Predictors of Pathologic Complete Response in Patients With Residual Flat Mucosal Lesions After Neoadjuvant Chemoradiotherapy for Locally Advanced Rectal Cancer: A Case Control Study

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Abstract

Background:

Accurate prediction of tumor response to neoadjuvant chemoradiotherapy (nCRT) remains challenging. There are few studies on pathologic complete response (ypCR) prediction in patients with residual flat mucosal lesions after treatment. This study aimed to identify variables for predicting the ypCR in patients with residual flat mucosal lesions after nCRT for locally advanced rectal cancer (LARC).

Methods:

Patients with residual flat mucosal lesions after nCRT who underwent radical resection between 2009 and 2015 were retrospectively collected through the LARC database at Peking University Cancer Hospital. Univariate and multivariate analyses of the association between clinicopathological factors and ypCR were performed, and a nomogram was constructed by incorporating the significant predictors.

Results:

Out of the 246 patients with residual flat mucosal lesions that were included in the final analysis, 56 (22.8%) had ypCR. Univariate and multivariate analyses showed that posttreatment serum carcinoembryonic antigen (post-nCRT CEA) ≤ 5 ng/ml, magnetic resonance-tumor regression grade (MR-TRG) 1 to 3, and residual mucosal lesion depth = 0 mm were significantly associated with a higher rate of ypCR. A nomogram was developed with a C-index of 0.735, and the calibration curve showed that the nomogram model had good predictive consistency.

Conclusion:

Post-nCRT CEA ≤ 5 ng/ml, MR-TRG 1 to 3, and residual mucosal lesion depth = 0 mm were predictive factors for ypCR in LARC patients with residual flat mucosal lesions after nCRT. We believe that mucosal re-evaluation before surgery is important as it may contribute to decision-making and facilitating non-operative management or organ preservation.

Background:

Rectal cancer is one of the most common tumors worldwide. Due to its insidious onset, most patients are diagnosed with locally advanced rectal cancer (LARC). Neoadjuvant chemoradiotherapy (nCRT) followed by total mesorectal excision (TME) has become the standard treatment for LARC. However, radical surgery still has many disadvantages, including postoperative complications (such as abdominal infection or anastomotic leakage) and dysfunction (such as urination, sexual dysfunction or anterior resection syndrome). According to the Consensus on the Watch and Wait Policy in Rectal Cancer Patients After

Neoadjuvant Treatment (2020 Version), the Watch and Wait strategy (W&W) or transanal local resection in patients with suspected clinical complete response (cCR) or near clinical complete response (near-cCR) after nCRT could alleviate the pain of surgery and avoid a series of problems caused by organ resection [1]. Pathological response is an important prognostic factor for LARC. Studies have shown that approximately 10%-33% of patients with LARC achieve pathological complete response (ypCR) after nCRT, while up to 70% patients demonstrate only partial response to treatment [2–6]. The use of the existing diagnosis and treatment methods, such as evaluation of clinical characteristics, imaging changes, and gross morphology of tumors, to improve the prediction of ypCR is of great significance. Although there have been previous studies on the predictors of ypCR in patients after nCRT, the conclusions were diverse and inconsistent. However, there are few studies on ypCR prediction in patients with residual flat mucosal lesions after treatment. Despite the fact that these patients exhibit a good tumor response and large degree of tumor regression, it is difficult to define their cCR or ypCR; This study retrospectively analyzed the predictive factors for ypCR in patients with flat mucosal lesions after nCRT for LARC to determine the optimal treatment for such patients.

Materials And Methods:

Patient selection

A total of 246 patients with residual flat mucosal lesions after nCRT and radical resection between 2009 and 2015 were retrospectively collected through the rectal cancer database at Peking University Cancer Hospital. Each patient enrolled in our study satisfied the following criteria: 1) age > 18 years; 2) pathologically proven rectal adenocarcinomas; 3) rectal tumors located < 15 cm from the anal verge; 4) clinically staged as cT3-4 and/or N+ rectal tumors; 5) patients treated with nCRT and radical surgery; and 6) patients with residual flat mucosal lesions after nCRT. Patients were excluded if they had 1) distant metastasis or recurrent disease; 2) previous chemotherapy or pelvic radiotherapy. The study was approved by the medical ethics committee of Peking University Cancer Hospital, and waived the informed consent (2021YJZ20).

Neoadjuvant and Surgical Treatment

All patients received preoperative long-course radiotherapy (LCRT) with concurrent chemotherapy followed by TME surgery.

