J Chin Med Assoc

ORIGINAL ARTICLE

The effect of Mitomycin-C in neoadjuvant concurrent chemoradiotherapy for rectal cancer

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Abstract

Background: Neoadjuvant concurrent chemoradiotherapy (nCCRT) followed by total mesorectal excision has become the standard of care for advanced rectal cancer, but the most effective regimen of chemotherapeutic agents has not yet been determined. The purpose of this study is to determine the effect of Mitomycin-C (MMC) in nCCRT for rectal cancer.

Methods: From 2000 to 2017, patients with rectal adenocarcinoma who received nCCRT followed by radical surgery were enrolled in our study. The patients were retrospectively separated into two groups according to nCCRT regimens (with or without MMC). Other factors related to cancer down-staging after nCCRT, disease-free survival (DFS) and overall survival (OS) were analyzed.

Results: One hundred ninety-five patients received radiotherapy (RT) + MMC + oral tegafur-uracil (UFUR), and 191 patients received RT + UFUR without MMC as neoadjuvant CCRT. Adding MMC might increase the down-staging rate (odds ratio [OR] = 1.520, $p = 0.058$), and down-staging had significant effect to improve OS (OR = 1.726, $p = 0.002$) and DFS (OR = 2.185, $p < 0.001$). The OS and DFS were improved in patients who received MMC, although this result did not reach a statistically significant difference. There was a higher incidence of low-grade toxicities in the MMC group, especially neutropenia, genitourinary side effects, and dermatological side effects ($p < 0.001$).

Conclusion: Adding MMC to the regimen of nCCRT for rectal adenocarcinoma is shown to increase tumor down-staging rate and improve disease-free and OS, although these benefits come at the cost of increased low-grade toxicities. Prospective randomized studies are needed to explore the role of MMC in nCCRT for rectal cancer.

Keywords: Mitomycin; Neoadjuvant therapy; Rectal neoplasms; Radiotherapy

1. INTRODUCTION

The foundation of curative treatment for rectal cancer is total mesorectal excision (TME). In early rectal cancer, TME alone has been considered to be sufficient for curative treatment. But in advanced rectal cancer, additions of chemotherapy and radiotherapy (RT) have been shown to improve the rates of disease-free survival and overall survival.[1–3] In addition, neoadjuvant concurrent chemoradiotherapy (nCCRT) performed before surgery has been found to be effective in local tumor control including tumor down-staging, increasing pathological complete response rate, and sphincter preservation.[4,5] Because of these findings, nCCRT has become a widely accepted practice in the treatment of advanced rectal cancer.

The standard protocol for the RT portion of nCCRT in our hospital is high-dose radiation (a total of 45Gy in 20 fractions).[4,6] However, the regimen for pre-operative chemotherapy has been variable. Intravenous or oral fluorouracil plus leucovorin (LV) are widely used,[6–8] while Mitomycin-C (MMC) plus fluorouracil,[9] or capecitabine plus oxaliplatin, have also been reported in the practice of neoadjuvant chemotherapy for rectal cancer.[10] A determination of the relative effectiveness of different neoadjuvant chemotherapeutic regimens for rectal cancer has not been established.

The purpose of this study is to evaluate the effect of MMC plus oral tegafur-uracil (UFUR) as the regimen of neoadjuvant CCRT compared with oral UFUR alone. We focused on the analysis of therapeutic outcomes between the two regimens including down-staging, overall and disease-free survival, and the complications of both acute and chronic stages.

2. METHODS

2.1. Patients

This study was approved by our institutional review board and informed consent from subjects was waived. From 2000 to 2017, patients with clinical T3, T4, or node-positive rectal adenocarcinoma staged by magnetic resonance imaging (MRI) or computed tomography (CT) scan (MRI was 66.1%) and

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Author Contributions: Dr Ling-Wei Wang and Dr Yu-Shih Liu contributed equally to this work.

