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Original Article

Tumor regression grade in locally advanced rectal cancer after neoadjuvant chemoradiotherapy: influencing factors and prognostic significance

Xingang Lu[1], Ruihua Qi[1], Ying Xu[1], Xiao Wang[1], Yibo Cai[2], Chunliang Wang[1]

[1]*Department of Colorectal Surgery, The First People's Hospital of Fuyang, Hangzhou 310022, Zhejiang, China;*
[2]*Department of Colorectal Surgery, Zhejiang Cancer Hospital, Hangzhou 310022, Zhejiang, China*

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Abstract: Objective: The extent of tumor regression varies widely among patients who receive neoadjuvant chemoradiotherapy (NACRT) followed by total mesorectal excision (TME) surgery. We evaluated the tumor regression grade (TRG) classification of patients and analyzed factors related to TRG and its value in predicting prognosis in locally advanced rectal cancer (LARC). Methods: This study retrospectively analyzed the clinicopathologic data of 269 consecutive patients with LARC treated from February 2002 to October 2014. The grade of TRG was based on the extent of primary tumor replaced by fibrosis. Clinical characteristics and relative survival were retrospectively analyzed. Results: There were 269 patients, among whom 67 patients (24.9%) achieved TRG0, whereas 46 patients (17.1%) showed TRG3. TRG1 and TRG2 were both found in 78 patients (29.0%). Clinicopathologic factors that were related to TRG included post-NACRT carcinoembryonic antigen (CEA) level (P=0.002), clinical T stage (P=0.022), pathologic T stage (P<0.001) and pathologic lymph node status (P=0.003). The 5-year overall survival (OS) was 74.6%, 55.1%, 47.4%, 28.3% for TRG0, TRG1, TRG2, TRG3, respectively (P<0.001). The 5-year disease-free survival (DFS) was 64.2%, 47.4%, 37.2%, 23.9% for TRG0, TRG1, TRG2, TRG3, respectively (P<0.001). Based on multivariate analysis, TRG was a significant predictor for both OS (P=0.039) and DFS (P=0.043). Conclusion: Clinicopathologic factors such as post-NACRT CEA level, clinical T stage, pathological T stage and pathological lymph node status are significantly associated with TRG. TRG is an independent predictor of survival. Therefore, it is reasonable to include the TRG for clinicopathologic assessment.

Keywords: Tumor regression grade, prognosis, locally advanced rectal cancer, neoadjuvant chemoradiotherapy

Introduction

Currently, the standard treatment of locally advanced rectal cancer, (LARC) is neoadjuvant chemoradiotherapy (NACRT) followed by total mesorectal excision (TME) surgery [1, 2]. The consensus is that NACRT is beneficial to the improvement of local control of the tumor and patient survival [3]. However, this requires tumors to have a good response to NACRT. Different patients respond differently to NACRT, from no response to complete response [4]. Therefore, it is crucial to accurately assess the response of patients to NACRT. The most commonly used method for assessing the tumor response is TNM downstaging and this is considered a favorable predictor of prognosis [5]. However, this approach has its limitations. For example, T stage involves only the depth of tumor invasion (i.e. the depth of tumor infiltrating to the intestinal wall), without taking the extent of remaining tumor into consideration. However, when a tumor is stage T2, after NACRT, even if only a small amount of tumor cells remain in the superficial muscle layer, the stage is still T2. That implies the tumor did not respond to NACRT, which is not in line with reality [6]. Tumor regression grading (TRG) has been an alternative method to evaluate the response of tumor to NACRT, and was first used by Mandard in 1994 for evaluating the response of esophageal cancer to preoperative chemoradiation [7]. Inspired by him, many scholars have applied TRG to other tumors to explore the accuracy of TRG in assessing tumor regression and patient prognosis [8, 9]. Although it has

been reported that TRG is associated with distant metastasis and disease-free survival (DFS) in colorectal cancer [10, 11], whether TRG can effectively predict prognosis remains to be confirmed. In addition, due to the coexistence of multiple TRG systems, no system is currently used as the gold standard, and the American Joint Committee on Cancer (AJCC) Staging Manual TNM system is widely used for the staging of rectal cancer. Therefore, based on the homogeneity of the data, the AJCC-TRG system was selected in this study.