Imaging assessment

Magnetic resonance imaging (MRI) was routinely used to determine the clinical stage of the patient before nCRT. After nCRT, the pelvic MR was reviewed again before surgery to determine the tumor's response to treatment and the magnetic resonance-tumor regression grade (MR-TRG) (Table 1) [7–9], which were determined by two radiologists.

Table 1
The magnetic resonance tumor regression grade score

Grade 1	Radiological complete response (absence of tumor signal and barely visible treatment related scar)
Grade 2	Good response (dense fibrosis; no obvious residual tumor, signifying minimal residual disease or no tumor)
Grade 3	Moderate response (> 50% fibrosis or mucin and visible intermediate signal)
Grade 4	Slight response (little areas of fibrosis or mucin but mostly tumor)
Grade 5	No response (intermediate signal intensity, same appearances as original tumor/tumor regrowth)

Criteria for flat mucosal lesions

After radical surgery, the gross tumor specimens were evaluated by experienced pathologists. The depth of the lesion was recorded by vertical measurement in the deepest part of the lesion. The flat mucosal lesions were defined as tumors that regressed after treatment and remained as superficial ulcers or scars with a depth of less than or equal to 5 mm (Fig. 1).

Statistical data and clinicopathological data

Data on covariates of interest were collected including age, sex, height (H), weight(W), body mass index (BMI), pretreatment serum carcinoembryonic antigen (pre-nCRT CEA) and carbohydrate antigen199 (pre-nCRT CA199) levels, posttreatment serum carcinoembryonic antigen (post-nCRT CEA) and carbohydrate antigen 199(post-nCRT CA199)levels, tumor distance from the anal verge (tumor distance), time interval between chemoradiotherapy and surgery (time interval), and MR-TRG. The tumor size and residual mucosal lesion depth (lesion depth) were recorded, and the ypCR was finally determined by paraffin pathology.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics 25.0. Categorical variables were assessed using the Chi square (2*2) or Fisher's exact test (2*C), where applicable. A p value < 0.05 was considered significant. Multivariate analysis was performed using a binary logistic regression model (Forward: LR). R software (4.0.4) and the rms software package were used to construct the nomogram prediction model. The bootstrap method was used for internal validation of the predictive model of the nomogram. The number of repeated sampling times was 1000. The concordance index (C-index) was used to evaluate the predictive performance of the model. Calibration of the nomogram for predicting ypCR rates was performed by comparing the predicted probability and the actual status after bias correction.

Results:

A total of 246 patients with residual flat mucosal lesions were included in the final analysis, and 56 (22.8%) of them had ypCR. Patient characteristics and clinicopathological data are shown in Table 2. The mean lesion depth was 0.31 ± 0.19 cm.

Table 2
Patients characteristics

Characteristic	Results
Age(year)	56.46 ± 11.49
Sex	
Men	157 (63.8%)
Women	89 (36.2%)
BMI (kg/m ²)	23.97 ± 3.31
Tumor distance (cm)	4.91 ± 2.04
Pre-nCRT CEA (ng/ml)	9.45 ± 20.40
Pre-nCRT CA199 (u/ml)	29.16 ± 55.76
Post-nCRT CEA (ng/ml)	3.56 ± 6.21
Post-nCRT CA199 (u/ml)	18.06 ± 33.30
MR-TRG	
Grade 1	1 (0.4%)
Grade 2	17 (6.9%)
Grade 3	157 (63.8%)
Grade 4	69 (28.0%)
Grade 5	2 (0.8%)
Time interval (w)	8.92 ± 2.41
Tumor residual size(cm)	2.07 ± 1.04
Lesion depth(cm)	0.31 ± 0.19
ypCR	
Yes	56 (22.8%)
No	190 (77.2%)

Univariable analysis

Univariate analysis showed that age, sex, BMI, tumor distance, time interval, pre-nCRT CEA, pre-nCRT CA199, post-nCRT CA199, and tumor maximum diameter were not related to the ypCR.

There was a difference in the rate of ypCR between the post-nCRT CEA ≤ 5 ng/mL group and the post-nCRT CEA > 5 ng/mL group (25.2% vs. 3.6%, $p = 0.010$). Similarly, the incidences of ypCR were significantly higher in the MR-TRG 1–3 group (29.7% vs. 5.6%, $p = 0.000$) and the lesion depth = 0 mm group (51.3% vs. 17.4%, $p = 0.000$) (Table 3).