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

Journal of Chinese Medical Association. (2022) 85: 1120-1125.

Received November 8, 2021; accepted July 14, 2022.

doi: 10.1097/JCMA.0000000000000819.

received nCCRT and radical surgery at our institution were candidates of this study. All subjects underwent chest CT, abdominal ultrasonography, and whole-body bone scan to exclude the possibility of distant metastases. The exclusion criteria included lost follow-up after the therapy, distant metastasis before curative resection, surgical margin involvement, or those who did not receive radical resection.

The patient selection flowchart is found in Fig. 1. Data of 505 patients were initially retrieved from the radiation oncology database. The patients were retrospectively divided into two groups: group A included those who received neoadjuvant CCRT in the period between May 2001 and October 2010, during which time the chemotherapeutic regimen was oral UFUR; group B included patients who received nCCRT in the period between November 2010 and August 2017, when nCCRT patients received oral UFUR along with one dose of MMC at day 1 of nCCRT.

2.2. Methods

Radiation therapy (RT) was administered with a linear accelerator producing 10 MV X-rays (Clinac 2100 C, 2100 CD; Varian, Palo Alto, CA), and a three-dimensional conformal technique was used. The entire pelvis was treated with AP-PA plus bilateral portals daily. RT was delivered once per day with a 2.25-Gy fraction, 5 days per week. The total dose was 45 Gy over 4 weeks. For T4 disease, a boost with 5.4 Gy/3 fractions was given.

Concurrent chemotherapy with oral UFUR (combined in a 1:4 molar ratio; TTY Biopharm, Taipei, Taiwan), 200 mg/m^2/day in three divided doses, was administered from days 1 to 28, during the entire course of RT. Oral LV (Wyeth Lederle Laboratories, Taipei, Taiwan), 45 mg/day in three divided doses was prescribed to potentiate the effect of UFUR. The patients were monitored weekly by interview, physical examination, and complete blood count. The oral chemotherapy was continued after RT with a dose of 250 mg/m^2/day in another 28-day cycle on days 36–63. The patients in group B received an extra single cycle of MMC (Kyowa Hakko Kirin, Japan), 6 mg/m^2 given as an intravenous push on day 1.

Surgical resection was scheduled at 6–8 weeks after neoadjuvant CCRT. Reversal of diversion stoma was performed about 3 to 6 months after surgery if no anastomotic complications (leakage or fistula formation) occurred.

Adjuvant chemotherapy with infusional FOLFOX: oxaliplatin, 5-fluorouracil (5-FU) and LV, was given to patients with pathological stage III at 1 month after surgery. The doses of oxaliplatin, 5-FU and LV were 85, 3000, and 150 mg/m^2, respectively. Adjuvant chemotherapy was administered for 48 hours biweekly for a total of 12 cycles. For the patients with pathological stage I and stage II, adjuvant chemotherapy was administrated with oral UFUR for 6 to 12 months. The adverse events were collected and reported using the U.S. National Cancer Institute's Common Terminology Criteria for Adverse Events version 5.0.[11]

Patients were followed postoperatively every 3 months during the first 2 years and every 6 months thereafter. Local recurrence was found by digital examination, colonoscopy, or pelvic imaging. Distant metastasis was defined as the appearance of new lesions in other organs outside the pelvis by image studies. The amount of time patients remained in follow-up was determined by the date of last clinic visit or the day disease recurrence was diagnosed. The study ended on December 31, 2019. The mean follow-up time was 68.6 months, and median follow-up time was 58.1 months. The primary outcome of our study was down-staging after nCCRT. Successful down-staging was defined as a decrease by at least one stage according to AJCC, between initial clinical stage before nCCRT, and the pathological stage after surgery. The secondary outcome included side effect of chemoradiotherapy, overall and disease-free survival.

