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ORIGINAL ARTICLE

Analyses of predictive factors for pathological complete remission in neoadjuvant therapy for locally advanced rectal cancer

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Summary

Purpose: *To analyze relevant factors for pathological complete remission (pCR) after neoadjuvant therapy for locally advanced rectal cancer.*

Methods: *The clinical data of 531 patients with the American Joint Committee on Cancer (AJCC) stage II or III rectal cancer from January 2014 to December 2017 were retrospectively analyzed. Among these patients, 100 (18.83%) patients achieved pCR. Univariate and multivariate logistic regression analyses were applied to analyze the predictive factors for pCR after neoadjuvant therapy.*

Results: *According to univariate analysis, carcinoembryonic antigen (CEA) before chemo-radiotherapy (CRT) (p=0.021), tumor (T) stage before CRT (p=0.002), interval between the end of CRT and surgery (p<0.001) and maximum depth of tumor invasion before CRT (p=0.039) influenced significantly pCR. Multivariate analysis manifested that the CEA level before CRT [p=0.037, odds ratio (OR) =0.435] and the interval between the end of CRT and surgery (p=0.004, OR=2.864) were significant predictive factors for pCR. Stratified analysis showed that low-level CEA before CRT (p=0.029) affected pCR only in non-smoking group.*

Conclusions: *pCR can be observed in some patients with locally advanced rectal cancer after neoadjuvant therapy. Low-level CEA before CRT and long interval between CRT and surgery are predictive factors for pCR of preoperative neoadjuvant therapy for locally advanced rectal cancer, but low-level CEA is effective in predicting pCR in non-smokers only.*

Key words: *neoadjuvant therapy, pathologic complete remission, predictive factors, rectal cancer*

Introduction

Colorectal cancer is one of the malignancies severely threatening human health [1,2]. Besides, rectal cancer shows an increasing incidence rate year by year and a low early detection rate. Moreover, most rectal cancer patients have been already in locally middle and advanced stage at the time of diagnosis.

As for the treatment of locally advanced rectal cancer, the standard mode is the combined therapy of preoperative neoadjuvant CRT + total mesorectal excision (TME). Numerous studies have verified that preoperative neoadjuvant CRT for local advanced rectal cancer is more effective in reducing local recurrence rate and improving survival in comparison with surgery alone or postoperative adjuvant therapy [3-5]. Neoadjuvant CRT is important for the treatment of locally advanced rectal cancer, through which patients can have their tu-

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mor stage regressed. However, the pCR rate after neoadjuvant CRT is only 11-27%. Therefore, it is necessary to establish a predictive model for the efficacy of preoperative neoadjuvant therapy for rectal cancer, realizing individualized treatment and efficacy prediction.

In this study, 531 patients with rectal cancer were retrospectively analyzed, a number of research factors were included, patients with pCR were paired, and factors impacting pCR after neoadjuvant therapy for locally advanced rectal cancer were investigated.

Methods

Subjects

A total of 531 patients pathologically diagnosed with locally advanced rectal cancer from January 2014 to December 2017 were enrolled in this study, including 360 males and 171 females.

Inclusion criteria: Patients with stage II-III, who received neoadjuvant therapy (preoperative neoadjuvant CRT in the interval waiting for surgery), received preoperative fluorouracil (FU)-based neoadjuvant concomitant chemotherapy and conventional fractionated radiation therapy, had a Karnofsky performance scale (KPS) score of ≥70 and a distance of less than 12 cm between the tumor and anal verge. Signed informed consents were obtained from all participants before study entry and the study was approved by the ethics committee of the Second Affiliated Hospital of Soochow University.

Therapeutic regimens

A) Radiotherapy: The gross tumor volume of the primary tumor (GTVt) included the primary tumor, the entire rectum at the level where the primary tumor was located, and nodal gross tumor volume (GTVn) referred to enlarged lymph node with a diameter of more than 1 cm. The clinical target volume (CTV) covered GTV, total mesorectum, presacral soft tissue, presacral lymph nodes, circumintestinal lymph nodes, obturator, internal iliac lymphatic drainage area and T4 or anal canal invasion including external iliac lymph chain, which was adjusted according to the location of the tumor. CTV or GTV was expanded 1 cm in all direction to form the planning target volume (PTV). The irradiation dose used was the dose of conventional radiation therapy (311patients) or that of three-dimensional (3D) intensity-modulated radiation therapy (IMRT, 220patients).

B) Chemotherapy: (1) Concomitant chemotherapy: Oral Fu-based chemotherapeutics, including 5-FU or Xeloda. Chemotherapy regimens included CAPOX, FOLFOX4, De Gramont and Xeloda alone. (2) Induction chemotherapy: Patients received such chemotherapy at 6-8 weeks waiting for surgery after one week of the concomitant CRT.

