Original Article

The benefit of adjuvant chemotherapy in pathological T1–3N0M0 rectal mucinous adenocarcinoma: no improvement survival outcomes based on long-term survival analysis of large population data

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Background: Currently, the benefits of the administration of adjuvant chemotherapy (AT) in pathological low-risk rectal mucinous adenocarcinoma (RM) with T1–3N0M0 are unclear. The objective of this study is to retrospectively investigate the clinical significance of AT in terms of survival outcomes for patients with pathological T1–3N0M0 RM using data from a large population.

Methods: The patient data were collected from the Surveillance, Epidemiology, and End Results (SEER) Program. The Chi-squared test was used to analyze categorical variables. The survival curves were compared using the log-rank test and the Kaplan-Meier method. A multivariate proportional hazards regression (Cox) model was applied to identify the independent prognostic factors of survival outcomes. Propensity score matching (PSM) was utilized to eliminate the differences between groups and estimate AT's effect.

Results: The median follow-up duration for the rectal cancer (RC) cohort was 116 months. Multivariate analyses revealed that RM was a significant adverse prognostic factor, correlating with poorer overall survival (OS) and cancer-specific survival (CSS) for RC [hazard ratio (HR): 1.226, 95% confidence interval (CI): 1.094–1.375, P<0.001; HR: 1.446, 95% CI: 1.242–1.683, P<0.001]. Among patients with RM, the rates of 5-year OS and CSS were 68.6% and 79.3% in the AT (–) group, respectively. Additionally, the AT (+) group exhibited similar rates of 65.6% for 5-year OS and 74% for CSS (P=0.80, P=0.26). Subtype analysis according to preoperative therapy status showed that AT also did not significantly affect survival outcomes (P=0.65, P=0.34; P=0.90, P=0.76).

Conclusions: Our study found that RM is a poor prognostic factor in pathological T1–3N0M0 RC. However, AT does not appear necessary to improve survival outcomes of pathological T1–3N0M0 RM.

Keywords: Rectal cancer (RC); mucinous adenocarcinoma; adjuvant chemotherapy (AT); survival

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Introduction

Colorectal cancer (CRC) is one of the most common malignant tumors worldwide, constituting approximately 10% of cancer cases and deaths (1). Rectal cancer (RC) poses a higher risk of recurrence compared to colon cancer due to the complex pelvic anatomical structure, which results in the complexity of RC optimal management (2,3). In recent decades, with the rapid development of neoadjuvant chemoradiotherapy and the widespread use of total mesorectal excision (TME), although the risk of local recurrence (LR) has significantly decreased, distant metastasis remains a major reason for therapy failure in resectable RC (4,5). Adjuvant chemotherapy (AT) plays a crucial role in controlling distant metastasis by eradicating remaining circulating tumor cells and micrometastases in patients with high-risk factors for CRC after curative surgery (6,7). Nevertheless, in comparison to colon cancer, there remains insufficient evidence to conclusively demonstrate the oncological benefits of AT in RC, partly due to the complexities associated with preoperative treatment administration (3,7,8). Furthermore, the existing national guidelines and clinical practices for the administration of AT for RC exhibit incomplete uniformity, particularly following neoadjuvant chemoradiotherapy (2,3,9).

Rectal mucinous adenocarcinoma (RM) represents a subset of RC, accounting for approximately 10% (10), which is distinguished by an abundance of extracellular mucin components. RM exhibits distinct oncology features compared to rectal adenocarcinoma (RA), in terms of the mechanism of oncogenesis, clinicopathologic characteristics, genetic features, and therapeutic responsiveness (11-13). However, there is a lack of consensus on the survival prognosis of RM (14,15). The majority of studies indicate that RM is a potential predictor of poor prognosis associated with low survival rates and a higher likelihood of recurrence (16-19), possibly attributed to its more aggressive oncological behavior. However, the therapy administration for RC does not differentiate histological type between mucinous and non-mucinous adenocarcinomas to determine whether more aggressive postoperative supplementary treatment is needed. In addition, studies have demonstrated that RM exhibits less sensitivity to chemotherapy (19-21). A pooled analysis from 3 prospective clinical trials showed that RM is related to a lower pathological complete response and tumor downstaging rates after neoadjuvant therapy (20). Shin *et al.* found that RM has a lower T-downstage rate after preoperative radiochemotherapy than non-mucinous adenocarcinoma (21). Currently, the administration of AT in RM is controversial. Our previous study showed the survival benefits of high-risk RM with positive lymph nodes (19), but the validity of the same for lower-risk RM with pathological T1–3N0M0 remains unclear.