2.3. Statistics

Comparisons of patient and disease characteristics between the two groups were assessed by Student's *t*-test for means and Chi-Squared test for categorical data (Fisher's exact test for small cells). The therapeutic outcome data were analyzed with

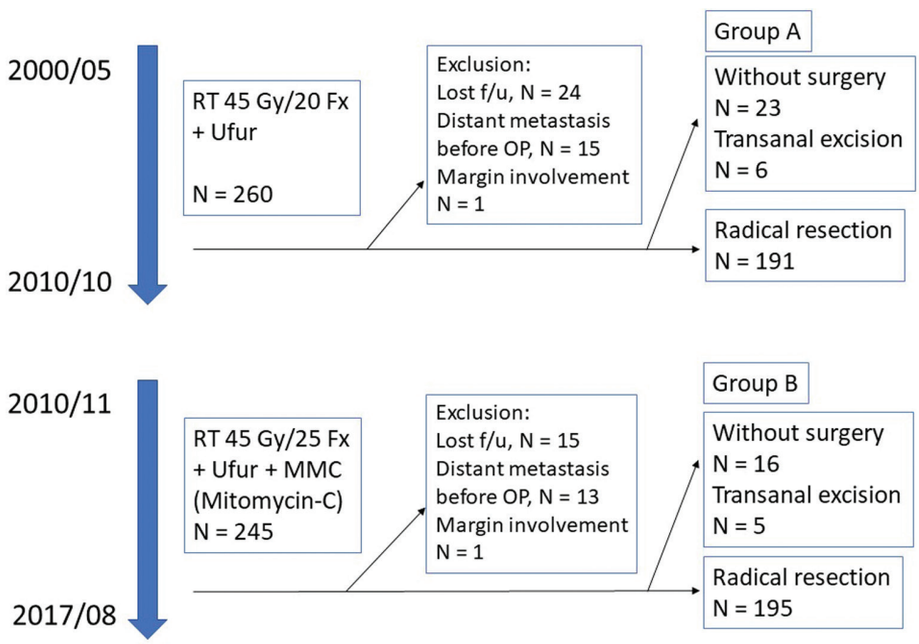

Fig. 1 Patient selected flowchart. Three hundred eighty-six patients were enrolled, of which 191 patients received RT + UFUR without MMC (group A), and 195 patients received RT + MMC + UFUR (group B). MMC = Mitomycin-C; RT = radiotherapy; UFUR = oral tegafur-uracil.

multivariate logistic regression or linear regression. Overall and disease-free survival analyses were carried out with the Kaplan-Meier estimator, and the Log-rank test was used to compare group survival rates. A p-value <0.05 was considered significant. The analysis was performed based on IBM SPSS statistics 25.

3. RESULTS

A total of 386 patients who had rectal adenocarcinoma were included in our study. The patients were separated into two groups; group A (n = 191) received RT plus oral UFUR as neoadjuvant therapy, and group B (n = 195) received MMC at the first day of neoadjuvant therapy in addition to UFUR. The percentage of MRI study before RT was higher in group B (60.9% in group A, 70.7% in group B, p = 0.028). The patient and disease characteristics are summarized in Table 1. Group B had more advanced clinical N stage (p = 0.003), clinical American Joint Committee on Cancer stage (p = 0.001), and pre-RT carcinoembryonic antigen level (p < 0.001). The type of surgery was similar between two groups (Table 2). Group B patients received higher doses of RT during nCCRT, including mean dose (46.14 Gy vs 45.16, p < 0.001) as well as the number of patients who received more than 50 Gy (19.5% vs 5.8%, p < 0.001).

