Original Article

Good response to neoadjuvant chemoradiotherapy predicts good oncological outcome in locally advanced rectal cancer

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Background: After pre-operative concurrent long course chemoradiotherapy (CRT), pathologic complete response (pCR) has been reported with better oncologic outcomes in many articles, whether a moderate response (TRG1) can translate into good clinical outcome remains uncertain.

Methods: A total of 132 locally advanced rectal cancer patients with neoadjuvant chemoradiotherapy followed by radical surgery were recruited. Their clinicopathologic characteristics and clinical records were retrospectively reviewed. The association between clinicopathologic parameters and pathological response was conducted, and the multivariable analysis of the association between pathologic response and survival was performed.

Results: With a median follow-up of 21.5 months, gender was the only factor associated with pCR (TRG0), while dual-agent chemotherapy regimen was linked with a lower likelihood of good response (TRG0-1). Good response (TGR0-1) remained significant associated with overall survival (OS) and disease-free survival (DFS) after multivariate adjustment. TRG1 was linked with better DFS compared with TRG2-3.

Conclusions: Patients with post-CRT good response (TRG0-1) demonstrate an excellent local and remote control, especially with those non-pCR patients (TRG1) getting better outcomes.

Keywords: Locally advanced rectal cancer (LARC); neoadjuvant chemoradiotherapy; tumor regression grade; clinical outcomes

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Introduction

Neoadjuvant chemoradiotherapy (CRT) followed by total mesorectal excision has become the standard treatment for patients with locally advanced rectal cancer (LARC). Neoadjuvant CRT is related to preferable locoregional control and lower therapy compliance compared to postoperative CRT (1). Nowadays, most authorities have recommended the form of concurrent long-course CRT (2-4), either concurrent with 5-fluorouracil (5-FU) or Capecitabine (5), especially in patients with threatened or involved mesorectal fascia (MRF), tumor with adjacent organ invasion or low position tumor. The tumor pathological response to the CRT is evaluated by tumor regression grade (TRG) (6), which is a semi-quantitative scoring of the relative proportion of residual tumor to

stromal fibrosis. Several studies have reported a higher rate of pathological complete response (pCR) of tumor (10–30%) using neoadjuvant chemotherapy with radiation (7,8). Patients who have achieved a pCR are associated with an improved long-term outcome (9,10). Habr-Gama (11) has supported a non-operative policy "watch and wait" in those patients with clinical complete response whose local failure rate was reported only 3% (12). What's more, a near pCR, moderate response (TRG1), can possibly translate into much better clinical outcomes after surgery compared to those who remain massive residual tumor in the resected specimens. The aim of this retrospective study was to investigate the predictors of clinicopathologic parameters and treatment-related variables on tumor regression grade, disease-free survival (DFS), and overall survival (OS).

Methods

Patients

The retrospective study enrolled consecutive patients undergoing preoperative CRT and curative resection from March 2014 to December 2017 at People's hospital of Jiangsu Province, People's Republic of China. Tumor stage was evaluated using a combination of colonoscopy, chest and abdominal enhanced CT, and pelvic enhanced MRI before CRT, according to 7th American Joint Committee on Cancer staging system (AJCC) TNM staging system. The enrolled patients met the inclusion criteria: (I) patho-histologically confirmed adenocarcinoma; (II) T3–4 or N+ disease in initially; (III) received preoperative CRT followed by radical resection. Patients were excluded if they harbored metastatic disease before or during preoperative treatment or died within 1 month postoperatively. The demographics, preoperative treatment, primary tumor characteristics, and follow-ups were reviewed in details.

This study was approved by the Ethics Committee of Jiangsu Province People's Hospital, in accordance by the Helsinki Declaration. Written informed consent was required for participation.