C) Surgical plan: TME was conducted at 5-12 weeks after the completion of concomitant CRT.

Data collection and processing

The basic clinical data (gender, age, hemoglobin, red blood cell count and smoking history), in the interval between the end of CRT and surgery, CEA and carbohydrate antigen 19.9 (CA19.9) before and after CRT and TNM staging of patients were collected and recorded. The general clinical data, and CRT-related conditions were compared between two groups so as to screen out

Table 1. Basic characteristics of enrolled patients

Characteristics	*n (%)*
Age (y), mean±SD	55.46±10.37
Gender	
Male	360 (67.80)
Female	171 (32.20)
Smoker	
Yes	207 (38.98)
No	324 (61.02)
Hb before CRT (g/L), mean±SD	127±20
≤90	27 (5.08)
>90	504 (94.92)
RBC count before CRT (10^12/L), mean±SD	4.52±0.48
≤3.5	26 (4.90)
>3.5	505 (95.10)
CEA before CRT (ng/mL), mean±SD	13.85±30.26
≤5	281 (52.92)
>5	250 (47.08)
CA19.9 before CRT (U/mL), mean±SD	45.13±87.49
≤37	409 (77.02)
>37	122 (22.98)
T stage before CRT	
T2	35 (6.59)
T3	186 (35.03)
T4	310 (58.38)
N+ before CRT	498 (93.79)
Concomitant chemotherapy regimen	
CAPOX	432 (81.36)
FOLFOX4	50 (9.42)
De Gramont	23 (4.33)
Xeloda alone	26 (4.90)
Induction chemotherapy	345 (64.97)
Interval between CRT and surgery (weeks), mean±SD	7.82 (5.63-12.81)
≤8	286 (53.86)
>8	245 (46.14)
Distance between tumor and anal verge before CRT (cm)	5.09±2.11
Maximum tumor thickness before CRT (cm), mean±SD	2.04±0.72
Tumor diameter before CRT (cm), mean±SD	5.33±2.08
Radiotherapy CTV dose (Gy), mean±SD	45.16±0.35
Radiotherapy GTV dose (Gy), mean±SD	49.27±2.41

the predictive factors for pCR after neoadjuvant therapy for rectal cancer.

Evaluation of efficacy

Evaluation criteria for pCR: The tumor specimens resected were evaluated by two expert pathologists according to the American Joint Committee on Cancer (AJCC) Pathological Cancer Staging Manual. PCR meant complete regression of the tumor, with only fibrous tissues observed. Moreover, patients were divided into two groups (pCR group and non-pCR group) in accordance with postoperative pathology.

Statistics

All statistical analyses were performed using SPSS 19.0 software (SPSS Inc., Chicago, IL, USA). The normality test was conducted in all quantitative data: normally distributed data were expressed as mean± standard deviation (SD), and *t*-test was performed for the comparison of the mean values, while non-normally distributed data were described as median (inter-quartile range), and independent sample rank test was performed for comparisons between groups. All qualitative data were tested using x^2 test or Fisher's exact test. Univariate and multivariate logistic regression analyses were performed to

Table 2. Comparisons between pCR and non-pCR groups

Characteristics	*PCR* *n (%)*	*Non-pCR* *n (%)*	*p value*
Age(y)	53.47±10.06	55.82±10.74	0.211
Gender			0.783
Male	68(68)	292(67.75)	
Female	32(32)	139(32.25)	
Smoker			0.514
Yes	35(35)	172(39.91)	
No	65(65)	259(60.09)	
Hb before CRT (g/L), mean±SD	128±19	126±21	0.832
RBC count before CRT (10^12/L), mean±SD	4.58±0.37	4.49±0.50	0.576
CEA before CRT (ng/mL), mean±SD	13.80±29.62	14.11±32.08	0.025
Reduction ratio of CEA	0.32(0.60)	0.37(0.65)	0.438
CA19.9 before CRT (U/mL), mean±SD	44.49±89.24	46.35±83.92	0.527
Reduction ratio of CA19.9	0.05(0.64)	0.06(0.73)	0.906
T stage before CRT			0.002
T2	18(18)	17(3.94)	
T3	30(30)	156(36.19)	
T4	52(52)	258(59.86)	
N stage before CRT			0.619
N0	6(6)	27(6.26)	
N+	94(94)	404(93.74)	
Concomitant chemotherapy regimen			0.464
CAPOX	86(86)	346(80.28)	
FOLFOX4	10(10)	40(9.28)	
De Gramont	2(2)	21(4.87)	
Xeloda alone	2(2)	24(5.57)	
Induction chemotherapy			0.669
Yes	67(67)	278(64.50)	
No	33(33)	153(35.50)	
Interval between CRT and surgery (weeks)	8.4(1.2)	7.8(1.6)	<0.001
Distance between tumor and anal verge before CRT (cm), mean±SD	5.06±2.14	5.10±2.08	0.528
Maximum depth of tumor invasion before CRT (cm), mean±SD	1.89±0.76	2.07±0.70	0.018
Reduction ratio of depth of tumor invasion	0.38(0.28)	0.30(0.25)	<0.001
Tumor diameter before CRT (cm)	5.29(2.06)	5.35±2.09	0.343
Reduction ratio of tumor diameter	0.091(0.30)	0.089(0.27)	0.722
Radiotherapy CTV dose (Gy), mean±SD	45.16±0.37	45.16±0.34	0.860
Radiotherapy GTV dose (Gy)			0.065
<50	15(15)	116(26.91)	
≥50	85(85)	315(73.09)	