The therapeutic outcome is described in Table 3. The rate of pathological complete response was 21.0% and 22.1% in

Table 1

Patient and disease characteristics

	RT + Ufur (%)	RT + Ufur +MMC (%)	*p*
Number	191	195	
Age in years	63	62	0.241
<60	77 (40.3)	82 (42.1)	
>60	114 (59.7)	113 (57.9)	
Gender			0.976
Male	132 (67.2)	131 (67.1)	
Female	59 (32.8)	64 (32.9)	
Pre-RT T stage			0.678
cT1	0	0	
cT2	25 (13.1)	20 (10.3)	
cT3	137 (71.7)	155 (79.5)	
cT4	29 (15.2)	20 (10.2)	
Pre-RT N stage			0.003
cN0	48 (25.1)	23 (11.8)	
cN1	66 (34.6)	76 (39.0)	
cN2	77 (40.3)	96 (49.2)	
AJCC TNM staging			0.001
Stage II	48 (25.1)	24 (12.3)	
Stage III	143 (74.9)	171 (87.7)	
Distance from anus (cm)			0.704
<3.0	6 (3.1)	7 (3.6)	
3.0-6.0	109 (57.1)	105 (53.8)	
>6.0	76 (39.8)	83 (42.6)	
Pre-RT CEA (ng/mL) (average/median)	10.28/3.22	14.54/5.20	< 0.001
<3.5	99 (52.7)	75 (38.5)	
3.5-10	58 (30.9)	57 (29.2)	
>10	31 (16.4)	63 (32.3)	

AJCC = American Joint Committee on Cancer; CEA = carcinoembryonic antigen; RT = radiotherapy; TNM = tumor, lymphnodes, metastasis.

Table 2

Treatment characteristics

	RT + Ufur (%) (N = 191)	RT + Ufur +MMC (%) (N = 195)	*p*
Type of surgery			0.298
APR	36 (18.8)	29 (14.9)	
LAR	155 (81.2)	166 (85.1)	
Gap between completion of RT and surgery in weeks (median/range)	7.75 (3.4-25.3)	8.85 (4.1-24.6)	< 0.001
<6	71 (37.2)	23 (11.8)	
6-10	110 (57.6)	148 (75.9)	
>10	10 (5.2)	24 (12.3)	
RT dose in Gy (median/range)	45 (18.0-50.4)	45 (45.0-54.0)	<0.001
<45	5 (2.6)	1 (0.5)	
≥45 and <50	175 (91.6)	156 (80.0)	
≥50	11 (5.8)	38 (19.5)	
Adjuvant chemotherapy	64 (33.5)	112 (57.4)	0.002

APR = abdominoperineal resection; LAR = low anterior resection; MMC = Mitomycin-C; RT = radiotherapy.

Table 3

Therapeutic outcome

	RT + Ufur (%) (N = 191)	RT + Ufur +MMC (%) (N = 195)	*p*
Surgical pT stage			0.698
ypT0	40 (21.0)	43 (22.1)	
ypT1	5 (2.6)	8 (4.1)	
ypT2	46 (24.1)	44 (22.6)	
ypT3	90 (47.1)	91 (46.6)	
ypT4	10 (5.2)	9 (4.6)	
Surgical pN stage			0.117
ypN0	140 (73.3)	149 (76.4)	
ypN1	36 (18.8)	41 (21.0)	
ypN2	15 (7.9)	5 (2.6)	
Pathology stage			0.568
ypCR (complete response)	37 (19.4)	41 (21.0)	
yp stage I	46 (24.1)	47 (24.1)	
yp stage II	57 (29.8)	61 (31.3)	
yp stage III	51 (26.7)	46 (23.6)	
Tumor regression grade[a]			0.719
0	40 (21.0)	43 (22.1)	
1	96 (50.3)	104 (53.3)	
2	53 (27.7)	43 (22.0)	
3	2 (1.0)	5 (2.6)	
Down-staging	123 (64.3)	143 (73.3)	0.058
Post RT CEA (ng/mL) (median)	2.43	2.80	0.079
<3.5	126 (66.0)	126 (64.6)	
3.5-10	53 (27.7)	55 (28.2)	
>10	12 (6.3)	14 (7.2)	
Failure			0.100
None	123 (64.4)	140 (71.8)	
Local recurrence	11 (5.8)	9 (4.6)	
Distant metastasis	53 (27.7)	45 (23.1)	
Both	4 (2.1)	1 (0.5)	

AJCC = American Joint Committee on Cancer; CEA = carcinoembryonic antigen; MMC = Mitomycin-C; RT = radiotherapy.