In light of this context, the objective of this study is to retrospectively investigate the clinical significance of AT in terms of survival outcomes using data from a large population. The findings will provide a valuable reference for guiding personalized clinical decisions for patients with pathological T1–3N0M0 RM. We present this article in accordance with the STROBE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-271/rc).

Highlight box

Key findings

- Rectal mucinous adenocarcinoma (RM) is a poor prognostic factor in pathological T1–3N0M0 rectal cancer (RC).
- Adjuvant chemotherapy (AT) did not significantly improve survival outcomes in patients with pathological T1–3N0M0 RM.

What is known and what is new?

- In clinical practice, many high-risk factors are considered in the decision-making process for AT in RC.
- In this study, we found that there were no significant survival benefits with AT in patients with pathological T1–3N0M0 RM.

What is the implication, and what should change now?

- AT does not appear necessary to improve survival outcomes of pathological T1–3N0M0 RM.

Methods

Patient data source

The patient data were collected from the Surveillance, Epidemiology, and End Results (SEER) Program (the SEER*Stat version 8.4.1) (seer.cancer.gov), which is a large cancer database established by the National Cancer Institute. We collected the data of patients who were diagnosed with primary RC with pathological T1-3N0M0 from the SEER database between 2004 and 2017. Mucinous adenocarcinoma and mucin-producing adenocarcinoma, based on the International Classification of Diseases for Oncology, were identified in RM. *Figure 1* displays the specific selected process in detail. The data provides detailed patient information, including demographic information, survival time, overall survival (OS) and cancer-specific survival (CSS), systematic therapy mode, pathological

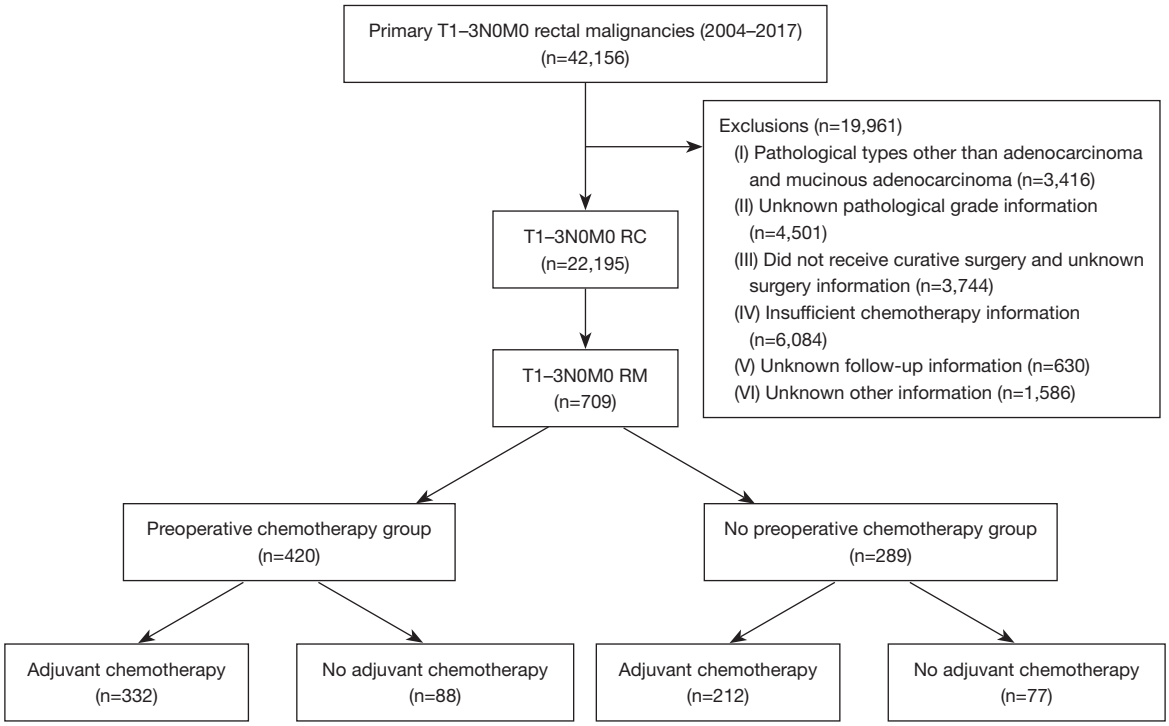

Figure 1 Flowchart of screening patients. RC, rectal cancer; RM, rectal mucinous adenocarcinoma.

