6)	60 (29.6)	<**.001**
Moderate	12 (26.1)	98 (62.4)	110 (54.2)	
Poor	11 (23.9)	22 (14.0)	33 (16.2)	
Tumor size (median, cm)[a]	5 (3–10)	5.2 (1–12)	5 (1–12)	**.019**
Distance from the anal verge (cm)	5 (1–15)	6 (1–15)	6 (1–15)	.22
BMI (median,range)	26.5 (17.9–40.3)	26.6(16.2–43.3)	26.6 (16.2–43.3)	.95
Colonscopic appearance				
Ulcerovegetan	30 (65.2)	105 (66.9)	135 (66.5)	.44
Polipoid	12 (26.1)	30 (19.1)	42 (20.7)	
Infiltrative	4 (8.7)	22 (14.0)	26 (12.8)	
Pre-CRT CEA (median, range)	2.3 (0.4–51.3)	3.5 (0.3–322)	3.0 (0.3–322)	**.03**
Pre-CRT CA 19-9 (median, range)	6.2 (0.8–71.2)	9.8 (0.6–664)	8.9 (0.6–664)	**.003**
Lactate dehydrogenase				
Normal	32 (69.6)	100 (63.7)	132 (65.0)	.46
High	14 (30.4)	57 (36.3)	71 (35.0)	
Median interval to surgery (d, range)	62.5 (25–120)	54 (19–119)	58 (19–120)	.037
Radiation dose (median, range, Gy)	50 (45–54)	50 (45–54)	50 (45–54)	.96
Concurrent chemotherapy				
Capecitabine	3 (6.5)	17 (10.8)	20 (9.9)	.57
5-Fluorouracil	43 (93.5)	140 (89.2)	183 (90.1)	
Type of surgery				
Low anterior resection	32 (69.6)	102 (65.0)	108 (65.9)	.61
Abdominoperineal resection	12 (26.1)	51 (32.5)	52 (31.7)	
Hartmann operation	2 (4.3)	4 (2.5)	4 (2.4)	

P value < 0.05 is statistically significant.
[a] Endoscopically,BMI: Body Mass Index (kg/m^2), CA 19-9: Carbohydrateantigen 19-9 (U/ml), CEA: Carcinoembryonic antigen (ng/mL), cN classification: Clinical node classification, cTNM classification: Clinical tumor-node-metastasis classification, ECOG: Eastern Cooperative Oncology Group,Non-pCR: Non-pathologic complete responce, pCR: Pathologic complete responce.

≤5 (p = .024), well-differentiated tumor (p = .002), pre-nCRT CEA level of ≤5 (ng/mL) (0.008) and median interval to surgery >8 weeks (p = .014) were the parameters significantly associated with pCR. There was found trend towards to statistical significance to be male gender (p = .058) (Table 3).

4. Discussion

During the last decade, there has been a major progress in the treatment of locally advanced rectal cancer due to advances in surgical methods and radiotherapeutic approaches. Today, therapeutic approach of locally advanced rectal cancer is the combination of three modalities: chemotherapy, radiotherapy and surgery.[12] The results vary in patients with or without pCR following the nCRT procedure; and pCR have been reported to be related with better prognostic results.[13] Although it is known that pCR following nCRT has a great importance with regards to outcomes, there are a limited number of studies suggesting clinical factors related with pCR. In these previous studies, the number of patients range between 99 and 562; and pCR rates were reported to be 11.4%–24%.[9,14–17] In our study the number of patients were similar with the previous studies (n = 203) and we reported a pCR rate of 22.7%.

Smoking is considered as a risk factor for patients with colorectal cancer.[18] Although the negative prognostic effect of smoking for pCR in patients with esophagus cancer is known, a clear data about this issue is not available in patients with rectum cancer.[19] We found out in our study that multivariate logistic regression analysis shows that smoking (current smoker and former smoker) is statistically associated with negative pCR (OR = 3.382, 95% CI = 1.377–8.307, P = .008). Although the relation between smoking and nCRT response is yet unknown and, overexpression of DNA repair enzymes because of smoking can be a reason. In studies with esophageal cancer and non-small cell lung cancer patients with smoking history, overexpression of DNA repair enzymes were detected and association between poor response with chemoradiotherapy was also reported.[20,21] Smoking induces a left shift in hemoglobin-oxygen disassociation curve and is related with elevated blood carboxy-hemoglobin. Relative tissue hypoxia may prevent this oxygen-dependent radiation effect and thus may cause

Table 2
Univariate analysis of predictors for pCR.