[a]The tumor regression grade was based on AJCC 7th edition.

group A and group B, respectively. Those who received MMC had a borderline higher down-staging rate (73.3% vs 64.3%, $p = 0.058$ by *t*-test). The other parameters of therapeutic outcome, including pathological stage and tumor regression grade, were similar in both groups. Further evaluation of factors that might influence down-staging rate was accomplished by binary logistic regression (Table 4). MMC had effects on increasing down-staging rate (odds ratio [OR] = 1.520. $p = 0.058$). Other factors, such as increasing RT dose and interval between RT and surgery, had no significant effect on down-staging.

Table 4

Logistic regression for factors that influence down-staging

	Odds ratio	95% confidence interval	*p*
Ufur + RT	-	-	-
Ufur + Mitomycin + RT	1.520	0.985-2.347	0.058
RT dose in Gy			
<45	-	-	-
≥45 and <50	2.484	0.493-12.527	0.270
>50	1.227	0.225-6.694	0.813
Gap between completion of RT and surgery in weeks			
<6	-	-	-
6-10	1.014	0.596-1.726	0.958
>10	0.649	0.276-1.523	0.320

RT = radiotherapy.

Table 5

Multivariate analysis for factors that influence overall- and disease-free survival

	Odds ratio	95% confidence interval	*p*
Overall survival			
Clinical T2	-	-	-
T3	2.019	1.076-3.789	0.029
T4	3.082	1.482-6.413	0.023
Down-staging	1.726	1.227-2.430	0.002
Ufur + RT	-	-	-
Ufur + Mitomycin + RT	1.343	0.898-2.007	0.101
Disease-free survival			
Clinical T2	-	-	-
T3	2.765	1.364-5.602	0.005
T4	2.895	1.205-6.956	0.017
Clinical N-stage			
N0	-	-	-
N1	1.750	0.945-3.242	0.075
N2	2.122	1.165-3.864	0.014
Down-staging	2.185	1.526-3.128	<0.001
Ufur + RT	-	-	-
Ufur + Mitomycin + RT	1.075	0.746-1.551	0.432

RT = radiotherapy.

Factors that influenced overall survival and disease-free survival were analyzed by Cox proportional hazard multivariate analysis (Table 5). The achievement of down-staging could improve both overall survival (OR = 1.726, $p = 0.002$) and disease-free survival (OR = 2.185, $p < 0.001$). However, adding MMC had no significant effect to overall survival and disease-free survival directly, although they had effects on increasing down-staging rate. The overall survival curve (Fig. 2) and disease-free survival curve (Fig. 3) showed distinct outcomes in patients with UFUR + RT + MMC, although this result did not reach significant difference statistically.

The acute complications after nCCRT were summarized at Table 6. Overall, severe complications were few (less than 1%) in both groups. It should be noted that group B patients did suffer from increased mild complication rates in white blood cell count, platelet count, lower GI symptoms, genitourinary problems, and skin toxicity such as dermatitis. In chronic complications such as anastomosis leakage or fistula, there was no difference between the two groups.

4. DISCUSSION

The standard treatment for advanced rectal cancer is composed of neoadjuvant chemoradiotherapy and subsequent TME, with

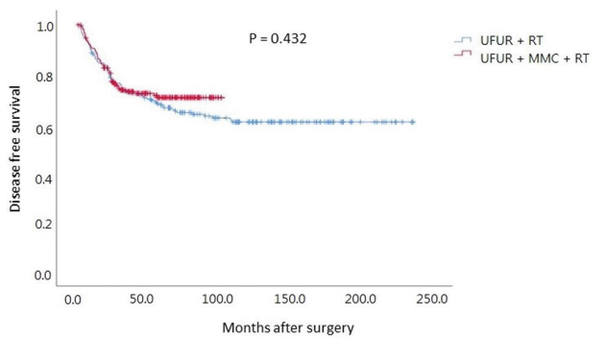

Fig. 3 The disease-free survival curves of group A and group B.