Treatment

A total of 50.0–50.4 Gy was delivered in 1.8–2.0 Gy per daily fractions to the pelvic area without tumor gross bonus. Concurrent chemotherapy regiments were classified into: Capecitabine 825 mg/m^2 bid D1–5 qw; Oxaliplatin 50 mg/m^2/qw + Capecitabine 625 mg/m^2 bid D1–5 qw; CPT-11 80 mg/m^2/qw + Capecitabine 625 mg/m^2 bid D1–5 qw. Radical surgical resection was conducted several weeks after completing CRT. The TME surgery procedure was mainly including Dixon, Miles, Hartmann, and so on. The resected specimens were reviewed by two experienced pathologists. The ypT stages of specimens and the tumor regression grade were evaluated on the basis of the 7th AJCC TNM staging system (13): (I) complete response (TRG score 0), no viable cancer cells; (II) moderate response: (TRG score 1), single cells or small groups of cancer cells; (III) minimal response: (TRG score 2), residual cancer outgrown by fibrosis and; (IV) poor response: (TRG score 3), minimal or no tumor kill.

Follow-up

Patients were either reviewed in outpatients or contacted by telephone every three months for the first 2 years after surgery, and every 6 months for the next 3 years. Chest, abdominal or pelvic CT, and pelvic MRI were performed every 6 months, and colonoscopy was conducted annually during follow-up. Overall survival was defined as the interval from surgery to the date of death or last follow-up, and DFS was defined as the time from surgery to the date of disease recurrence or last follow-up. Follow-up statistics were reviewed by February 28, 2018.

Statistical analysis

The statistical analysis was performed by the IBM SPSS Statistics 22.0 software (Chicago, IL, USA) and GraphPad Prism 5 software (San Diego, CA, USA). Continuous variables were evaluated by the parametric Student's *t*-test, while categorical variables were compared by the Chi-square test or Fisher's exact test. DFS and OS were calculated in the Kaplan-Meier model and comparisons were analyzed by Cox regression analysis. Variables that were significant in univariate analysis were applied to multivariate Cox regression analysis. Two-tailed $P \leq 0.05$ was considered statistically significant.

Results

Patient demographics

One hundred and forty-one LARC patients were accepted neo-adjuvant therapy, while 5 patients failed to operate due to extensive peritoneal or visceral metastasis, and 4 patients were only conducted palliative colostomy for local gross tumor. One hundred and thirty-two individuals finally

proceed to surgical operation, 62.1% (82/132) were males and 37.9% (50/132) were females. 95.5% of patients were T3–4 stage and 89.3% of patients were node positive. The median age was 58 years (range from 22 to 80), and the median interval days from the end of radiotherapy to surgery was 61 days (range from 29 to 122). Forty-four patients underwent Miles operation, 6 patients underwent Hartmann procedure and 82 patients were received Dixons, of whom 26 patients were given colostomy in preventing anastomotic leakage. Median follow-up time was 21.5 months (range from 1 to 38). Baseline characteristics are listed in *Table 1*.

Factors associated with pathologic response

Among the patients 19.7% (26/132) had gotten pCR (TRG0) and 19.7% (26/132) had gotten moderate response (TRG 1). Fifty-six point one percent (74/132) patients was observed with minimal response (TRG 2) and 4.5% (6/132) patients were diagnosed with response (TRG 3). Eight patients with the pCR and twenty with the TRG1 had a primary cT4 tumor, which were both classified as good response. Of note: 12 of 26 (46.2%) pCR patients previously had mesorectal lymph node metastases. No pre-treatment factors (age, cT, cN, type of pathology) but gender was significantly associated with pCR (P=0.001). Among treatment factors, good response occurred more frequently in those treated with combined dual-agent chemotherapy (P=0.048).

Toxicity

The combined incidence of grade 3–4 acute radiotherapy toxicity to the skin and bowel toxicity was 9.1%. In terms of grade 3 or above late radiotherapy toxicity to the bowel, and urinary tract was 10.6%. For grade 3 or above myelosuppression, the incidences of neutropenia, anemia, and thrombocytopenia were 10.6%, 2.27%, and 1.5%, respectively. The most common non-hematological grade 3 or above acute toxicity was diarrhea (5.7%). With regard to surgical complications, there were 10 patients (7.6%) with delayed wound healing, 10 patients (7.6%) with anastomotic leakages, 4 patients (3.0%) with anastomotic stenosis, and 3 patients (2.3%) with post-operative ileus. Thirty-day postoperative mortality was barely reported.