Materials and methods

Patients

This study was approved by the Institutional Review Board at the First People's Hospital of Fuyang. We enrolled 269 patients who underwent NACRT followed by TME surgery in our hospital from February 2002 to October 2014. The following inclusion criteria were adopted: 1. Rectal cancer was confirmed by 2 experienced pathologists through colonoscopic biopsy. 2. All patients were diagnosed with stage II or III through the lower abdomen or pelvic computed tomography (CT), pelvic or rectal magnetic resonance imaging (MRI), or endorectal ultrasonography (ERUS). 3. The location of the tumor was within 12 cm of the anal verge.

Treatment

All patients underwent preoperative pelvic radiotherapy with a total dose of 46 to 50.4 Gy in 28 fractions to the primary tumor, together with a concomitant daily oral intake of Xeloda. After radiotherapy, they received 1-2 cycles of XELOX/FOLFOX4 regimen chemotherapy or continue oral Xeloda. Then, after 6-8 weeks of rest, TME surgery was performed on each of the patients. All curative specimens were evaluated by 2 pathologists blinded to treatment data.

AJCC TRG system

Due to the widespread use of the American Joint Committee on Cancer (AJCC) TNM staging system, the AJCC-TRG system was used in this study to ensure the homogeneity of data despite the existence of multiple TRGs [12, 13]. The 4-tier AJCC-TRG system is shown (**Figure 1**) [14]: TRG0, no residual tumor cells; TRG1, single cells or small groups of cells; TRG2, residual cancer with desmoplastic response; TRG3, minimal evidence of tumor response.

Follow-up

The patients were reviewed every 3 months for the first two years after surgery, then, every 6 months for the next 3 years, and finally, the review frequency of patients was lengthened to once per year. The review projects included digital rectal examination, blood routine examination, liver function test, serum CEA and CA199 tests, chest radiograph, abdominal CT, rectum MR, colonoscopy, and positron emission tomography/computed tomography (PET/CT). All patients received these tests according to their actual condition.

Statistical analysis

All the data of the patients were dichotomized or multi-categorized and chi-square test or Fisher's exact test were used for analysis as appropriate. The overall survival (OS) and the disease-free survival (DFS) were analyzed using the Kaplan-Meier method through univariate analysis. The factors that were significant by the univariate analysis were included in the proportional hazards model. Two-sided $P<0.05$ was considered significant. All statistical analyses were performed using SPSS software, version 23.0.

Results

Patients

We retrospectively analyzed the data of 269 patients who were diagnosed with locally advanced rectal cancer and received preoperative CRT following by TME surgery. Among them, there were 189 males (70.3%) and 80 females (29.7%). The average age was 52.7 ± 11.5 (23-80). Overall, 67 patients (24.9%) achieved no residual tumor cells in the resection specimen (TRG0), whereas 46 patients (17.1%) showed minimal evidence of tumor response (TRG3). The numbers of patients diagnosed with TRG1 and TRG2 were both 78 (29.0%).

The association between TRG and different clinicopathologic factors

Table 1 shows the association of TRG with different clinicopathologic factors. The number

