Rectal cancer patients with downstaging after neoadjuvant chemoradiotherapy and radical resection do not benefit from adjuvant chemotherapy

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Background: Whether adjuvant chemotherapy is beneficial for rectal cancer patients who respond well to neoadjuvant chemoradiotherapy (NCRT) and undergo radical resection is controversial. This study aimed to assess the effect of adjuvant chemotherapy on the oncological outcomes of ypT0-2N0 rectal cancer patients after NCRT and radical resection, and identify the prognostic factors.

Methods: The clinical and pathological data of rectal cancer patients with ypT0-2N0 who underwent NCRT and radical resection between January, 2010 and June, 2018 were collected and retrospectively analyzed. The oncological outcomes of the chemotherapy (chemo) group and the non-chemotherapy (non-chemo) group were compared. Multivariate analysis, using a Cox proportional hazard model, was performed to identify independent predictors of oncological outcome.

Results: Of the 121 rectal cancer patients enrolled, 90 patients received postoperative adjuvant chemotherapy with no fewer than 3 cycles (the chemo group), and the other 31 patients with fewer than 3 cycles (the non-chemo group). There was no significant difference in the 5-year disease-free survival (DFS) or overall survival (OS) rates between the two groups (DFS: 79.1% *vs.* 82.9%, P=0.442; OS: 87.5% *vs.* 78.2%, P=0.667). cT4 is an independent risk factor for OS (HR =4.227, 95% CI: 1.128–15.838, P=0.02) and DFS (HR =4.878, 95% CI: 1.752–13.578). Preoperative consolidation chemotherapy with Capeox or FOLFOX after NCRT significantly improved the DFS rate (HR =0.212, 95% CI: 0.058–0.776, P=0.019).

Conclusions: Rectal cancer patients with ypT0-2N0 who underwent NCRT and radical resection did not benefit significantly from postoperative adjuvant chemotherapy. For these patients, cT4 was an independent risk factor for OS and DFS. Preoperative consolidation chemotherapy with Capeox or FOLFOX after NCRT can significantly improve DFS.

Keywords: Rectal cancer; adjuvant chemotherapy; neoadjuvant chemoradiotherapy (NCRT); downstaging; prognosis

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Introduction

For patients with locally advanced rectal cancer (LARC), total mesorectal excision (TME) and neoadjuvant chemoradiotherapy (NCRT) have been shown to significantly decrease the local recurrence rate and improve the overall survival (OS) rate (1). However, approximately 25–30% of patients still develop distant metastasis postoperatively (2,3). Adjuvant chemotherapy prevents and clears circulating tumor cells and micro-metastases, thereby reducing the risk of developing distant metastases. Current guidelines state that all patients with locally advanced rectal cancer who receive NCRT and radical resection should undergo adjuvant chemotherapy (4,5). However, recent research has supplied little evidence to suggest that adjuvant chemotherapy is beneficial for rectal cancer patients treated with NCRT and radical resection (6-9), especially for those who have already responded well to treatment (10,11). Currently, adjuvant chemotherapy is recommended for patients after NCRT and radical resection based on pretreatment clinical staging; however, pretreatment clinical staging can be inaccurate, and postoperative TNM staging is easier. Some researchers have suggested that adjuvant chemotherapy should be used selectively, based on the final pathological stage. According to the literature, pathological stage has a better predictive value than clinical stage or tumor regression classification in tumor prognosis (12-14). Patients with ypT0-2N0 rectal cancer are a subgroup that responds well to NCRT and have favorable oncological prognosis, with a 5-year disease-free survival (DFS) rate reaching 83–95% (12-14). Nevertheless, studies have shown that not all ypT0-2N0 rectal cancer patients benefit from adjuvant chemotherapy after NCRT and surgery, and controversy still surrounds the use of adjuvant chemotherapy for these patients (15-18), the prognostic factors of whom are rarely reported.