Table 3. Univariate analysis of relevant factors for pCR

Factors	*pCR n (%)*	*non-pCR n (%)*	x^2	*p value*
Age (y)			1.264	0.562
≤55	49 (49)	200 (46.40)		
>55	51 (51)	231 (53.60)		
Gender			2.095	0.783
Male	68 (68)	292 (67.75)		
Female	32 (32)	139 (32.25)		
Smoker			0.712	0.514
Yes	35 (35)	172 (39.91)		
No	65 (65)	259 (60.09)		
Hb before CRT (g/L)			1.369	0.437
≤90	3 (3)	24 (5.57)		
>90	97 (97)	407 (94.43)		
CEA before CRT (ng/mL)			6.195	0.021
≤5	66 (66)	215 (49.88)		
>5	34 (34)	216 (50.12)		
Reduction ratio of CEA			4.118	0.622
≤30	47 (47)	165 (38.28)		
>30	53 (53)	266 (61.72)		
CA19.9 before CRT (U/mL)			2.294	0.236
≤37	85 (85)	324 (75.17)		
>37	15 (15)	107 (24.83)		
T stage before CRT			11.579	0.002
T2	18 (18)	17 (3.94)		
T3	30 (30)	156 (36.19)		
T4	52 (52)	258 (59.86)		
N stage before CRT			0.186	0.619
N0	6 (6)	27 (6.26)		
N+	94 (94)	404 (93.74)		
Concomitant chemotherapy regimen			3.298	0.464
CAPOX	86 (86)	346 (80.28)		
FOLFOX4	10 (10)	40 (9.28)		
De Gramont	2 (2)	21 (4.87)		
Xeloda alone	2 (2)	24 (5.57)		
Induction chemotherapy			1.273	0.669
Yes	67 (67)	278 (64.50)		
No	33 (33)	153 (35.50)		
Interval between CRT and surgery (weeks)			13.270	<0.001
≤8	29 (29)	257 (59.63)		
>8	71 (71)	174 (40.37)		
Distance between tumor and anal verge before CRT (cm)			0.975	0.427
≤6	81 (81)	328 (76.1)		
>6	19 (19)	103 (23.90)		
Maximum depth of tumor invasion before CRT (cm)			5.821	0.039
≤2.5	93 (93)	354 (82.13)		
>2.5	7 (7)	77 (17.87)		
Reduction ratio of depth of tumor invasion			3.158	0.365
≤60	95 (95)	418 (96.98)		
>60	5 (5)	13 (3.02)		
Tumor diameter before CRT (cm)			1.382	0.269
≤5	51 (51)	254 (58.93)		
>5	49 (49)	177 (41.07)		
Radiotherapy GTV dose (Gy)			4.372	0.065
<50	15 (15)	116 (26.91)		
≥50	85 (85)	315 (73.09)		
Radiation therapy			0.909	0.764
Conventional radiation therapy	55 (55)	256 (59.40)		
IMRT	45 (45)	175 (40.60)		

Table 4. Multivariate logistic regression analysis of influencing factors for pCR

Factors	*B*	*S.E*	*OR (95%CI)*	*p value*
T stage before CRT	-0.511	0.316	0.676 (0.374-1.382)	0.236
Concomitant chemotherapy regimen	-0.324	0.263	0.802 (0.557-1.085)	0.415
CEA before CRT	-0.769	0.424	0.435 (0.214-1.010)	0.037
Interval between CRT and surgery	1.023	0.638	2.864 (1.259-5.473)	0.004
Distance between tumor and anal verge before CRT	-0.305	0.752	0.697 (0.321-2.017)	0.526
Tumor diameter before CRT	0.546	0.575	1.473 (0.692-9.504)	0.349
Radiotherapy GTV dose	0.897	0.829	2.528 (0.622-9.504)	0.272
Maximum depth of tumor invasion before CRT	-0.872	0.740	0.519 (0.136-1.679)	0.168