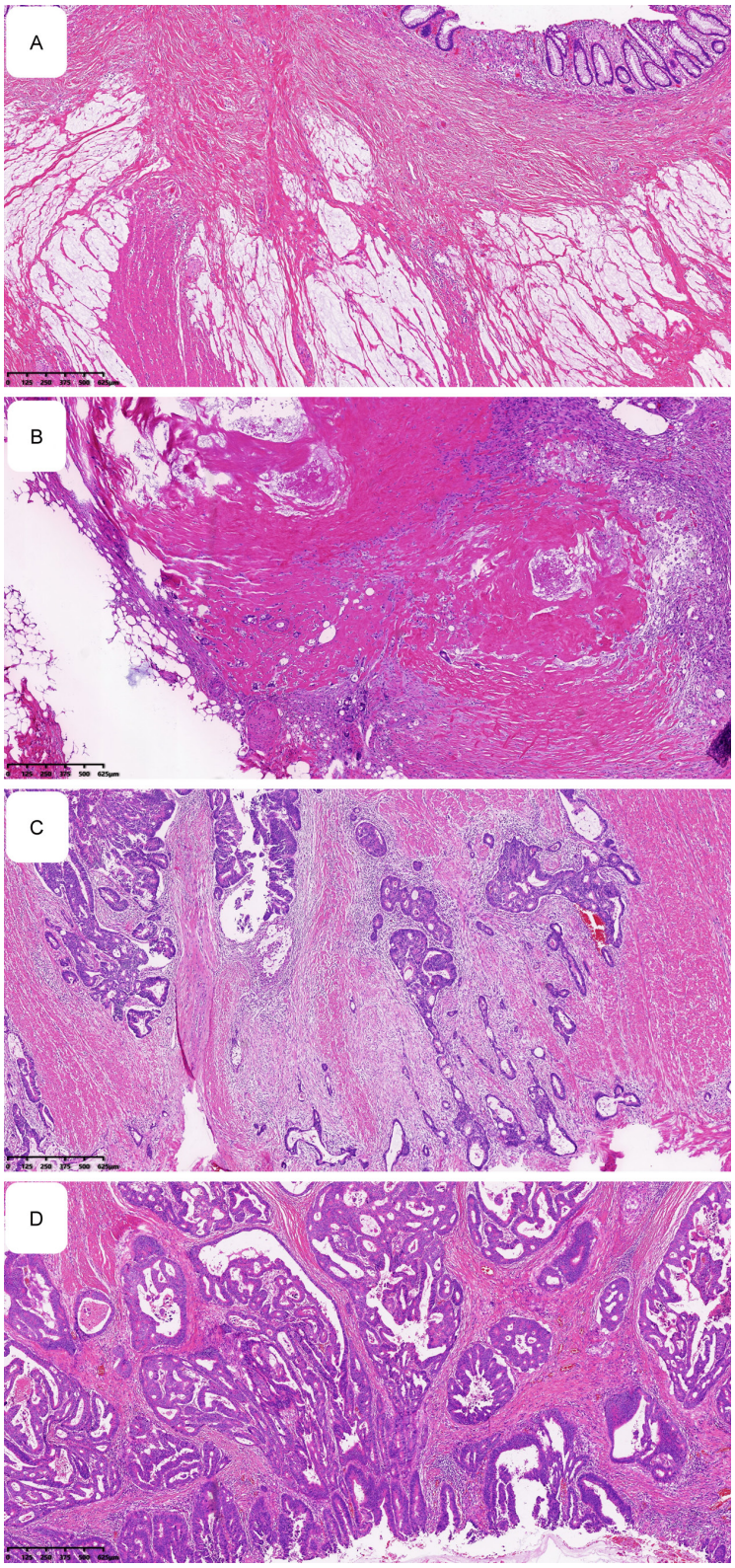

Figure 1. Tumor regression grading (TRG): A. TRG 0, no residual tumor cells; B. TRG 1, single cells or small groups of cells; C. TRG 2, residual cancer with desmoplastic response; D. TRG 3, minimal evidence of tumor response. Original magnification, ×200.

and proportion of patients at all levels of TRG were as follows: TRG0 (67, 24.9%), TRG1 (78, 29.0%), TRG2 (78, 29.0%), TRG3 (46, 17.1%). Age, gender, tumor location, chemotherapy regimens, pre-NACRT CEA levels and clinical lymph nodes status were all not significantly related to TRG. Patients with an elevated (>5 ng/mL) post-NACRT CEA level were more likely to have a poor tumor regression (71.4% for TRG2+3) than those with post-NACRT CEA≤5 ng/mL (42.3% for TRG2+3) (P=0.002). Additionally, both clinical T status (P=0.022) and pathologic T status (P<0.001) could significantly predict TRG. Pathologic N status was predictive of tumor regression after NACRT (P=0.003). Compared to patients with positive lymph nodes, those with negative lymph nodes (N1, 8.1%, N2, 17.6%) had a greater chance to reach TRG0 (32.4%).