This study aimed to evaluate the effect of adjuvant chemotherapy on the oncological prognosis and prognostic factors of ypT0-2N0 rectal cancer patients after NCRT and radical resection.

We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/atm-20-1278).

Methods

Patients and evaluation before the treatment

This retrospective study was conducted at the Department of Colorectal Surgery, Changhai Hospital, Shanghai, China. The study was performed in accordance with the ethical standards of our institutional research committee, and the principles of the 1964 Declaration of Helsinki and its later amendments. Informed consent was obtained from each individual participant included in the study.

The data of resectable locally advanced rectal cancer patients who received NCRT in the Department of Colorectal Surgery in Changhai Hospital between January, 2010 and June, 2018 were retrospectively analyzed. The inclusion criteria were: (I) low or middle rectal carcinoma (a distance of <10 cm between the inferior tumor edge and the anal verge); (II) pretreatment clinical stage was II/III; (III) no obvious distant metastasis; (IV) postoperative pathological results showed R0 resection; (V) pathological diagnosis of ypT0-2N0 after NCRT and radical resection; and (VI) completed neoadjuvant treatment and adjuvant treatment. The exclusion criteria were: (I) other malignant tumors present (except for locally advanced rectal cancers); (II) a history of malignant tumor or relapse; (III) managed by a watch-and-wait strategy after NCRT; or (IV) pathological results showed tumor deposits.

All of the patients underwent colonoscopy and pathological consultation before treatment to confirm the pathological diagnosis. Before treatment, chest computed tomography, magnetic resonance imaging, or computed tomography with intravenous contrast of the liver and pelvis were also performed for clinical staging. Clinicopathological classification and staging were based on the American Joint Committee on Cancer tumor-node-metastasis (TNM) staging system (19).

Treatment

All of the patients received intensity-modulated radiation therapy with concurrent oral administration of capecitabine: the total dosage was 45–50.4 Gy (1.8–2.0 Gy per time, 25–28 fractions). In the chemotherapy group (the chemo group), 48 patients underwent NCRT alone and 42 patients underwent combined chemotherapy. In the non-chemotherapy group (the non-chemo group), NCRT alone and combined chemotherapy was received by 18 and 13 patients, respectively.

The chemotherapy regimens included: oral capecitabine alone during radiotherapy (n=66) (825 mg/m^2 orally, twice a day, 5 days a week for 5 weeks); CapeOx as consolidation chemotherapy (n=48) (oxaliplatin 130 mg/m^2, intravenous infusion 2 h, day 1; capecitabine 1,000 mg/m^2 orally, twice

a day, 1–14 days, repeated every 3 weeks), FOLFOX as consolidation chemotherapy (n=7) (oxaliplatin 85 mg/m^2 intravenous infusion for 2 h, day 1, LV 400 mg/m^2 intravenous infusion for 2 h, day 1, 5-Fu 400 mg/m^2 intravenous infusion, day 1, then 1,200 mg/m^2/day × continuous intravenous infusion for 2 days).

All patients underwent radical total mesorectal excision (TME). The adjuvant chemo group comprised 90 patients (74.4%) including: (I) oral capecitabine (n=22); (II) CapeOx (n=59); (III) FOLFOX (n=9). The non-chemo group comprised 31 (25.6%) patients, including 8 patients who received fewer than 3 cycles of chemotherapy due to poor performance status, the other 23 patients in the non-chemo group did not receive adjuvant chemotherapy including 15 patients who had favorable pathology, 5 patients who refused chemotherapy, and 3 patients who experienced postoperative complications.

Follow up

Follow-up data were retrospectively obtained from the medical records. The follow-up ended on July 21, 2019. Each patient was followed-up every three months for the first two years, every six months for the next three years, and once a year thereafter. Digital rectal examination was performed and the levels of carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 19-9 were determined at every follow-up visit. Chest computed tomography, magnetic resonance imaging, or computed tomography with intravenous contrast of the liver and pelvis, and full colonoscopy were regularly undertaken. Disease-free survival was defined as the time between the surgery and tumor recurrence or distant metastasis. Overall survival was defined as the time between surgery and death or last follow-up.