Table 3
Univariable analysis results

Variable	N	Non-pCR	pCR	χ^2	p
Sex				0.752	0.386
Men	157	124 (79.0%)	33 (21.0%)		
Women	89	66 (74.2%)	23 (25.8%)		
Age(year)				0.787	0.375
≤60	153	121 (79.1%)	32 (20.9%)		
>60	93	69 (74.2%)	24 (25.8%)		
BMI (kg/m ²)				2.460	0.344 ^a
< 18.5	9	8 (88.9%)	1 (11.1%)		
18.5–23.9	118	86 (72.9%)	32 (27.1%)		
≥24	119	96 (80.7%)	23 (19.3%)		
Tumor distance (cm)				0.371	0.542
≤5	163	124 (76.1%)	39 (23.9%)		
>5	83	66 (79.5%)	17 (20.5%)		
Pre-nCRT CEA (ng/ml)				0.512	0.474
≤5	157	119 (75.8%)	38 (24.2%)		
>5	89	71 (79.8%)	18 (20.2%)		
Pre-nCRT CA199 (u/ml)				2.862	0.091
≤37	206	155 (75.2%)	51 (24.8%)		
>37	40	35 (87.5%)	5 (12.5%)		
Post-nCRT CEA (ng/ml)				6.620	0.010
≤5	218	163 (74.8%)	55 (25.2%)		
>5	28	27 (96.4%)	1 (3.6%)		
Post-nCRT CA199 (u/ml)				1.480	0.224 ^b
≤37	231	176 (76.2%)	55 (23.8%)		
^a Fisher's exact test					
^b Continuity Correction					

Variable	N	Non-pCR	pCR	χ^2	p
>37	15	14 (93.3%)	1 (6.7%)		
Time interval (w)				2.271	0.132
≤8	105	86 (81.9%)	19 (18.1%)		
>8	141	104 (73.8%)	37 (26.2%)		
Tumor residual size (cm)				0.148	0.700
>3	30	24 (80.0%)	6 (20.0%)		
≤3	216	166 (76.9%)	50 (23.1%)		
Lesion depth (mm)				21.438	0.000
≥1	207	171 (82.6%)	36 (17.4%)		
=0	39	19 (48.7%)	20 (51.3%)		
MR-TRG				16.658	0.000
TRG1-3	175	123 (70.3%)	52 (29.7%)		
TRG4-5	71	67 (94.4%)	4 (5.6%)		
^a Fisher's exact test					
^b Continuity Correction					

Multivariate logistic regression analysis

Considering that age and time interval might affect tumor development, and the p value of pre-nCRT CA199 was close to 0.05, we decided to include them in the multivariate logistic regression analysis. Multivariate logistic regression analysis showed that post-nCRT CEA $\leq$ 5 ng/ml ($p = 0.036$, odds ratio [OR] = 9.267, 95% confidence interval [CI]: 1.161–73.955), MR-TRG 1 to 3 ($p = 0.001$, OR = 6.397, 95% CI: 2.159–18.953), and residual mucosal lesion depth = 0 mm ($p = 0.000$, OR = 4.608, 95% CI: 2.127–9.981) were predictive factors for ypCR in LARC patients with residual flat mucosal lesions after nCRT (Table 4).

Table 4
Multivariate logistic regression analysis results

Variable	Odds Ratio	95%CI	p
post-nCRT CEA			
≤ 5ng/mL	9.267	1.161–73.955	0.036
>5ng/mL	1		
lesion depth			
0mm	4.608	2.127–9.981	0.000
≥1mm	1		
MR- TRG			
TRG1-3	6.397	2.159–18.953	0.001
TRG4-5	1		

Establishment and verification of the nomogram

A nomogram was constructed by incorporating the significant predictors identified by multivariate logistic regression, as shown in Fig. 2. Each subtype within these variables was assigned a score on the point scale, which were then added to obtain the total score and probability of ypCR. The original concordance index (orig_c-index) was 0.742, and the bias-corrected concordance index (bias_corrected_c_index) was 0.735. The results showed that the discrimination ability of the nomogram model was good. In addition, the calibration curve demonstrated that the nomogram model had good predictive consistency (Fig. 3).

Discussion:

Tumor response to nCRT is considered to be one of the important factors predicting the prognosis and influencing treatment strategy decisions. However, accurate prediction of the tumor response is still difficult to achieve. Consequently, ypCR patients continue to undergo TME surgery because the tumor response could not be accurately determined before tumor removal. For patients with low rectal cancer who need a definitive abdominoperineal (APR) procedure, the subsequent permanent stoma greatly decreases the quality of life. Increasing experience with the W&W strategy for cCR or near-cCR through several international registries or single center reports has stressed the importance of judging the status of tumor shrinkage before deciding the surgical plan. This retrospective study was a large sample study exploring the relationship between mucosal changes after nCRT and ypCR. It investigated the prediction of ypCR in patients with residual flat mucosal lesions after nCRT based on several classical factors, and established a nomogram with a maximum prediction efficiency of 60%.