Survival

With a median follow-up period of 21.5 months, 107 (81.1%) patients were being alive, and 100 patients (75.8%) were free of recurrence or metastasis, and others (5.3%) suffered from distant metastasis and underwent anti-cancer therapy. Twenty-two patients (16.7%) were died of tumor progress (3 local recurrence only), and 5 patients (3.8%) were died of other causes. Univariate analyses for OS have shown that cN2, pathologic pattern, operative procedure and tumor regression grade were statistically significant, but after multivariate adjustment, only TRG remained significant (HR =0.306, 95% CI: 0.096–0.976, P=0.045) (*Table 2* and *Figure 1* shown). Univariate analysis revealed that pathological T stage, and TRG could potentially influence DFS, but only TRG (HR =0.257, 95% CI: 0.103–0.643, P=0.004) remained significant after multivariate adjustment (*Table 2* and *Figure 1D* shown). There was no significant DFS and OS between pCR and non-pCR in (*Figure 1A,C* shown). We also compared the OS and DFS between TRG0, TRG1 and poor response (TRG2/3). The DFS between TRG1 and TRG2/3 was statistically significant (HR =0.397, 95% CI: 0.159–0.993, P=0.048), but not in OS. No significant differences in OS and DFS between TRG0 and TRG1 (*Table 3* shown).

Discussion

Short-term therapeutic efficacy

Neo-adjuvant CRT followed by radical surgery is the current standards for local advanced rectal cancer. The combination of chemotherapy and radiation has been proved to further improve tumor downstage in an effort to increase surgical resection and the pCR rate more than with preoperative radiation alone. Recent studies have shown the pCR rate range from 14% to 28% (14-18), and our study got a similar pCR rate of 19.7%. We also discovered a same proportion about 19.7% of near pCR (TRG1). These patients with better tumor regression can obtain an effort to maximize surgical resection of previous marginal and unresectable tumors, which can effectively reduce the local recurrence.

In the clinic, post-CRT MRI is routinely used to investigate the tumor regression compared with pre-CRT MRI by Dworak's standard. Cui Y has utilized pre-treatment radiomics analysis of multiparametric MRI for prediction of pCR after neoadjuvant CRT (19). However, we still encounter over-stage in post-CRT MRI. It has been suggested that MRI is often difficult to differentiate between viable tumor, residual fibrotic non-tumor tissue, and desmoplastic reaction, resulting in poor agreement

Table 1 Baseline characteristics were listed

Clinical characteristics	Total	Complete response			Good response		
		pCR	non-pCR	P	TRG0-1	TRG2-3	P
Gender				0.001*			0.199
Female	50	18	32		24	26	
Male	82	8	74		32	50	
Age (year, median)	58 [22–80]						
T stage before CRT				0.566			0.789
cT2	6	2	4		2	4	
cT3	76	14	62		34	42	
cT4	50	10	40		20	30	
N stage before CRT				0.858			0.967
cN0	14	2	12		6	8	
cN1	54	10	44		22	32	
cN2	64	14	50		28	36	
Anal edge distance	2–11 cm						
Pathological pattern				0.807			0.967
Adenocarcinoma	98	20	78		48	50	
Mucinous	34	6	28		8	26	
Circumferential involvement				0.632			0.325
≤1/2	36	8	28		18	18	
>1/2	96	18	78		38	58	
Chemotherapy				0.148			0.048*
Single-agent	36	4	32		10	26	
Dual-agents	96	22	74		46	50	
Interval (day, median) CRT to surgery	61 [29–122]			0.643			0.709
≤8 weeks	44	10	34		20	24	
>8 weeks	88	16	72		36	52	
Operative procedure				0.746			0.005*
Miles	44	10	34		20	24	
Dixon	56	10	46		30	26	
Dixon with preventive colostomy[a]	26	6	20		6	20	
Hartmann	6	0	6		0	6	

*, P<0.05. CRT, chemoradiotherapy; TRG, tumor regression grade.