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics 22.0 (IBM SPSS Statistics, IBM Corporation, Armonk, NY, USA). Categorical values were reported as frequency and percentage, and continuous values were reported as the mean ± standard deviation (SD) or median with range, depending on whether the values were normally distributed or not. Categorical variables were statistically analyzed by the chi-square test and continuous variables were compared using the Student's t-test or the Mann-Whitney test. Survival analysis was performed using the Kaplan-Meier curve method, and differences in survival between the groups were compared with the log-rank test. Multivariate analysis, using a Cox proportional hazard model, was performed to identify independent predictors of overall survival (OS) and disease-free survival (DFS). P<0.05 (two sided) was considered statistically significant.

Results

This study included 121 patients, of whom 88 (72.7%) were male and 33 (27.3%) were female. The patients had an average age of 57.0±10.8 (range, 25–81) years old. There were 14, 67, and 40 cases of cT2, cT3, cT4 patients, respectively; 66 cases underwent NCRT, and 55 cases underwent consolidation chemotherapy after NCRT with CapeOx or FOLFOX. The median interval between the end of radiotherapy and surgery was 8.9 weeks (range: 2.7–16 weeks). All of the patients received R0 resection with negative distal and circumferential margins. The results of postoperative pathology showed there were 47, 8, and 66 patients with ypT0, ypT1, and ypT2, respectively. There were 90 (74.4%) and 31 (25.6%) patients in the chemo group and non-chemo group, respectively. The age of patients in the chemo group was significantly lower than that in the non-chemo group (55.6±10.6 *vs.* 61.2±10.4 years, P=0.012). The incidence of anastomotic leakage in the non-chemo group was significantly higher than that in the chemo group (19.4% *vs.* 6.7%, P=0.042) (*Table 1*).

The median follow-up time for all patients was 40.1 months (IQR, 26.2–63.2). In the chemo and non-chemo groups, the median follow-up time was 40.4 (IQR, 27.9–64.7) and 39.2 (IQR, 24.8–60.5) months, respectively. There was no significant difference between the two groups (P=0.642). During follow-up, 24 patients relapsed, of whom 3 were local recurrences, and 21 were distant metastases. The median relapse time was 37.5 (range, 5.3–113.1) months. There were 19 cases of recurrence in the chemo group, of which 16 cases were distant metastasis, and 3 cases were pelvic recurrence. In the non-chemo group, 4 cases had distant metastasis, and 1 case had concurrent distant metastasis and pelvic recurrence. During follow-up, 12 patients died including 9 in the chemo group and 3 in the non-chemo group.

The 5-year DFS and OS rates for all patients were 80.2% and 85.0%, respectively. In the chemo group and non-chemo group, the 5-year DFS and OS rates were 79.1% and 82.9% (P=0.442), and 87.5% and 78.2% (P=0.667), respectively (*Figure 1*).

Table 1 Demographic and clinicopathological characteristics of patients with ypT0-2N0

Variable	Chemo (n=90)	Non-chemo (n=31)	P
Age, mean ± SD, y	55.6±10.6	61.2±10.4	0.012
Gender			0.097
Male	69	19	
Female	21	12	
Distance to anal verge, mean ± SD, cm	3.9±2.0	3.5±1.6	0.349
cT			0.264
cT2	11	3	
cT3	46	21	
cT4	33	7	
cN			0.753
cN0	32	12	
cN1-2	58	19	
CEA before treatment, ng/mL			0.809
≤5	36	10	
>5	22	7	
Miss	32	14	
Preoperative treatment			0.648
NCRT	48	18	
NCRT + Capeox or FOLFOX	42	13	
Interval between radiotherapy and operation, w			0.817
<6	9	2	
6–8	27	9	
>8	54	20	
Operation type			0.824
APR	31	10	
LAR	59	21	
No. of retrieved lymph nodes			0.168
<12	59	16	
≥12	31	15	
Anastomotic leakage			0.042
Yes	6	6	
No	84	25	
Postoperative hemorrhage			0.403
Yes	2	0	
No	88	31	
Incision infection			0.854
Yes	5	2	
No	85	29	
ypT			0.700
ypT0	36	11	
ypT1	5	3	
ypT2	49	17	
Follow-up, median (interquartile range), m	40.8 (27.9–64.7)	38.8 (24.8–60.5)	0.965