Mucosal appearance of residual disease and ypCR:

The appearance of post-treatment residual mucosal lesions is important for assessing the treatment response. It is generally believed that the typical endoscopic signs of cCR after chemoradiation therapy include the disappearance of the tumor with healing of the mucosa, decrease in size and complete normalization of the tumor bed, or residual red or white scarring with telangiectasia but without palpable abnormalities [10–12]. However, the reliability of these signs is not very satisfactory, and consistency between cCR and ypCR has not been clarified yet.

Among the 246 patients in our study, 207 patients had incompletely flat lesions (lesion depth > 0 mm), of which 36 (17.4%) were ypCR. However, among the 39 patients with completely flat mucosa (lesion depth = 0 mm), the ypCR rate was as high as 51.3%. The results showed that a lesion depth = 0 mm was associated with ypCR. This suggests the possibility of assessing the post-treatment tumor response by digital rectal exam (DRE) and endoscopy, and if the residual lesions are found to be almost completely flat, these patients could be managed by the W&W strategy. However, there are some other studies that are worth noting. Fraser et al. and Jemma Bhoday et al. showed that most patients with ypT0 or pCR status did not exhibit mucosal complete clinical response[8, 13]. Therefore, we believe that it may be necessary to combine other parameters to improve the accuracy of ypCR prediction. Consequently, in our study, we explored the synergistic effect of lesion depth, MR-TRG, and post-nCRT CEA for predicting ypCR. The results revealed that the ypCR rate could reach 54.5% (in lesions with depth = 0 mm and MR-TRG 1 to 3) and 55.6% (in lesions with depth = 0 mm and post-nCRT CEA $\leq$ 5 ng/ml) by utilizing the combination of two variables.

MR-TRG and ypCR:

Our results also showed that MR-TRG 1 to 3 could be an effective indicator for ypCR. We merged MR-TRG 1/2/3 together as a good response to make it more practical for clinical application similar to other published data. The MR-TRG stage was chosen as the observed variable rather than MR-T staging because although MRI can provide additional details of the extensive pelvic anatomy compared to ERUS or endoscopy, its accuracy for ypT staging after neoadjuvant therapy is low. The sensitivity of MR for the assessment of post-treatment ypT staging was less than 50%, while the sensitivity for the evaluation of ypT0 was only 19.1%[14, 15].

Similar to our study, Patel et al. reported that good MR-TRG (grade 1 to 3) was significantly associated with a favorable pathology [16]. Battersby et al. also suggested that MR-TRG appears to be the most encouraging method for assessing the tumor response to neoadjuvant therapy, and MR-TRG could be used as a key criterion to assess the complete response on the basis of frequent follow-up [17]. Our results are consistent with the above studies. Thus, in patients with lesion depth = 0 mm, we may use MR-TRG more convincingly to find the candidates suitable for the W&W strategy.

Serum CEA and ypCR:

Previous studies have shown that serum CEA levels might predict the response to treatment and clinical outcome, while the preoperative CEA level was a strong predictor of decreased overall survival and

systemic recurrence [18–20]. Whether serum CEA could predict ypCR after nCRT is also worth investigating. In our study, multivariate logistic regression analysis showed that a low level of post-nCRT CEA was associated with a higher incidence of ypCR. Our results were consistent with those of other studies by Kleiman et al. and Peng J et al [21, 22]. We believe that the reason why pre-nCRT CEA had no association with ypCR was that it was obtained before treatment. Hence, it predominantly reflected the tumor's biologic status rather than its response to nCRT, which is in agreement with Yoon DAE Han's view [23].

However, there is no uniform CEA cut-off value to predict ypCR. Peng J et al. used post-nCRT CEA of ≤ 2 ng/mL as the cut-off value, and they claimed that low post-nCRT CEA levels were associated with ypCR [22]. Moureau–Zabotto et al., Das et al., and Steinhagen et al. reported similar findings with a cut-off of 5 ng/mL or 2.5 ng/mL [24–26]. The CEA cut-off value defined by Peng et al. was 5.33 ng/mL, and that by Sun et al. was 5 ng/mL [27, 28]. In our study, we set the CEA cut-off value as 5 ng/ml because it is the maximum threshold of the normal value, which is more in line with diagnostic protocols.