Variable	pCR (%) n = 46	Non-pCR (%) n = 157	Total (%) n = 203	P value
Age (years)				
≥60	18 (39.1)	71 (45.2)	89 (43.8)	.46
<60	28 (60.9)	86 (54.8)	114 (56.2)	
Gender				
Female	11 (23.9)	57 (36.3)	68 (33.5)	.11
Male	35 (76.1)	100 (63.7)	135 (66.5)	
Smoking				
Yes	14 (30.4)	82 (52.2)	96 (47.3)	**.009**
No	32 (69.6)	75 (47.8)	107 (52.7)	
ECOG				
0-1	44 (95.7)	138 (87.9)	182 (89.7)	.17
2	2 (4.3)	19 (12.1)	21 (10.3)	
Comorbidity				
Yes	28 (60.9)	85 (54.1)	113 (55.7)	.41
No	18 (39.1)	72 (45.9)	90 (44.3)	
cN classification				
cN-	34 (73.9)	70 (44.6)	104 (51.2)	**<.001**
cN+	12 (26.1)	87 (55.4)	99 (48.8)	
Tumor differentiation				
Well	23 (50.0)	37 (23.6)	60 (29.6)	**.001**
Moderately-Poorly	23 (50.0)	120 (76.4)	114 (70.4)	
Tumor size (median,cm)[a]				
≤5	34 (73.9)	78 (49.7)	112 (55.2)	**.004**
>5	12 (26.1)	79 (50.3)	91 (44.8)	
Distance from the anal verge (cm)				
<5	15 (32.6)	48 (30.6)	63 (31.0)	.37
≥5 and < 10	23 (50.0)	66 (42.0)	89 (43.8)	
≥10	8 (17.4)	43 (27.4)	51 (25.1)	
BMI (median,kg/m^2)				
<25	18 (39.1)	63 (40.1)	81 (39.9)	.90
≥25	28 (60.9)	94 (59.9)	122 (60.1)	
Colonscopic appearance				
Ulcerovegetan	30 (65.2)	105 (66.9)	135 (66.5)	.44
Polipoid	12 (26.1)	30 (19.1)	42 (20.7)	
Infiltrative	4 (8.7)	22 (14.0)	26 (12.8)	
Albumin (mg/dl)				
≥35	44 (95.7)	140 (89.2)	129 (90.6)	
<35	2 (4.3)	17 (10.8)	19 (9.4)	.18
Pre-nCRT NLR				
<3	32 (69.6)	92 (58.6)	124 (61.1)	.18
≥3	14 (30.4)	65 (41.4)	79 (38.9)	
Pre-nCRT PLR				
<160	28 (60.9)	83 (52.9)	111 (54.7)	.33
≥160	18 (39.1)	74 (47.1)	92 (45.3)	
Hemoglobin (g/dL)				
≤10	5 (10.9)	18 (11.5)	23 (11.3)	.91
>10	41 (89.1)	139 (88.5)	180 (88.7)	
Pre-nCRT CEA (ng/mL)				
≤5	19 (41.3)	38 (24.2)	57 (28.1)	**.01**
>5	27 (58.7)	119 (75.8)	146 (71.9)	
Pre-nCRT CA 19-9 (U/ml)				
≤37	43 (93.5)	138 (87.9)	181 (89.2)	.41
>37	3 (6.5)	19 (12.1)	22 (10.8)	
Lactate dehydrogenase				
Normal	32 (69.6)	100 (63.7)	132 (65.0)	.46
High	14 (30.4)	57 (36.3)	71 (35.0)	
Median interval to surgery (weeks)				
≤8	12 (26.1)	82 (52.2)	94 (46.3)	**.002**
>8	34 (73.9)	75 (47.8)	109 (53.7)	
Radiation dose (Gy)				
>50	18 (39.1)	62 (39.5)	80 (39.4)	.96
≤50	28 (60.9)	95 (60.5)	123 (60.6)	
Concurrent chemotherapy				
Capecitabine	3 (6.5)	17 (10.8)	20 (9.9)	.57
5-Fluorouracil	43 (93.5)	140 (89.2)	183 (90.1)	
Type of surgery				
Low anterior resection	32 (69.6)	102 (65.0)	108 (65.9)	.61
Abdominoperineal resection	12 (26.1)	51 (32.5)	52 (31.7)	
Hartmann operation	2 (4.3)	4 (2.5)	4 (2.4)	

P value < 0.05 is statistically significant.
[a] Endoscopically,BMI: Body Mass Index (kg/m^2), CA 19-9: Carbohydrateantigen 19-9 (U/ml), CEA: Carcinoembryonic antigen (ng/mL), cN classification: Clinical node category, ECOG: Eastern Cooperative Oncology Group, nCRT: Neoadjuvant chemoradiotherapy, NLR: Neutrophil-lymphocyte ratio, Non-pCR: Non-pathologiccompleteresponce, pCR: Pathologiccompleteresponce, PLR: Platelet-lymphocyte ratio.

Table 3
Logistic regression analysis of predictors for pathologic complete responce.