TNM stage, pathological type, etc. Marital status includes single and married, and single includes unmarried, divorced and widowed. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Statistical analysis

The Chi-squared test was used to analyze categorical variables. The Kaplan-Meier method and log-rank test were used to compare the survival curves. A multivariate proportional hazards regression (Cox) model was applied to identify the independent prognostic factors of OS and CSS. Additionally, we utilized propensity score matching (PSM) to eliminate the differences between groups and estimate AT's effect on these groups. P values less than 0.05 were considered significant statistical differences. IBM SPSS statistical software (version 27) was used for the statistical analysis, and GraphPad Prism (version 9.3.1) was used to create the figures.

Results

Patient characteristics

We analyzed 42,156 patients diagnosed with pathological T1–3N0M0 primary rectal malignancies identified in the SEER database between 2004–2017. *Figure 1* shows the detailed selection process. Finally, after curative surgery, 22,195 patients with pathological T1–3N0M0 RC meeting inclusion criteria were selected, of which 21,486 were RA and 709 were RM. We found that RM was more likely to have single status, poor grade, and advanced T stages compared to RA (P=0.002, P<0.001, P<0.001; Table S1). In addition, RM had a high proportion of receiving preoperative chemotherapy and AT (40.8% *vs.* 32%, P<0.001; 23.3% *vs.* 19%, P=0.009; Table S1).

RM is a poor prognostic factor for RC

For the overall cohort, the median follow-up duration covered 116 months. The findings from multivariate analyses showed RM as a significant adverse prognostic factor, associated with a worse OS and CSS for RC [hazard ratio (HR): 1.226, 95% confidence interval (CI): 1.094–1.375, P<0.001; HR: 1.446, 95% CI: 1.242–1.683, P<0.001; Table S2]. AT is an independent prognostic factor in T1–3N0M0 RC for OS rather than CSS (HR: 0.868, 95% CI: 0.815–0.924, P<0.001; HR: 1.068, 95% CI: 0.982–1.161, P=0.12; Table S2).

Table 1 Baseline characteristics of patients with pT1–3N0M0 RM

Variable	AT (–) group (N=544)	AT (+) group (N=165)	P
Age (years)			0.001
<70	315 (57.9)	120 (72.7)	
≥70	229 (42.1)	45 (27.3)	
Gender			0.35
Male	334 (61.4)	108 (65.5)	
Female	210 (38.6)	57 (34.5)	
Race			0.25
White	451 (82.9)	140 (84.8)	
Black	54 (9.9)	10 (6.1)	
Other	39 (7.2)	15 (9.1)	
Marital status			0.005
Single	249 (45.8)	55 (33.3)	
Married	295 (54.2)	110 (66.7)	
Household income			0.07
< $60,000	179 (32.9)	67 (40.6)	
≥ $60,000	365 (67.1)	98 (59.4)	
Regional nodes examined			0.64
<12	253 (46.5)	85 (51.5)	
≥12	291 (53.5)	80 (48.5)	
Grade			0.36
I/II	459 (84.4)	144 (87.3)	
III/IV	85 (15.6)	21 (12.7)	
Pathologic T			0.001
pT1–2	234 (43.0)	48 (29.1)	
pT3	310 (57.0)	117 (70.9)	
Sphincter preservation			0.001
No	119 (21.9)	57 (34.5)	
Yes	425 (78.1)	108 (65.5)	
Preoperative chemotherapy			0.08
No	332 (61.0)	88 (53.3)	
Yes	212 (39.0)	77 (46.7)	

Data are presented as n (%). RM, rectal mucinous adenocarcinoma; AT, adjuvant chemotherapy.

AT does not improve survival of pathological T1–3N0M0 RM

Subsequently, we compared the demographic and clinical characteristics of RM between the AT (–) group and the AT (+) group. Compared to the AT (–) group, the AT (+) group likely had relatively younger ages (<70 years), married status, advanced T stages, and a lower rate of sphincter preservation (P=0.001, P=0.005, P=0.001, P=0.001; *Table 1*). Although marital status is generally not considered a prognostic factor in biological research, there were married patients who had a higher rate of receiving AT (P=0.005). In the overall RM cohort, the rates of 5-year OS and CSS were 68.6% and 79.3% in the AT (–) group, respectively. Additionally, the AT (+) group exhibited similar rates of 65.6% for 5-year OS and 74% for CSS (P=0.80, P=0.26; *Figure 2A,2B*). Subgroup analysis based on the T stage showed a similar result without a significant statistical difference (P=0.65, P=0.34; P=0.90, P=0.76 *Figure 2C-2F*). Univariate analysis found no statistically significant survival benefits with AT in T3N0M0 RM (HR: 1.056, 95% CI: 0.81–1.378, P=0.80; HR: 1.217, 95% CI: 0.859–1.723, P=0.26; *Table 2*).