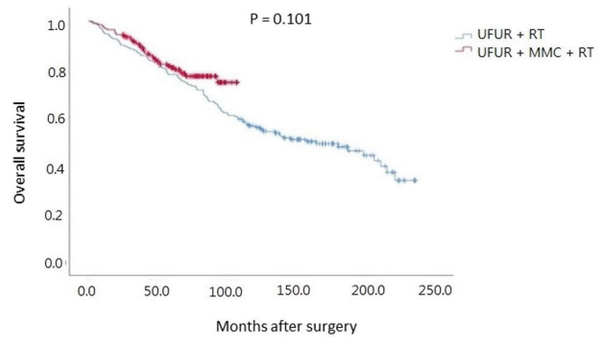

Fig. 2 The overall survival curves of group A and group B.

Table 6

Therapeutic complication (acute and chronic)

	RT + Ufur (%) (N = 191)	RT + Ufur +MMC (%) (N = 195)	*p*
Acute toxicity WBC (/μL)			<0.001
>4500	149 (80.1)	109 (55.9)	
3000-4500	37 (17.4)	60 (30.8)	
2000-3000	3 (1.5)	26 (13.3)	
1000-2000	0	0	
<1000	2 (1.0)	0	
Hgb (g/dL)			0.468
>12	151 (79.1)	149 (76.4)	
10-12	34 (17.8)	35 (17.9)	
8-10	4 (2.1)	11 (5.7)	
<8	2 (1.0)	0	
PLT (/uL)			0.001
>100	186 (97.4)	171 (87.7)	
80K-100K	4 (2.1)	16 (8.2)	
50K-80K	0	8 (4.1)	
<50K	1 (0.5)	0	
UGI toxicity			0.453
0	132 (69.1)	127 (65.2)	
1	56 (29.3)	58 (29.7)	
2	3 (1.6)	10 (5.1)	
LGI toxicity			0.002
0	5 (2.6)	7 (3.6)	
1	40 (20.9)	69 (35.4)	
2	142 (74.4)	118 (60.5)	
3	3 (1.6)	1 (0.5)	
4	1 (0.5)	0	
GU toxicity			<0.001
0	95 (49.7)	43 (22.1)	
1	63 (33.0)	104 (53.3)	
2	32 (16.8)	48 (24.6)	
3	1 (0.5)	0	
Skin toxicity			<0.001
0	66 (34.6)	11 (5.6)	
1	104 (54.4)	134 (68.7)	
2	21 (11.0)	50 (25.7)	
Chronic toxicity			
Anastomosis leak	15 (7.9)	9 (4.6)	0.025
Fistula	9 (4.7)	5 (2.6)	0.159

GU = genitourinary; LGI = lower GI; MMC = Mitomycin-C; RT = radiotherapy; UGI = upper GI.

additional adjuvant chemotherapy if needed. The regimen of neoadjuvant chemotherapy varies between practitioners and institutions. The patients in our hospital received oral UFUR alone as neoadjuvant chemotherapy during the period from May 2000 to October 2010, and UFUR plus MMC during the period from November 2010 to August 2017 to procure better outcome.

Of the 323 patients that underwent low anterior resection during the period in which subjects were included in the study, two of them (0.6%) were found to be distal margin positive. These patients were excluded from our study. In fact, a positive circumferential margin still raises major concerns in rectal surgery, as it is related to early recurrent and cancer-related death.[12] In our study, these 2 patients all suffered from disease recurrence and expired within 2 years after primary surgery.

