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ORIGINAL ARTICLE

Effect of postoperative adjuvant chemotherapy on the prognosis of patients with ypT0-3N0 rectal cancer undergoing neoadjuvant chemoradiotherapy*

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Abstract

Objective The aim of this study was to investigate the effect of adjuvant chemotherapy (AC) on the prognosis of patients with ypT0-3N0 rectal cancer undergoing neoadjuvant chemoradiotherapy.

Methods The study participants were 110 patients with locally advanced rectal cancer. Thirty-four patients did not receive postoperative AC treatment, and the other 76 patients received postoperative AC treatment. The differences in the 5-year overall survival (OS) and disease-free survival (DFS) between the two groups were compared.

Results Age was an important determinant of the patients' decision to undergo postoperative treatment. Patients who did not receive AC treatment were significantly older than those who received AC treatment ($P < 0.05$). The tumor location (distance above anal margin) in the AC group was significantly larger than that in the non-AC group ($P < 0.05$). Moreover, there was no significant difference in the 5-year DFS and OS between the two groups. Postoperative AC did not significantly improve the prognosis of patients with rectal cancer. Age, tumor differentiation, and the number of resected lymph nodes were independent factors affecting the OS of patients ($P < 0.05$). Older patients, patients with lower degree of tumor differentiation, and patients with <12 resected lymph nodes showed worse prognosis ($P < 0.05$).

Conclusion Patients with rectal cancer whose ypT0-3N0 stage is reduced after neoadjuvant chemoradiotherapy, especially those without adverse prognostic factors, do not need AC after surgery.

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Key words: rectal cancer; postoperative adjuvant chemotherapy; neoadjuvant chemoradiotherapy; total mesorectal excision

Neoadjuvant chemoradiotherapy (NCRT) combined with radical resection is the main treatment strategy for locally advanced rectal cancer [1]. Compared with postoperative radiotherapy and chemotherapy, NCRT can effectively reduce the local recurrence rate and reduce the toxicity and side effects. NCRT can also promote tumor shrinkage and increase the success rate of sphincter preserving surgery, which helps patients undergo better functional rehabilitation [2]. The 2020 National Comprehensive Cancer Network (NCCN) ®) guidelines point out that for patients with locally advanced rectal cancer undergoing NCRT and radical surgery, a 6-month perioperative adjuvant chemotherapy (AC) should be generally implemented regardless of postoperative pathological stage [3]. However, previous studies have failed to observe the survival benefit of AC in some patients who have reached the descending stage, such as patients with ypT1-3 or ypN0 [4]. Therefore, the purpose of this retrospective study was to evaluate the need for AC in the subgroup of patients with ypT0-3N0 rectal cancer and to identify potential prognostic factors affecting recurrence and mortality in these patients.

Materials and methods

Research object

The study participants were 110 patients with locally advanced rectal cancer treated in the general surgery department of Dazhou Central Hospital from January 2010 to December 2016. The inclusion criteria were (1) age 18–70 years; (2) first definite diagnosis; (3) having received NCRT and radical surgery; (4) middle and low

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rectal cancer (< 12 cm from the anal verge); (5) pathological stage was T0–T3, with no lymph node (LN) metastasis or distant metastasis (ypT0-3N0M0). The exclusion criteria were (1) patients who died at the hospital; (2) those with incomplete clinical data or follow-up data; and (3) those who underwent intestinal surgery for other diseases. This retrospective study was approved by the ethics review committee of Dazhou Central Hospital, which waived the need for obtaining patients' informed consent. The demographic characteristics of patients and intraoperative and postoperative parameters, such as age, gender, tumor location, operation type, pathological stage, and LNs, were collected through the electronic medical record system and tumor differentiation.