Table 2 Univariable and multivariable associations between clinical outcomes (OS and DFS) and tumor regression grade (TRG)

Clinical characteristics	OS		DFS	
	HR (95% CI)	P	HR (95% CI)	P
Univariate				
Gender				
Female	0.563 (0.220–1.440)	0.231	0.940 (0.459–1.926)	0.867
Male	1.00		1.00	
Age	1.004 (0.948–1.042)	0.822	0.988 (0.960–1.017)	0.413
T stage before CRT				
cT2	1.00		1.00	
cT3	1.498 (0.308–7.286)	0.616	2.015 (0.641–6.336)	0.231
cT4	0.874 (0.356–2.147)	0.769	0.851 (0.402–1.803)	0.674
N stage before CRT				
cN0	1.00		1.00	
cN1	0.350 (0.078–1.564)	0.169	0.903 (0.300–2.719)	0.857
cN2	0.278 (0.103–0.752)	0.012*	0.685 (0.321–1.464)	0.329
Pathological pattern				
Adenocarcinoma	0.353 (0.152–0.819)	0.015*	0.494 (0.241–1.012)	0.054
Mucinous	1.00		1.00	
Circumferential involvement				
≤1/2	0.562 (0.189–1.668)	0.299	1.231 (0.582–2.605)	0.587
>1/2	1.00		1.00	
Interval (CRT to surgery)				
≤8 weeks	0.730 (0.289–1.841)	0.505	0.962 (0.461–2.007)	0.918
>8 weeks	1.00		1.00	
Chemotherapy				
Single agent	1.325 (0.506–3.472)	0.567	1.304 (0.615–2.766)	0.489
Dual agents	1.00		1.00	
Operative procedure				
Miles	1.00		1.00	
Dixon	0.171 (0.034–0.870)	0.033*	0.538 (0.121–2.392)	0.416
Hartmann	0.198 (0.043–0.908)	0.037*	0.330 (0.075–1.451)	0.142
Pathological response				
pCR	0.388 (0.090–1.664)	0.202	0.493 (0.173–1.407)	0.186
non-pCR	1.00		1.00	
Tumor regression				
TRG0–1	0.226 (0.077–0.670)	0.007*	0.229 (0.094–0.558)	0.001*
TRG2–3	1.00		1.00	

Table 2 *(continued)*

Table 2 *(continued)*

Clinical characteristics	OS		DFS	
	HR (95% CI)	P	HR (95% CI)	P
N stage after CRT				
pN0	1.00		1.00	
pN1	0.895 (0.201–3.978)	0.884	0.224 (0.087–0.581)	0.002*
pN2	1.262 (0.229–6.951)	0.789	0.941 (0.338–2.622)	0.907
Multivariable				
Tumor regression	0.306 (0.096–0.976)	0.045*	0.257 (0.103–0.643)	0.004*
N stage before CRT	0.411 (0.142–1.192)	0.102	0.536 (0.212–1.355)	0.188
Pathological pattern	0.620 (0.230–1.672)	0.345	–	–
Operative procedure			–	–
Miles	1.00			
Dixon	0.266 (0.044–1.625)	0.152		
Hartmann	0.394 (0.075–2.065)	0.270		

*, P<0.05. CRT, chemoradiotherapy.