The image study for clinical stage before neoadjuvant therapy included CT scan and MRI. Overall, 66.8% of the patients received MRI study, and 33.2% received CT scan. As we know that MRI had better accuracy for T-stage judgments than CT scan because MRI had better ability to identify rectal wall laminar structure,[13] the large number of CT scan in our study may lead to inaccurate clinical stage, although the ratio of CT, MRI was similar in both group of patients.

Group B had more subjects with advanced initial clinical stages. This may be related to the fact that MMC was added to the UFUR regimen in 2010, ten years after the group A patients underwent nCCRT. In the earlier period, while neoadjuvant therapy had just practiced for rectal cancer, CCRT arranged in preoperative period had a benefit to reduce anastomotic complications compared with postoperative radiation. However, there was still concern about inaccuracies in clinical staging that induced overtreatment. Recent studies have all agreed that preoperative CCRT provides vital down-staging of tumors helps achieve R0 resection[14] as well as sphincter preservation rate.[15] Because the role of neoadjuvant CCRT has become clear, many more patients with advanced rectal cancer, including those with T4 tumor, undergo CCRT before surgery. Indeed, the two study groups were treated in quite different periods. Though the technique of pelvic radiation remained almost the same during these two periods, the gap between RT and surgery was larger in group B.

In our analysis, the MMC group that had more advanced initial clinical stages received more RT doses to the primary site (mean 46.4 Gy vs 45.1 Gy, $p < 0.001$). In our RT protocol, those who have T4 tumors receive an extra bolus RT dose, so it is reasonable that these patients would receive higher RT doses over time. Because this study is retrospective and not randomized, we were unable to control for this variable. We did perform Cox proportional hazard and found pre-RT T stage and RT-surgery gap are related to overall survival. Pre-RT T stage and N stage are related to disease-free survival (Table 5).

MMC is a well-known radiosensitizer, and it has an important role in anal cancer therapy.[16–18] MMC plus 5-FU are also used for salvage treatment for metastatic colorectal cancer after previous oxaliplatin or target therapy, with favorable toxicity profiles and cost efficacy.[19–21] In this study, the toxicity of MMC, including grade 1 and grade 2 neutropenia and thrombocytopenia, was higher when compared with UFUR alone, but there were no significant differences in grade 3 or grade 4 neutropenia or thrombocytopenia, nor were there differences in other toxicity symptoms such as nausea/vomiting between two groups. Overall, the cases of severe toxicity (more than grade 3) were few in our study. Also, the rates of severe toxicity with the use of MMC in published literature are all reported as less than 10%.[22,23] For the efficacy, group B did not have higher pCR rate despite adding MMC in the regimen (Table 3). The possible reasons are the relatively low dose (6 mg/m^2) and only one injection of MMC was given in our protocol. Radiation with or without oral UFUR might already have profound down-staging effect for rectal cancer, regardless of whether more chemotherapy drug was given. Anyhow, the down-staging effect was more prominent in group B (Table 4). Our protocol may be a reasonable

choice for older patients with low rectal cancer, who are not candidates for more aggressive chemotherapeutic regimens such as FOLFOX due to higher toxicity.[24]

Our study is limited by its retrospective design, which is associated with the risk of selection bias. However, there were still some advantages in our study design, including uniform protocol, large case number, and long follow-up time. We believe that our experience may provide support for an alternative regimen of neoadjuvant chemoradiation for rectal cancer. Prospective randomized studies are needed to explore the exact role of MMC in nCCRT for rectal cancer.

In conclusion, adding MMC to the regimen of nCCRT for rectal adenocarcinoma contributes to preoperative tumor downstaging and can potentially improve disease-free survival rates and overall survival rates. Because of increased low-grade toxicity, MMC should be used with caution in combination with RT and oral UFUR in older patients and those with impaired bone marrow function.

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