Treatment protocol

All patients underwent NCRT according to the standard treatment protocol. The treatment included two courses of preoperative chemotherapy: (1) fluorouracil (5-FU) 2000 mg/m^2, calcium folinate (LV) 200 mg/m^2, intravenous drip once a day for 8 weeks; and (2) oral capecitabine (Shanghai Roche Pharmaceutical Co., Ltd., China, gyzz h20073024, specification 0.5 g), 800 mg/m^2, twice a day for 8 weeks. The irradiation dose was 180 cGy/D, divided into 25 doses. The patients received a total dose of 4500–5040 cGy within 5 weeks. The whole pelvis was treated with radiotherapy using the three-dimensional conformal radiotherapy planning system. The upper edge of the tumor bed field was the L5/S1 junction, and the lower edge was the lower edge of the sciatic tubercle. The lateral edge of radiotherapy was located 1.5 cm outside the pelvis and the posterior edge wrapped the whole sacrum. Radical resection of rectal cancer was performed 6–8 weeks after the completion of NCRT. The types of surgery included low anterior resection, abdominal resection, or sphincter preserving surgery (colostomy). Total mesorectal resection (TME) and LN resection were performed according to the following principles: (1) high/low ligation of inferior mesenteric artery (IMA), LN was resected along the vascular route; and (2) the mesorectal capsule containing the rectum and adjacent lymphovascular tissue was completely resected. The AC regimen included (1) intravenous drip of 5-FU 2000 mg/m^2 and LV 200 mg/m^2 for 24 h, once every 2 weeks for 16 weeks; and (2) capecitabine 800 mg/m^2, twice a day for 16 weeks.

Follow-up

All patients underwent regular follow-up, including physical examination, colonoscopy, and blood tests such as whole blood cell count and serum carcinoembryonic antigen levels. Patients also underwent imaging examinations such as abdominal ultrasound and chest X-ray. When recurrence was suspected, computed tomography or magnetic resonance imaging was performed.

Statistical analyses

SPSS 20.0 and GraphPad prism software (version 5.0) were used for data processing. The discrete data are expressed as the number of cases, and the continuous data are expressed as mean ± standard deviation. Disease-free survival (DFS) was defined as the time between the date of initial operation and the date of recurrence. Overall survival (OS) was defined as the date of the first operation and the time of the last visit or death. Survival was calculated using Kaplan–Meier curve. The significance of the difference among subgroups was calculated by log-rank test. Stepwise multivariate Cox regression analysis was used to find out the independent prognostic factors related to survival. Results having $P < 0.05$ were considered statistically significant.

Results

General information of the whole group of participants

Pathological examination confirmed that only two cases had local recurrence, with a recurrence rate of 1.8%. While 76 patients received 5-FU-based AC treatment, 38 patients failed to receive AC treatment due to other complications, older age, or patients' rejection of AC treatment.

Comparison of clinical characteristics between the two groups

Among the 110 patients, 34 (30.9%) underwent TME alone and 76 (69.1%) underwent TME combined with 5-FU-based AC. Univariate analysis showed that age was an important determinant affecting the patients' choice of postoperative treatment. Patients who did not receive AC treatment were significantly older than those who received AC treatment ($P < 0.05$). The tumor location, defined according to its distance from the anal margin, was significantly larger in the AC group than in the non-AC group ($P < 0.05$). Other clinical parameters, including sex, pathological T stage, degree of differentiation, type of operation, and LN resection, showed no significant difference between the two groups ($P > 0.05$; Table 1).

Effect of AC on patient survival

Subgroup analysis was performed based on the age of patients. There was no significant difference in the 3-year DFS ($\chi^2 = 0.068$, $P = 0.793$) and 3-year OS ($\chi^2 = 0.063$, $P = 0.801$) between the TME + AC group and TME group of patients aged ≤ 60 years (Fig. 1). Moreover, there was no significant difference in the 3-year DFS ($\chi^2 = 3.147$, $P = 0.076$) and 3-year OS ($\chi^2 = 1.783$, $P = 0.181$) between the

Table 1 Comparison of the clinical characteristics between the two groups of patients

Index	TME + AC (n = 76)	TME (n = 34)	t/χ^2	P
Age	61.8 ± 12.5	69.8 ± 10.3	–3.266	0.001
Sex			0.052	0.820
Female	52	24		
Male	24	10		
Distance from the anal margin (cm)			7.616	0.022
< 4	20	10		
4–7.9	31	21		
8–12	25	3		
Degree of differentiation			0.292	0.589
Poorly differentiated	4	1		
Well-differentiated	72	33		
Modus operandi			0.146	0.702
Low pre-excision	65	30		
Abdominal perineum was combined with radical resection	11	4		
T stage			0.148	0.929
0	6	2		
1	30	14		
2	40	18		
Number of lymph node excisions			0.028	0.866
< 12	46	20		
≥ 12	30	14		