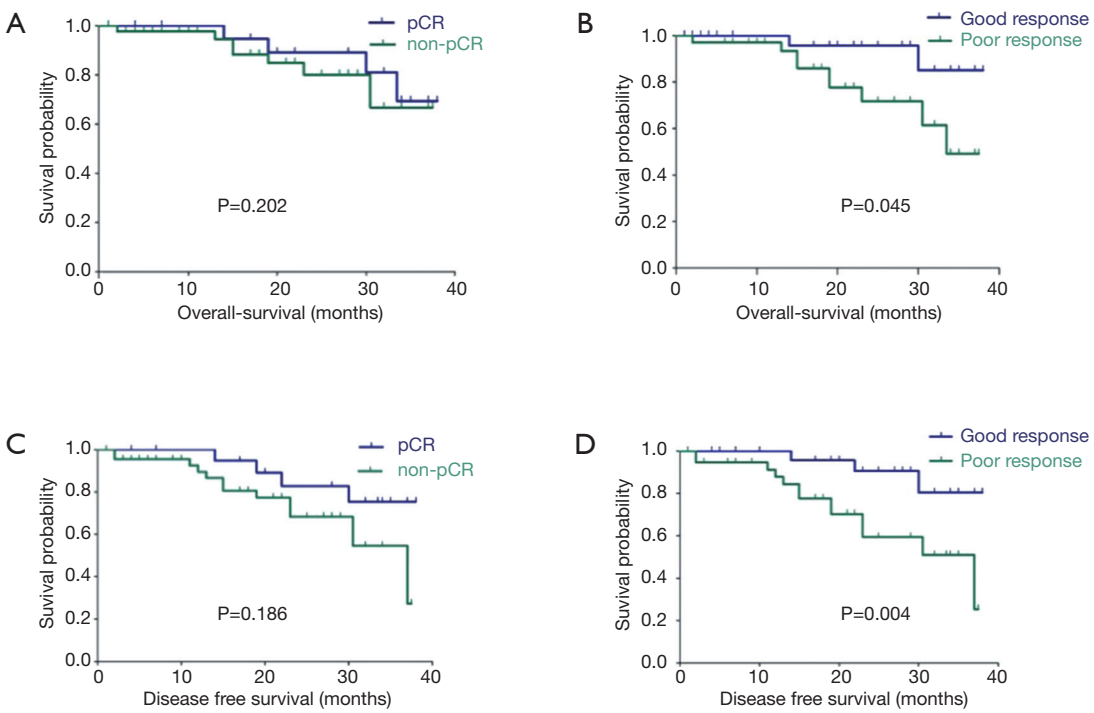

Figure 1 Oncologic outcomes according to tumor regression grade. (A) The comparison in OS between pCR and non-pCR patients (P=0.202); (B) the comparison in OS between patients with good response (TRG0-1) and poor response (TRG2-3) (P=0.004); (C) the comparison in DFS between pCR and non-pCR patients (P=0.186); (D) the comparison in DFS between patients with good response (TRG0-1) and poor response (TRG2-3) (P=0.045).

Table 3 Multivariable associations between clinical outcomes (OS and DFS) and tumor regression grade (TRG).

Tumor regression	OS		DFS	
	HR (95% CI)	P	HR (95% CI)	P
TRG0 *vs.* TRG1				
TRG0	1.118 (0.157–7.961)	0.911	0.953 (0.134–6.772)	0.962
TRG1	1.00		1.00	
TRG1 *vs.* TRG2-3				
TRG1	0.476 (0.181–1.250)	0.132	0.397 (0.159–0.993)	0.048*
TRG2-3	1.00		1.00	
TRG0 *vs.* TRG2-3				
TRG0	0.024 (0.00–3,742.4)	0.540	0.582 (0.00–9,275.2)	0.582
TRG2-3	1.00		1.00	

*, P<0.05.

between MRI staging and pathologic staging in both T and N stages (20). To avoid the bias we evaluated tumor regression grade according to 7th AJCC neo-adjuvant pathologic stage.

Numerous retrospective studies have previously identified various disease-related variables as potential predictors of pCR, which included tumor size, pre-treatment T/N category, cytotoxic therapy, low tumor grade and so on. In our study we only found significance between gender and pCR with limited clinical and pathologic data.