TRG as a prognostic factor for OS and DFS

The 5-year OS rate and 5-year DFS rate for 269 patients who received NACRT followed by TME surgery were 53.2% and 44.6%, respectively. As listed in **Table 2**, by univariate analysis, TRG was a significant predictor for patient survival outcome (**Figures 2**, **3**). The 5-year OS rate for TRG3 was 28.3% and the 5-year OS rate of any degree of TRG was higher than TRG3: TRG2, 47.4%; TRG1, 55.1%; TRG0, 74.6% (P<0.001). The 5-year DFS also showed the same trend (23.9%, 37.2%, 47.4%, 64.2% for TRG3, TRG2, TRG1, TRG0, respectively, P<0.001). Furthermore, the post-NACRT CEA level, pathologic T status, and pathologic N status were also strong predictors of

Table 1. Association of TRG with different clinicopathologic factors

Factor	TRG0 (n=67)	TRG1 (n=78)	TRG2 (n=78)	TRG3 (n=46)	Total (n=269)	P
Gender						0.066
Male	43	49	62	35	189	
Female	24	29	16	11	80	
Age (years)						0.387
<60	50	58	51	36	195	
>60	17	20	27	10	74	
Tumor location (cm)						0.456
<5	45	42	49	26	162	
5-10	22	34	28	18	102	
>10	0	2	1	2	5	
Differentiation						0.273
Well-differentiated	2	3	4	2	11	
Moderately-differentiated	53	61	67	42	223	
Poorly-differentiated	12	14	7	2	35	
Histologic typing						0.089
Adenocarcinoma	50	67	71	41	229	
Mucinous adenocarcinoma	13	7	6	5	31	
Signet ring cell carcinoma	4	4	1	0	9	
Chemotherapy regimens						0.694
Single-capecitabine/5-FU	5	5	9	4	23	
XELOX/FOLFOX	62	73	69	42	246	
Pre-NACRT CEA (ng/mL)						0.503
$<5*10^{-6}$	30	34	39	26	129	
$>5*10^{-6}$	37	44	39	20	140	
Post-NACRT CEA (ng/mL)						0.002
$<5*10^{-6}$	62	73	66	33	234	
$>5*10^{-6}$	5	5	12	13	35	
Clinical T stage						0.022
T2	2	0	0	0	2	
T3	25	39	25	12	101	
T4	40	39	53	34	166	
Clinical N stage						0.449
N0	31	36	33	15	115	
N+	36	42	45	31	154	
Pathologic T stage						<0.001
T0	61	0	0	0	61	
T1	0	3	0	0	3	
T2	2	23	13	8	46	
T3	4	36	50	30	120	
T4	0	16	15	8	39	
Pathologic N stage						0.003
N0	56	51	42	24	173	
N1	5	16	25	16	62	
N2	6	11	11	6	34	

Abbreviation: TRG, Tumor regression grade; NACRT, Neoadjuvant chemoradiotherapy; CEA, Carcinoembryonic antigen.

OS and DFS (all *P* values less than 0.001). We incorporated all significant factors from the univariate analysis into the multivariate analysis model (**Table 3**). TRG proved to be an indepen-

Table 2. Univariate analysis of different variables on OS and DFS

Clinical/Pathologic factor	No.	5-y OS %	P	5-y DFS %	P
All	269	53.2		44.6	
Gender			0.470		0.239
Male	189	51.9		40.7	
Female	80	56.3		53.8	
Age (years)			0.056		0.090
<60	195	48.7		41.5	
>60	74	64.9		52.7	
Tumor location (cm)			0.792		0.777
<5	162	51.9		43.2	
5-10	102	55.9		47.1	
>10	5	40.0		40.0	
Differentiation			0.178		0.154
Well-differentiated	11	72.7		63.6	
Moderately-differentiated	223	53.4		45.7	
Poorly-differentiated	35	45.7		31.4	
Histological typing			0.914		0.657
Adenocarcinoma	229	54.1		45.4	
Mucinous adenocarcinoma	31	48.4		41.9	
Signet ring cell carcinoma	9	44.4		33.3	
Chemotherapy regimens			0.455		0.583
Single-capecitabine/5-Fu	23	43.4		43.5	
XELOX/FOLFOX	246	54.1		44.7	
Pre-NACRT CEA (ng/mL)			0.060		0.060
$<5*10^{-6}$	129	58.1		50.4	
$>5*10^{-6}$	140	48.6		39.3	
Post-NACRT CEA (ng/mL)			<0.001		<0.001
$<5*10^{-6}$	234	57.3		47.4	
$>5*10^{-6}$	35	25.7		25.7	
Clinical T stage			0.176		0.168
T2	2	0		0	
T3	101	55.4		49.5	
T4	166	52.4		42.2	
Clinical N stage			0.213		0.120
N0	115	58.3		48.7	
N+	154	49.4		41.6	
Pathologic T stage			<0.001		<0.001
T0	61	78.7		68.9	
T1	3	66.7		33.3	
T2	46	76.1		71.7	
T3	120	40.0		29.2	
T4	39	25.6		23.1	
Pathologic N stage			<0.001		<0.001
N0	173	64.2		55.5	
N1	62	35.5		25.8	
N2	34	29.4		23.5	
AJCC-TRG			<0.001		<0.001
TRG0	67	74.6		64.2	
TRG1	78	55.1		47.4	
TRG2	78	47.4		37.2	
TRG3	46	28.3		23.9	