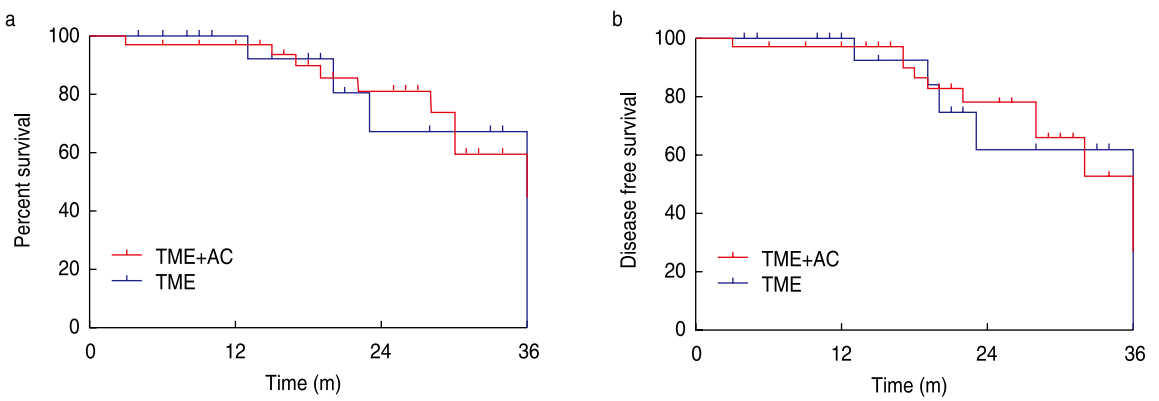

Fig. 1 The 3-year OS and DFS of patients aged ≥ 60 years in the TME + AC group and TME group. (a) The 3-year OS of patients aged ≥ 60 years in the TME + AC group and TME group; (b) The 3-year DFS of patients aged ≥ 60 years in the TME + AC group and TME group

TME + AC group and TME group of patients aged > 60 years (Fig. 2).

Multivariate analysis of the overall survival of patients with rectal cancer

Cox multivariate analysis showed that age, tumor differentiation, and the number of resected LNs were independent factors affecting the OS of patients (P < 0.05). Older patients, patients with lower degree of tumor differentiation, and patients with < 12 resected LNs showed worse prognosis (P < 0.05; Table 2).

Discussion

The survival benefit of AC in patients with lower stage of ypT0-3N0 rectal cancer after NCRT remains controversial. Our study shows that postoperative AC has no survival benefit for patients with lower stage of ypT0-3N0 rectal cancer, which suggests that careful consideration be taken when administering AC in these patients, especially for patients with rectal cancer without adverse prognostic factors. The EORTC 22921 randomized controlled study also failed to support the use of 5-FU AC in patients with 5-year OS [5]. In addition,

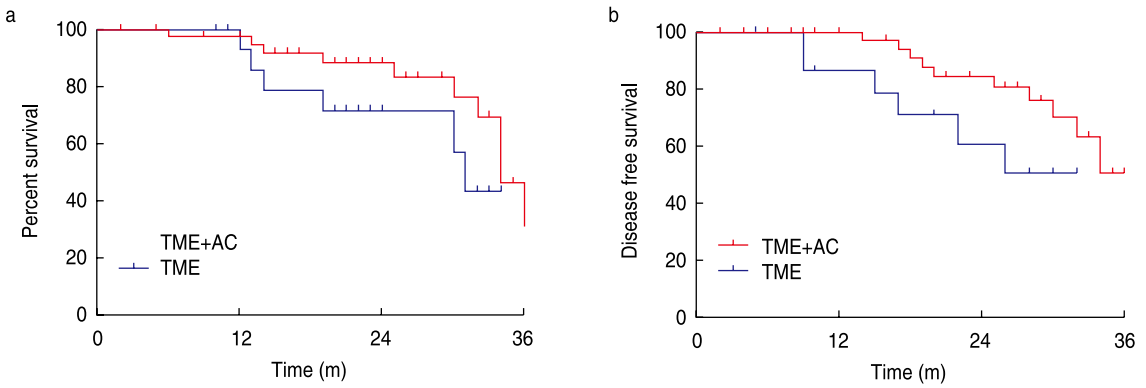

Fig. 2 The 3-year OS and DFS of the patients aged < 60 years in the TME + AC group and TME group. (a) The 3-year OS of the patients aged < 60 years in the TME + AC group and TME group; (b) The 3-year DFS of the patients aged < 60 years in the TME + AC group and TME group

Table 2 Multivariate analysis affecting overall survival in patients with rectal cancer