Only few patients can achieve a pCR, a strict pathologic remission. We found that some patients with near pCR (TRG1) had a survival and local control approximate to those with a pCR (21-23). Conversely, some papers have reported these patients with near pCR had unexpectedly poor outcomes (DFS or OS) and harbored nodal metastases, which was corresponding to those poor responders at all (24,25). In our study, we classified TRG0-1 with ypN0 as good responder, and discovered dual-drug chemotherapy related to better tumor shrinkage. But no difference was found between the two dual-agent regimens. It has been observed that combinations such as 5-FU/Oxaliplatin or Irinotecan/5-FU have higher response rates than single agents such as 5-FU alone (26), which consists with our results. While increased gastrointestinal, mucosal, and hematologic toxicity were observed in the dual-drug group, especially grade 3 or above of neutropenia and acute diarrhea. It was recently reported a retrospective cohort study based on 2,094 patients that lengthening the interval (>13 weeks) from CRT to surgery improves the pathological response (27). However, we didn't find a longer interval translated into an increase in pCR (TRG0) or near pCR (TRG1) rate. It was considered that insufficient number of cases and a higher proportion of N2 patients in the long interval group weak the tumor shrinkage. However, we observed higher surgical morbidity about delayed incision healing and anastomotic haemorrhage in shorter interval group due to radiotherapy induced tissue swelling and inflammation (28,29). Furthermore, surgeons found soft tissue fibrosis and friability in most of patients after neoadjuvant CRT, while the fibrosis did not translate into a significantly increased technical difficulty of operation or postoperative complications.

Long-term survival

The median follow-up time is 21.5 months, as most patients with progressive disease suffered from distance metastasis rather than local relapse. Most recurrences occurred within the first 2 years, and distant metastasis became the dominating outcome, which developed up to 73.3% in progressive patients. Although pathologic pattern, N stage before CRT, tumor regression, operative procedure and N stage after CRT were shown an association with DFS or OS, only tumor regression grade was a potential factor for OS and DFS after multivariate adjustment.

Tumor regression grade has been implemented to predict oncologic outcomes in many articles with inconsistent results, probably due to the lack of uniform pathologic response evaluation or definitions for TRG. A systematic

review has demonstrated the prognostic value of TRG in predicting long-term survival (DFS and OS) (30).

In our study patients with pCR having 1-year DFS of 100%, compared to those with non-pCR of 89.5%. These results reflect an outcome similar to that in other studies where patients having pCR have excellent outcomes (31). The 1-year DFS were 100% in patients with good response (TRG0-1), compared to those with poor response (TRG2-3) of 88.0%, which supported the fact that TRG 0-1 own the similar survival and local control to those with a pCR. We postulated that our data reflected prognosis more accurately in patients with T3 with risk factors, T4 and/or N2 disease, treated with neoadjuvant CRT. Also, our cohort contained patients with advanced diseases, the inclusion criteria is also the reason for the different survival figures. However, our subgroup with a pCR unexpectedly could not predict statistically better long-term outcomes. It was retrospectively found two patients with pCR had distant metastasis in the short term and died soon (14 and 13 months after surgery), which exceptionally effected the long-term survival of pCR group. The possible reasons were that both patients might already have had simultaneous metastasis before CRT with insufficient intensity of chemotherapy regimen and the tumor was sensitive to radiation but strongly invasive and metastatic. And the follow-up time is limited, the survival advantage of pCR may be not yet reflected. TRG1 has better local and remote control in DFS compared with TRG2-3, leading to the non-pCR group has obtained a better outcome. It strongly supported that TRG1 could demonstrate an excellent local and remote control among this partial non-pCR group.

Limits in our study are obvious and need to be improved, including lack of postoperative CRM status, deficiency of follow-up time and missing information of adjuvant chemotherapy. We lack CRM status in some of our pathological specimens, which has been shown an independent prognostic factor, predicting local recurrence, distant metastasis and OS (32). The long-term result from EORTC 22921 and similar studies showed that adjuvant chemotherapy after preoperative radiotherapy did not affect DFS or OS in cT3–4 resectable rectal cancer (33). However, studies have shown that adding oxaliplatin to adjuvant and/or neo-adjuvant treatment can improve DFS (34,35). In our study, we didn't mention the relationship between adjuvant chemotherapy and survival for the insufficient follow-up.

In conclusion, neoadjuvant CRT for LARC patients is effective and leads to an acceptable outcome. Tumor regression after CRT is the most significant prognostic factor in OS and DFS, after multivariate adjustment. Pathologic assessment of tumor regression, better tumor regression (TRG0-1) after CRT can also be used to predict the oncologic outcomes amongst other factors.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2019.01.17). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the Ethics Committee of Jiangsu Province People's Hospital, in accordance by the Helsinki Declaration (as revised in 2013). Written informed consent was required for participation.

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