Table 5. Subgroup analysis on the effect of CEA before CRT on pCR in smokers or non-smokers

	CEA before CRT (ng/mL)		*x^2*	*p value*
	≤5 n (%)	*>5 n (%)*		
Non-smoker				
non-pCR	146 (56.81)	111 (43.19)	5124	0.29
pCR	50 (74.63)	17 (25.37)		
Smoker				
non-pCR	69 (39.66)	105 (60.34)	2.376	0.258
pCR	16 (48.48)	17 (51.52)		

evaluate the predictive factors for pCR after neoadjuvant CRT for locally advanced rectal cancer. P<0.05 suggested that the difference was statistically significant.

Results

Baseline characteristics

A total of 531 patients were included, among which 50 (18.83%) patients had pCR after surgery. The mean age was years (55.46±10.37). There were 207 (38.98%) patients with smoking history. The mean value of CEA level before CRT was 13.85±30.26 ng/mL, and that of CA19.9 content before CRT was 45.13±87.49 U/mL. T4 stage cancer was detected in 310 (58.38%) patients before CRT. The mean interval between CRT and surgery was 7.81±1.49 weeks. The mean maximum depth of tumor invasion before CRT was 2.04±0.72 cm (Table 1).

Analyses on relevant factors influencing pCR

Parameters including gender, age, smoking history, hemoglobin before CRT, red blood cell count before CRT, CEA before CRT and its reduction ratio, CA19.9 before CRT and its reduction ratio, T stage before CRT, N stage before CRT, concomitant chemotherapy regimen, induction chemotherapy, interval between the end of CRT and surgery, radiotherapy CTV dose, radiotherapy GTV dose, distance from the tumor to the anal verge, maximum depth of tumor invasion before CRT and its reduction ratio, tumor diameter before CRT and its reduction ratio and radiotherapy technique were analyzed. Among them, CEA before CRT (p=0.025), T stage before CRT (p=0.002), interval between the end of CRT and surgery (p<0.001) and maximum depth of tumor invasion before CRT (p=0.018) showed significant differences between different groups (Table 2).

Results of univariate and multivariate analyses

Based on univariate analysis, pCR was affected by CEA before CRT (p=0.021), T stage before CRT (p=0.002), interval between the end of CRT and surgery (p<0.001) and maximum depth of tumor invasion before CRT (p=0.039) (Table 3). Multivariate logistic regression analysis revealed that CEA level before CRT [p=0.037, odds ratio (OR) =0.435] and interval between the end of CRT and surgery (p=0.004, OR=2.864) were predictive factors for pCR (Table 4).

Stratified analysis of the effect of CEA before CRT on pCR in smokers or non-smokers

Low-level CEA before CRT in non-smokers (p=0.029) affected pCR, while that in smokers (p=0.258) had no impact on pCR (Table 5).

Discussion

PCR is achieved in some locally advanced rectal cancer patients receiving preoperative neoadjuvant CRT [3]. These patients often have better prognosis compared with non-pCR patients. However, the influencing factors of neoadjuvant CRT on pCR after neoadjuvant CRT for locally advanced rectal cancer are unclear. Besides, analyzing the influencing factors for pCR and establishing an effective predictive model are conducive to helping patients undergo optimal treatment. Therefore,

this paper aimed to investigate the predictive factors for pCR after preoperative neoadjuvant CRT for locally advanced rectal cancer. German CAO/ARO/AIO 94 studies have indicated that the group receiving preoperative CRT for rectal cancer had reduced local recurrence rate, increased anal preservation rate and decreased treatment related toxic side effects [6]. Based on the results of Saurer et al. [6], preoperative CRT combined with TME radical surgery is used as a standard therapeutic approach for the treatment of locally advanced rectal cancer.