cT, clinical T stage before treatment; cN, clinical N stage before treatment; CEA, carcinoembryonic antigen; NCRT, neoadjuvant chemoradiation; LAR, low anterior resection; APR, abdominoperineal resection.

Cox univariate analysis revealed that cT, preoperative treatment, and number of retrieved lymph nodes were the prognostic factors for DFS (P=0.002, 0.005, and 0.007, respectively). Meanwhile, cT and ypT were the prognostic factors for OS (P=0.014 and 0.046). Cox multivariate analysis showed that cT4 (HR =4.227, 95% CI: 1.128–15.838, P=0.02) is an independent risk factor for OS, as well as an independent risk factor for DFS (HR =4.878, 95% CI: 1.752–13.578, P=0.002). Preoperative consolidation chemotherapy with CapeOx or FOLFOX (HR =0.212, 95% CI: 0.058–0.776, P=0.019) after NCRT significantly improved DFS (*Tables 2-4*).

Discussion

This study showed that rectal cancer patients who underwent NCRT and radical resection with postoperative pathological diagnosis of ypT0-2N0 did not benefit significantly from adjuvant chemotherapy.

For locally advanced rectal cancer, the standard treatment is NCRT and surgery, followed by adjuvant chemotherapy. The theoretical basis for postoperative chemotherapy for rectal cancer stems from patients with colon cancer benefiting from postoperative chemotherapy (20-23).

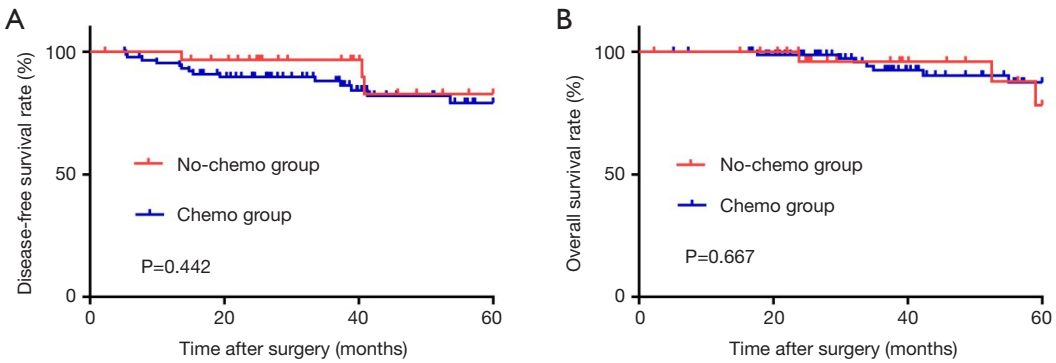

Figure 1 Oncological outcomes of 121 patients with ypT0-2N0 rectal cancer. (A) The 5-year disease-free survival rate in patients with ypT0-2N0 between the chemo and non-chemo groups. (B) The 5-year overall survival rate in patients with ypT0-2N0 between the chemo and non-chemo groups.