Time interval between chemoradiotherapy and surgery and ypCR:

Studies showed that prolonging the time interval could increase the ypCR rate [29–31]. However, most of the studies were retrospective studies, consequently, this result should be treated with caution. A multicenter randomized, controlled trial (GRECCAR-6) from France reported that there was no difference in the ypCR rate between the 7-week and 11-week groups [32]. Another prospective study found similar results [33]. In our study, there was no statistical difference in the ypCR rate between the two groups (≤ 8 weeks group and > 8 weeks group). When we changed the cut-off value to 12 weeks, the ypCR rate of patients in the > 12 weeks group was higher, but there was no statistical difference. To date, the optimum interval between nCRT and surgery for LARC, in fact, remains controversial. Prospective, randomized, multicenter trials with larger samples are required to draw definitive conclusions.

Limitations:

Our study has some limitations. Firstly, since all the included patients had flat lesions—this selection bias might have excluded some patients with a poor tumor response, which might have affected the comparison of ypCR rates. We believe that if all patients were included in the analysis, the final results would be more comparative. Secondly, lymph node metastasis was not considered in this study. However, studies have shown that N staging is not associated with ypCR [23, 31]. In addition, clinical lymph node staging cannot confirm pathological lymph node staging [34]. Lastly, evaluation and measurement of the lesions using fixed specimens may not be totally consistent with the fresh specimens, and without visual details when compared with endoscopic features.

Future Perspective:

Despite these limitations, the present study consolidated the importance of mucosal changes after nCRT, especially the ypCR predicting value of the combination of residual mucosal lesion depth, MR-TRG, and post-nCRT CEA levels. The nomogram we built might have limited value in patients with different baseline stages or treatment schedules, however, it still reflects the significant factors influencing ypCR rate for reference. In the watch and wait era, our data may further support routine endoscopic re-evaluation before making a surgical plan.

Conclusion:

Patients with residual flat mucosal lesions after nCRT for LARC should be treated with caution when making treatment strategies. Post-nCRT CEA ≤ 5 ng/ml, MR-TRG 1 to 3, and residual mucosal lesion depth = 0 mm are predictive factors for ypCR in LARC patients with residual flat mucosal lesions after nCRT. A nomogram based on these three independent risk factors has a good predictive performance in predicting ypCR. We believe that mucosal re-evaluation before surgery is important and may contribute to decision-making as well as facilitating non-operative management or organ preservation.

Abbreviations

nCRT

neoadjuvant chemoradiotherapy

ypCR

pathological complete response

LARC

locally advanced rectal cancer

MR-TRG

magnetic resonance-tumor regression grade

TME

total mesorectal excision

W&W

Watch and Wait strategy

cCR

clinical complete response

near-cCR

near clinical complete response

MRI

Magnetic resonance imaging

pre-nCRT CEA

pretreatment serum carcinoembryonic antigen

post-nCRT CEA

posttreatment serum carcinoembryonic antigen

pre-nCRT CA199

pretreatment serum carbohydrate antigen199

post-nCRT CA199

posttreatment serum carbohydrate antigen199

C-index

concordance index

Declarations

Ethics approval and consent to participate

The study was approved by the medical ethics committee of Peking University Cancer Hospital, and waived the informed consent(2021YJZ20).

Consent for publication

Not applicable.

Competing interests

The authors declared no conflicts of interest.

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Chang-Long Li: acquisition of data, analysis & interpretation of data, drafting the article;

Lin Wang: design & organizing the study, acquisition of data, analysis & interpretation of data, revising the article;

Guan Zhen: radiological assessment, acquisition of data;

Yi Zhao: acquisition of data, analysis & interpretation of data;

Ting-Ting Sun: analysis & interpretation of data;

Zhong-Wu Li: acquisition of data;

Wei-Hu Wang: acquisition of data;

Ai-Wen Wu: final approval of the article; conception and design of the study, interpretation of the data

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Availability of data and materials

Original data are available on request by emailing the corresponding author

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Figures

Figure 1

Typical findings of residual flat mucosal lesions after nCRT on examination of the gross resected specimens: The images a, b, c, d, e, and f show lesions with a depth of 0 mm, 1 mm, 2 mm, 3 mm, 4 mm, and 5 mm, respectively

Figure 2

Nomogram to predict the probability of achieving ypCR

Figure 3

Calibration curve for predicting ypCR