Variable	OR	95% CI	P value
Gender			
Male (Female)	2.485	0.971–6.359	.058
Smoking			
No (yes)	3.382	1.377–8.307	**.008**
cN classification			
cN- (cN+)	3.800	1.644–8.788	**.002**
Tumor differentiation			
Well (Moderately + Poorly)	3.566	1.595–7.972	**.002**
Tumor size (cm)[a]			
≤5 (>5)	2.608	1.133–6.002	**.024**
Pre-nCRT CEA (ng/mL)			
≤5 (>5)	3.067	1.348–6.977	**.008**
Median interval to surgery (weeks)			
>8 (≤8)	2.981	1.245–7.134	**.014**

P value < 0.05 is statistically significant.
[a] Endoscopically,CEA: Carcinoembryonic antigen (ng/mL), cN classification: Clinical node classification, OR:Odds ratio, CI: Confidence interval.

decreased pCR.[22] When these results are evaluated together, these reports might explain why smoking nCRT patients have poor pathological responses. However, the evaluation of relation between treatment response and smoking requires further investigation.

The tumor regression associated with radiation-induced necrosis is a time-dependent condition and the increased period between completion of nCRT and surgery may increase pCR ratio.[14] Although the optimum time interval between nCRT and surgery is not yet known definitely, the 6–8 week interval is historically considered standard.[23] We found that an interval above 8 weeks between the completion of nCRT and surgery was significantly associated with a higher pCR rate (OR = 2.981, 95% CI = 1.245–7.134, P = .014). In a study made by Malady et al., it is similary stated that an interval that is longer than 8 weeks is an independent predictive value for pCR.[14] In studies made by Zeng et al.,[24] and Wolthuis et al.,[25] it is stated that intervals longer than 7 weeks is predictive for pCR. In opposing studies, longer intervals of nCRT and surgical resection were not predictive values for pCR.[26–28] Most of the studies were retrospective, and intervals between nCRT and surgery were changing during the studies, and there is no solid data about this topic. So further prospective randomized studies are required.

Pre-nCRT tumor size and pCR can be inversely proportional. In a study with 297 patients done by Garland et al., pre-nCRT tumor size was only evaluated by an endoscopist and patients were divided into 3 distinct groups as <3.5 cm, 3.5–7 cm and >7. Clinical tumor size was reported as an independent predictor for pCR (p = .036).[9] In a study with 249 patients done by Park et al., it is found that the tumor size of ≤4 cm before treatment was stated as significant in univariate analysis. In this study, tumor size were evaluated with digito-rectal examination, colonoscopic and radiologic imaging technics.[16] In an another study with 99 patients done by De Felice et al., the endoscopic tumor size of ≤5 cm was found to be significant in multivariate logistic regression analysis (p = .035).[17] In our study, the condition in which the endoscopic tumor size before nCRT was ≤5 cm was associated significantly with increased pCR ratio (OR = 2.608, 95%, CI = 1.133–6.002, P = .024). Tumor diameters that were measured radiologically, endoscopically and real

tumor sizes can be questionable due to different calculation scales. The use of only a measuring technique as in our study may be a better approach. Even though different calculation scales were present, our results shows that big tumor diameter before treatment was associated with low pCR like in other studies. Thus, pre-nCRT endoscopic tumor size may be effective on individual therapy decisions.

The clinical lymph node involvement before nCRT effects significantly the pCR and, it is more possible to achieve pCR through nCRT for those with negative lymph involvement. In this sense, in a study with 197 patients done by Garland et al., patients with clinical negative lymph involvement were found to be having a significant increase in pCR ratio (OR = 4.384, 95% CI = 1.011–19.017, P = .048).[9] In another study with 138 patients, it is stated that decreased pCR is associated with clinical lymph involvement positivity at during diagnosis.[29] In our study, like in these two retrospective studies, negative lymph involvement was found to be significantly more associated with pCR (OR = 3.800, 95%, CI = 1.644–8.788, P = .002). When these findings are considered, clinical lymph node positivity may be a marker for a more aggressive disease which is less sensitive to local treatments. These patients may have lesser possibility to be able to get benefit from non-operative methods. However, in order to determine whether patients with clinical lymph node positivity at diagnosis are suitable for non-operative methods or not, further studies are required.

Serum CEA levels are widely used as tumor markers for preoperative prognostic and for early diagnosis of postoperative recurrent disease in patients with colorectal cancer.[30] In various early studies, CEA levels before treatment were reported to be significantly related with pCR.[15,31,32] In our study, CEA >5 ratio (normal range = 0–5) before treatment in non-pCR patient group were found to be higher compared to pCR patient group and multivariate analysis showed to be statistical significancy (p = .008).

The limitation of our study was it is being retrospective and were used different radiological techniques for the clinical staging before nCRT. Thus, prospective studies with wide numbers of patients and standard uniform radiological techniques are required. That way, it will be possible to determine predictive factors for pCR and classify patients to plan pCR patients less invasive surgery and non-pCR patients more agressive and new treatment methods.

In conclusion, our study demonstrated that no smoking history, clinical negative lymph involvement, tumor size of ≤5 cm, well-differentiated tumor, pre-nCRT CEA level of ≤5 (ng/mL) and median interval to surgery of >8 weeks were independent predictive factors for pCR. These findings may help clinicians to predict the prognosis of patients and improve better treatment approach.

Conflicts of interest

None of the authors has any proprietary interests or conflicts of interest related to this submission.

This submission has not been published anywhere previously and that it is not simultaneously being considered for any other publication.

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