Index	B	SE	Wald	P	RR	95%CI
Age (≥ 60/< 60)	0.852	0.352	7.174	0.010	2.587	1.264–4.564
Sex (female/male)	0.239	0.213	1.154	0.298	1.336	0.787–1.874
Tumor differentiation (low/high)	1.284	0.529	4.726	0.032	3.554	1.036–11.935
AC (yes/no)	−1.512	0.137	2.689	0.089	0.328	0.115–0.551
T stage (T2/T0-1)	0.102	0.354	0.250	0.587	1.103	0.625–2.120
No. of lymph node (≥ 12/< 12)	−0.744	0.230	2.541	0.000	0.642	0.379–1.109

three other randomized prospective trials (PROCTOR-SCRIPT, CHRONICLE, and I-CNR-RT) showed that AC had no significant benefit on promoting survival in such patients. The PROCTOR-SCRIPT and CHRONICLE studies, which used 5-FU/LV or capecitabine as the AC protocol, showed that AC did not provide benefits in terms of DFS, OS, or recurrence rate [6]. The I-CNR-RT study used a smaller dose of 5-FU/LV as AC (5-FU 350 mg/m^2 and folic acid 20 mg/m^2) and reported that AC could not improve DFS, OS, or the rate of distant metastasis [7].

However, some retrospective cohort studies found that postoperative AC had significant survival benefits for some patients with locally advanced rectal cancer [8]. Garlipp *et al.* [9] conducted propensity score matching analysis on 1040 patients with rectal cancer who received 5-FU/capecitabine/oxaliplatin AC pretreatment and revealed improvement in the DFS of these patients. Tiselieus *et al.* [10] retrospectively investigated 436 patients with stage III rectal cancer who received NCRT, surgical treatment, and 5-FU/LV as AC and reported that AC could improve the prognosis of patients. Overall, conflicting conclusions from previous studies have posed a dilemma regarding the use of AC in patients with rectal cancer undergoing NCRT and surgery. Therefore, it is necessary to evaluate the need for AC in descending rectal cancer and identify specific populations that could benefit from this treatment.

The response of patients with locally advanced rectal cancer to NCRT is difficult to predict. Therefore, postoperative pathological stage rather than preoperative clinical stage may be a reliable predictor and can be used as the basis for determining the necessity of AC [11]. The results of this study and those of another study by Govindarajan *et al.* show that the reduction of ypT0-3N0 in patients before NCRT does not benefit from AC [12]. Yu *et al.* [13] conducted a retrospective cohort study of 203 patients with ypT0-3N0 and showed that the addition of AC had no effect on the 5-year DFS, which is consistent with our results.

In rectal cancer, the number of resected LNs is regarded as an indicator of radical surgery and accurate staging. According to the NCCN guidelines, only patients with at least 12 LNs can fully meet the staging criteria [14]. However, some studies questioned this guideline because it was observed that patients who received NCRT seemed to have fewer resected LNs than did those who did not receive NCRT. Furthermore, it was found that resection of < 12 LNs was associated with good DFS and OS. The reduction in the number of resected LNs can be considered as an individual's response to radiotherapy and chemotherapy, rather than a sign of insufficient surgical clearance. LNs on the mesorectum are vulnerable to irradiation. Therefore, radiotherapy can lead to lymphocyte apoptosis or interstitial atrophy [15]. In addition, from an anatomical perspective, the total number and size of LNs in rectal specimens are lesser than

those in colon specimens. Therefore, anatomical features and radiation effects are attributed to the reduced number of LNs harvested in patients receiving NCRT [16]. In our study, poor differentiation of tumor was identified as a prognostic factor corresponding to the poor 5-year DFS.

Microscopically, poorly differentiated tumors have a high tendency for invasion, which is a high-risk feature of stage II rectal cancer. In the study of Park *et al.*, poorly differentiated tumor was recognized as an independent adverse prognostic factor affecting DFS.

In conclusion, this study found that patients with ypt0-3n0 rectal cancer may not need AC, especially those without adverse prognostic factors. One of the limitations of this study is that age is still an important determinant and poses a potential choice bias in the decision regarding postoperative treatment. In our study, the age distribution between AC and non-AC patients was significantly unbalanced in patients receiving NCRT and surgery. In addition, AC was administered to younger patients with fewer complications and better physical capability. Another limitation is the retrospective nature of data collection, which lowers the level of evidence. For example, the tumor location (distance above the anal margin) is different between patients treated with AC and patients not treated with AC. Finally, this study was a single institution retrospective cohort study, which may also lead to potential selection bias. Larger prospective, randomized studies may provide more convincing evidence in the future. Nevertheless, we believe that the current results provide important information for clinical judgment on the effectiveness of AC in the subgroup of patients with ypT0-T3N0 rectal cancer.

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Conflicts of interest
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Author contributions
All authors contributed to data acquisition, data interpretation, and reviewed and approved the final version of this manuscript.

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