Table 2 Univariate analysis of the 5-year DFS and OS rates in patients with a pathological diagnosis of ypT0-2N0

Variable	Total (n=121)	DFS		OS	
		5-year rate	P	5-year rate	P
Age, y			0.236		0.440
≤60	71	87.4		89.1	
>60	50	67.3		78.4	
Gender			0.110		0.309
Male	88	85.9		89.3	
Female	33	60.9		73.1	
Distance to anal verge, cm			0.618		0.624
≤5	102	80.1		83.7	
>5	19	81.0		91.7	
cT			0.002		0.014
cT2-3	81	88.7		96.5	
cT4	40	66.8		72.1	
cN			0.720		0.211
cN0	44	81.9		89.6	
cN1-2	77	79.0		81.1	
CEA, ng/mL			0.052		0.087
≤5	46	80.0		87.8	
>5	29	53.7		57.2	
Preoperative treatment			0.005		0.158
NCRT	66	68.8		78.8	
NCRT + Capeox or FOLFOX	55	96.4		94.4	

Table 2 (*continued*)

Table 2 (*continued*)

Variable	Total (n=121)	DFS		OS	
		5-year rate	P	5-year rate	P
Interval between radiation and operation, weeks			0.742		0.522
≤8	47	79.4		87.6	
>8	74	79.3		81.7	
Operation type			0.326		0.164
APR	41	76.8		78.5	
LAR	80	81.5		89.7	
Nnumber of retrieved lymph node			0.007		0.104
<12	75	90.3		92.9	
≥12	46	67.2		76.7	
Anastomotic leakage			0.105		0.054
Yes	12	74.1		75.0	
No	109	81.3		86.2	
Postoperative hemorrhage			0.558		0.627
Yes	2	100		84.6	
No	119	79.8		100	
Incisional infection			0.765		0.297
Yes	7	85.7		0	
No	114	80.2		86.6	
ypT			0.127		0.046
ypT0	47	86.5		96.9	
ypT1-2	74	76.3		77.1	
Adjuvant chemotherapy			0.442		0.667
Yes	90	82.9		78.2	
No	31	79.1		87.5	

cT, clinical T stage before treatment; cN, clinical N stage before treatment; CEA, carcinoembryonic antigen; NCRT, neoadjuvant chemoradiation; LAR, low anterior resection; APR, abdominoperineal resection; DFS, disease-free survival; OS, overall survival.

However, the efficacy of adjuvant chemotherapy for treating rectal cancer is not clear (24). Previous studies that have shown adjuvant chemotherapy to benefit patients with rectal cancer have involved patients with rectal cancer who did not receive NCRT before radical resection (25-27). However, studies involving patients with rectal cancer who received NCRT and radical resection have failed to prove that these patients can benefit from adjuvant chemotherapy (6-9).

The prognosis of patients with tumor regression and T or N downstaging after NCRT for rectal cancer has been shown to improve significantly. Rödel *et al.* analyzed 385 patients with rectal cancer who underwent NCRT before surgery in the CAO/ARO/AIO-94 study and found that the 5-year disease-free survival rates of TRG4, TRG2 + 3, and TRG0 + 1 patients according to postoperative pathology were 86%, 75%, and 63%, respectively (P=0.006) (12). Multivariate analysis revealed postoperative ypT to be an important independent prognostic factor for disease-free survival (12). Rectal cancer patients with ypT1-2N0 after NCRT and surgery have a better prognosis than

Table 3 Multivariate analysis of the DFS rate in patients with ypT0-2N0

Variable	Total	Hazard ratio	95% Confidence interval	P
cT			1.752–13.578	0.002
cT2-3	81	1		
cT4	40	4.878		
Preoperative treatment			0.058–0.776	0.019
NCRT	66	1		
NCRT + CapeOx or FOLFOX	55	0.212		
No. of retrieved lymph nodes			0.690–5.314	0.212
<12	75	1		
≥12	46	1.915		

DFS, disease-free survival; cT, clinical T stage before treatment; NCRT, neoadjuvant chemoradiation.