Abbreviation: TRG, Tumor regression grade; NACRT, Neoadjuvant chemoradiotherapy; CEA, Carcinoembryonic antigen; OS, Overall survival; DFS, Disease-free survival.

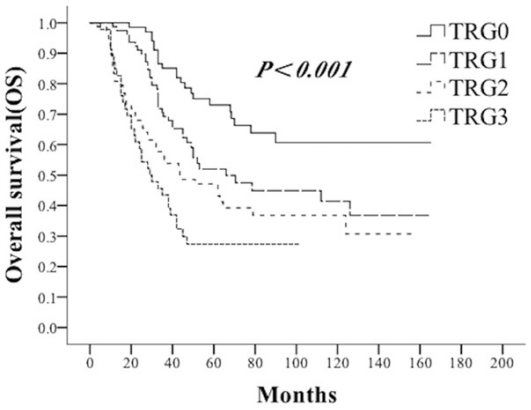

Figure 2. Overall survival of 269 patients with LARC after NACRT followed by TME surgery according to AJCC-TRG.

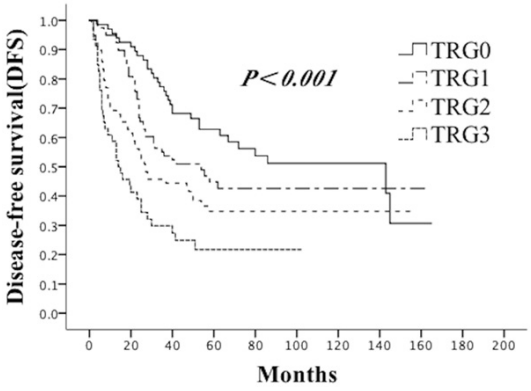

Figure 3. Disease-free survival of 269 patients with LARC after NACRT followed by TME surgery according to AJCC-TRG.

dent predictor for OS (hazard ratio [HR], 1.246; 95% confidence interval [CI], 1.012-1.534; P=0.039) and DFS (hazard ratio [HR], 1.230; 95% confidence interval [CI], 1.006-1.503; P=0.043). Other factors including post-CRT CEA (P=0.006 for OS and P=0.003 for DFS), pathological T status (P=0.004 for OS and P=0.028 for DFS), and pathological N status (P<0.001 for OS and P<0.001 for DFS), were all independent predictors for survival outcome.

Discussion

NACRT followed by TME surgery has been widely used as a standard treatment for LARC [15]. Studies have found that after NACRT, a series of changes emerged in tumor tissues, including necrosis, inflammation, and fibrosis [14]. However, the treatment response of patients varies considerably, from no tumor cell residue to no regressive change. For patients with excellent regression, some scholars have proposed the "watch and wait" strategy [16] to help them avoid invasive surgery [17]. By calculating the ratio of tumor cells to fibrosis in the tumor tissue, TRG was proposed to assess the regression of the tumor tissue after NACRT [18]. Currently, although there are differences in the understanding of whether TRG can accurately assess the survival outcome of patients, most studies have shown that TRG can accurately predict prognosis. Our study also showed that AJCC-TRG was an independent predictor of OS and DFS (P=0.039 and 0.043). At the same time, as the classification of TRG increases, the prognosis of patients gets worse. Therefore, it is reasonable to use TRG when evaluating the response to NACRT.