CEA is widely used in monitoring the diagnosis, treatment and prognosis of colorectal cancer. Park et al. analyzed patients undergoing preoperative radiotherapy and found that the response rate of patients with locally advanced rectal cancer was decreasing with the increase in CEA level before CRT (>5 ng/mL) [7]. Tomono et al. and De Felice et al. thought that CEA ≤5 ng/mL before neoadjuvant therapy is related to pCR and the regression rate [8,9]. However, a study by Kalady et al. showed that CEA ≤2.5 ng/mL before treatment was not correlated with pCR (p=0.21) [10]. In this study, the mean value of CEA before CRT was 13.85±30.26 ng/mL. Univariate analysis showed that CEA ≤5 ng/mL before neoadjuvant therapy was associated with pCR (p=0.021). In addition, multivariate logistic regression analysis indicated that low-level CEA before CRT was one of the predictive factors for pCR. Previous studies [11,12] have pointed out that CEA level is elevated in smokers. Therefore, the effectiveness of CEA level before CRT in predicting pCR in smokers and non-smokers was analyzed in this study. In our study, there were 207 (38.98%) smokers and stratified analysis suggested that low-level CEA (≤5 ng/mL) influenced pCR in non-smokers, but had no evident effect in smokers, which is in line with the findings of Wallin et al. [13].

The exact time of interval between the end of neoadjuvant CRT and surgery remains to be determined. A study reported that if the interval between neoadjuvant CRT and surgery is over 7 weeks, there is a relatively high pCR rate [14]. Based on this study, it is considered that it is better to perform surgery at 6-8 weeks after neoadjuvant CRT. In our study, the mean interval between the end of CRT and surgery was 7.81±1.49 weeks, showing statistical significance in both univariate and multivariate analyses (using 8 weeks as the interval cutpoint), implying that the pCR rate is higher if the interval exceeds 8 weeks, and it is one of the predictive factors.

Research revealed that tumor regression rate of preoperative CRT for rectal cancer has low accuracy in predicting and evaluating the regression of T stage. In this study, 18 (18%) patients were in T2 before CRT, and 52 (52%) were in T4 in the pCR group. In the non-pCR group, there were 17 (3.94%) cases of T2 and 258 (59.86%) cases of T4 before CRT. A maximum depth of tumor invasion of ≤2.5 cm before CRT was detected in 93 (93%) patients in the pCR group and 354 (82.13%) patients in the non-pCR group. Univariate analysis suggested that T stage before CRT (p=0.002) and the maximum depth of tumor invasion (p=0.039) in the pCR group were better than in the non-pCR group, but multivariate analysis indicated that there were no statistically significant differences in these factors.

With the advent of IMRT and volumetric modulated arc modulation (VMAT), the concomitant tumor radiotherapy dose enables patients to have the optimal dose of radiotherapy on the basis of normal organ protection. A phase II study with pCR revealed that a higher dose leads to a higher pCR rate [15]. In this study, the mean dose of GTV was 49.27 Gy, and no statistically significant difference was noticed in univariate analysis, although very close to statistical significance (p=0.065). Therefore, it is speculated that application of irradiation dose 50 Gy may obtain a higher pCR rate if the sample size is enough.

Studies have revealed that the regression rate of rectal cancer patients with hemoglobin ≥90 g/L is overtly higher than that of those with hemoglobin <90 g/L [10,16]. In this study, the effects of pre-treatment hemoglobin ≤90 g/L and >90 g/L on pCR of preoperative CRT in patients with rectal cancer were compared, but no statistically significant difference was found (p>0.05). Also, in this study, 4 different regimens including 5-FU, capecitabine and oxaliplatin were used in concurrent chemotherapy, and univariate and multivariate analyses suggested that CRT regimens did not affect pCR. Considering that this study was a retrospective analysis, it might be related to the application of various chemotherapy regimens, changes in chemotherapy regimens during treatment and failure to strictly follow the chemotherapy cycle time.

Previous studies, especially a new model predicting the sensitivity of preoperative CRT for rectal cancer established by using gene expression profiling, have proved that molecular biomarkers such as p53, p21, cyclooxygenase-2 (COX-2), epidermal growth factor receptor (EGFR), thymidylate synthase (TYMS) and single nucleotide polymorphism (SNP) are correlated with pCR in locally advanced rectal cancer [12,18]. These results contribute to predicting the efficacy of preoperative

neoadjuvant therapy. It is believed that combining clinical factors, imaging factors and molecular markers (including TYMS and SNPs) with gene expression profiling in the future could more accurately predict the efficacy of neoadjuvant therapy, thus realizing individualized treatment of locally advanced rectal cancer.

Conclusions

CEA before CRT, T stage before CRT, interval between the end of CRT and surgery, maximum depth of tumor invasion before CRT and ADC value before CRT and its growth rate are the factors determining whether pCR is achieved via neoadjuvant therapy for locally advanced rectal cancer. Low-level CEA before CRT and long interval between the end of CRT and surgery are predictive factors for pCR after neoadjuvant therapy for locally advanced rectal cancer, but low-level CEA is only effective in the prediction of pCR in non-smokers.

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Conflict of interests

The authors declare no conflict of interests.

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