Table 4 Multivariate analysis of the OS rate in patients with ypT0-2N0

Variable	Total	Hazard ratio	95% Confidence interval	P
cT			1.128–15.838	0.032
cT2-3	81	1		
cT4	40	4.227		
Anastomotic leakage			0.735–16.621	0.116
Yes	12	1		
No	109	3.495		
ypT			0.819–11.270	0.097
ypT0	47	1		
ypT1-2	74	3.038		

OS, overall survival; cT, clinical T stage before treatment.

patients with ypT3-4N0 (14). Postoperative pathological T and N staging is significantly better for predicting the prognosis than clinical stage before NCRT (12-14). This study showed that ypT0-2N0 rectal cancer patients had favorable prognosis after NCRT and surgery; however, 11 patients (12.4%) still had distant metastases during the follow-up period, including 4 patients whose pathological results showed pathological complete response (pCR). In Cox multivariate analysis, cT instead of ypT was found to be an independent prognostic factor for DFS and OS. This is probably because we only recruited ypT0-2N0 patients with good response to neoadjuvant chemoradiotherapy. Consistent with our results, Shahab *et al.* found that cT is an independent prognostic factor of OS for patients who show good response to preoperative chemoradiotherapy and surgery (28). Our further analysis showed that cN is not an independent risk factor for these patients, which can possibly be attributed to the accuracy of lymph node metastasis assessment being lower than that of cT staging with MRI (29,30). Shahab *et al.*, also did not find cN to be an independent risk factor of OS in the patients with good response to preoperative radiotherapy (28).

In Zhao *et al.*'s comparison of prognoses between patients with ypT0-2 rectal cancer, there was no significant difference in OS rate or recurrence-free survival (RFS) rate in patients with or without adjuvant chemotherapy (15). This suggests that the ypT0-2 patients in that study did not benefit from postoperative adjuvant chemotherapy (15). Lee *et al.* also reported that adjuvant chemotherapy failed to improve the local recurrence, DFS, and OS rates in patients with ypT0-2N0, but that adjuvant chemotherapy could significantly decrease the local recurrence rate in patients with ypT3-4N0 (16). A multicenter retrospective study of 1,016 patients with ypT0-2 rectal cancer after NCRT and surgical resection showed that adjuvant chemotherapy failed to significantly improve the 5-year local recurrence and distant metastasis rates (17). These findings are consistent with our results that rectal cancer patients with ypT0-2N0 who underwent NCRT and radical resection did not benefit significantly from postoperative adjuvant chemotherapy. Despite the 5-year OS rate of the chemo group being 9%, which was higher than that of the non-chemo group, there was no significant difference (P>0.05).

Few previous studies have found that consolidation

chemotherapy can improve the DFS rate, although most of them have shown that consolidation chemotherapy can increase the pathological complete response (pCR) rate (31,32). However, finding out if consolidation chemotherapy can improve DFS was not the direct focus of these studies. Our study shows preoperative consolidation chemotherapy with CapeOx or FOLFOX after NCRT can significantly improve DFS.

There are several limitations in the current study. Firstly, this is a single-center, retrospective study with a small number of patients. Besides, there were fewer patients in the non-chemo group than in the chemo group. Secondly, some baseline characteristics, including age and anastomotic leakage, were different in the non-chemo and chemo groups. Thus, multivariate analysis was utilized to avoid the possible bias. Thirdly, the data of the level of differentiation in the tumors and serum CEA of patients before NCRT were incomplete. As ypT0-2N0 patients represent a large proportion of patients with rectal cancer after neoadjuvant chemoradiotherapy, randomized clinical trials should be performed in the future.

Conclusions

Rectal cancer patients with a pathological diagnosis of ypT0-2N0 after NCRT and radical resection did not benefit significantly from postoperative adjuvant chemotherapy. cT4 is a high risk factor for patients with ypT0-2N0 rectal cancer. Preoperative chemotherapy with CapeOx or FOLFOX can significantly improve the DFS rate for patients.

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Footnote

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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. Ethical approval from the Ethics Committee of Changhai Hospital was not required, because of the study's retrospective case-control nature. The study was conducted in accordance with the Declaration of Helsinki (as is revised in 2013) and approved by the ethical standards of our institutional research committee. Informed consent was taken from all individual participants.

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