It has been reported in previous studies that the pre-NACRT CEA level is a significant predictor for tumor response to preoperative CRT in LARC patients. Patients with an elevated pre-NACRT CEA level (CEA>5 ng/ml) will have a poor tumor regression [19, 20], but it was found in the present study that the pre-NACRT CEA level is not associated with TRG (P=0.503). However, after further research, the post-NACRT CEA level was found significantly correlated to TRG. When CEA≤5 ng/L, patients have a greater chance to achieve good regression (P=0.002). This is consistent with experience. After NACRT, the tumor shrinks, resulting in a decrease of tumor load, so the concentration of CEA also decreases. Furthermore, we found that the post-NACRT CEA level was an independent prognostic factor for OS and DFS. This finding is meaningful in helping clinicians assess the response of tumors to NACRT and survival outcome, and thereby beneficial to the implementation of a "watch and wait" strategy [21].

In our study, we found that the pathologic T stage after NACRT was a prognostic factor compared to the clinical T stage before NACRT [22]. Moreover, the pathologic T stage was closely related to the classification of TRG. The reason might be that after NACRT, the tumor tissue undergoes a series of regressive changes, including necrosis, inflammation, and fibrosis, which are all key factors in establishing links to the survival outcome. Clinical T staging

Table 3. Multivariable analysis of different variables on OS and DFS

Factor	OS			DFS		
	HR	95% CI	P	HR	95% CI	P
AJCC-TRG	1.246	1.012-1.534	0.039	1.230	1.006-1.503	0.043
Pathologic T stage	1.296	1.008-1.543	0.004	1.199	1.020-1.409	0.028
Pathologic N stage	1.574	1.262-1.963	<0.001	1.464	1.186-1.807	<0.001
Post-NACRT CEA	1.871	1.200-2.917	0.006	1.932	1.258-2.966	0.003

Abbreviation: AJCC, American Joint Committee on Cancer; TRG, Tumor regression grade; NACRT, Neoadjuvant chemoradiotherapy; CEA, Carcinoembryonic antigen; OS, Overall survival; DFS, Disease-free survival; HR, Hazard ratio; CI, Confidence interval.

is not associated with these histopathologic changes and therefore cannot predict prognosis. Lymph node status has been reported in numerous previous studies as the strongest independent prognostic factor [23]. By our multivariate analysis, the pathologic lymph node status was also shown to be an independent predictor of prognosis and was associated with TRG. The more lymph node metastasis, the worse the tumor regression. Although no significant relationship between the clinical lymph node status and TRG and prognosis was found in our study, this may reflect the low accuracy of imaging assessment of lymph node metastasis in LARC. In terms of the strong association between the lymph node status and prognosis and TRG grading, it is necessary to accurately assess the situation of lymph node metastasis. The accuracy of lymph node status assessment is affected by the number of the removed lymph nodes. Although it is required by the current guidelines that there should be at least 12 surgically removed lymph nodes, some operations do not meet the requirements due to the factors of age, gender, tumor grade or location, surgical resection, or quality of surgery, resulting in the inaccuracy of lymph node staging.

Based on the good predictive function of TRG grading on prognosis, it is reasonable to evaluate the TRG response of patients to NACRT. However, in our study, other factors such as post-NACRT CEA level, pathologic T stage, and lymph node status were also independent predictors of prognosis. Therefore, the best way to predict the prognosis of patients after NACRT should be a combination of TRG with the above-mentioned influence factors for risk stratification of patients. The ultimate goal is to provide patients with a more precisely individualized treatment.

There are limitations in this study. First, as a retrospective study, there may be selectivity bias, so more prospective studies are needed to confirm the accuracy of the results. Also, as a single-center study, the collection of samples is not representative. In addition, our study does not address the study of lymph node TRG grading, which may be a direction for the future research. The strength of this study is the use of the AJCC-TRG system. Due to the widespread use of the AJCC-TNM staging system, the homogeneity of the data is guaranteed by using the AJCC-TRG system for analysis.

In summary, for patients with LARC undergoing NACRT, TRG can accurately predict the prognosis. Moreover. TRG is closely related to many clinicopathologic factors such as post-NACRT CEA level, pathologic T stage, and lymph node status. In the risk stratification of patients, the effects of TRG and post-NACRT CEA level, pathologic T stage and lymph node status should be fully considered in order to provide patients with individualized treatment.

Disclosure of conflict of interest

None.

Address correspondence to: Chunliang Wang, Department of Colorectal Surgery, The First People's Hospital of Fuyang, No. 429, Beihuan Road, Fuchun Street, Fuyang District, Hangzhou 310022, Zhejiang, China. Tel: +86-0571-61758042; Fax: +86-05716-3349039; E-mail: chunliangwang1973@126.com

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