According to preoperative therapy status, patients with T3N0M0 RM were divided into the preoperative chemotherapy and the no preoperative chemotherapy groups. In the preoperative chemotherapy group, AT did not significantly affect survival outcomes (P=0.49, P=0.88, P=0.96, P=0.50, P=0.38, P=0.60; Figure S1). Similarly, there were also no survival benefits with AT in the no preoperative chemotherapy group (P=0.26, P=0.08, P=0.60, P=0.60, P=0.53, P=0.34; Figure S2). Univariate and multivariate analyses found that AT was not an independent prognostic factor for T1-3N0M0 RM whether preoperative therapy status (P=0.49, P=0.88; P=0.26, P=0.08; *Table 3* and Table S3).

PSM

To control for confounding factors, we used PSM to balance the AT (–) group and the AT (+) group. After PSM, there were no significant statistical differences in the demographic and clinical characteristics between groups (*Table 4*). No significant survival benefits were also found for AT in T1–3N0M0 RM in the matched cohort, regardless of

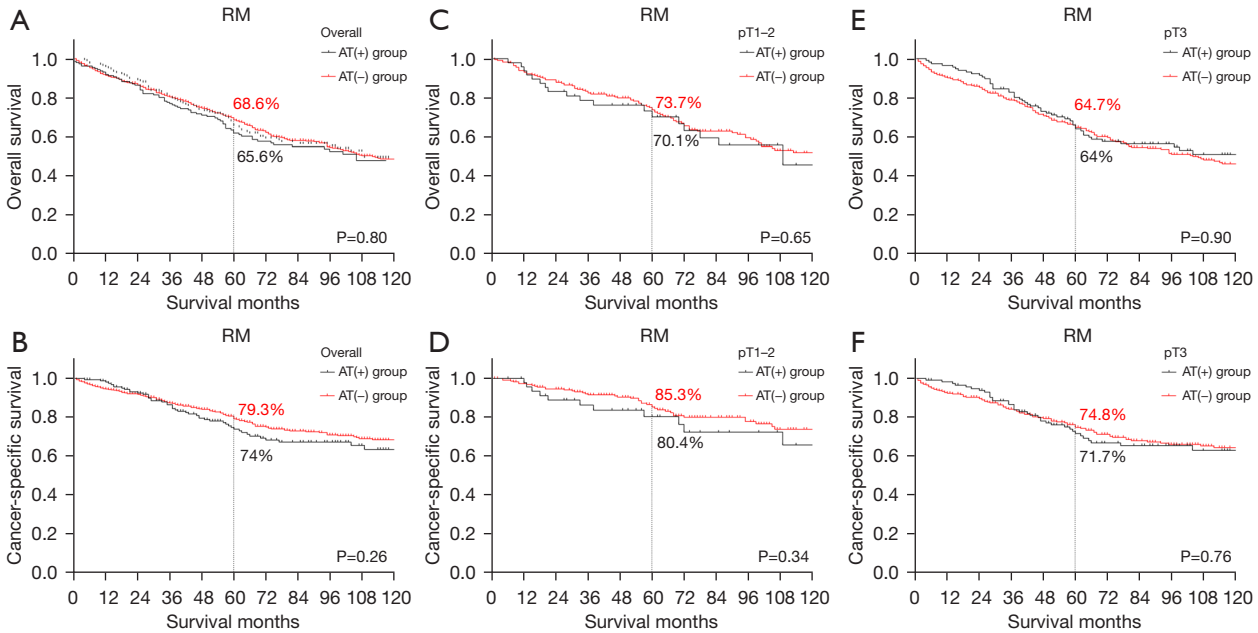

Figure 2 Kaplan-Meier curves for the overall RM cohort and the subtype based on the T stage. RM, rectal mucinous adenocarcinoma; AT, adjuvant chemotherapy.

preoperative chemotherapy status (P=0.63, P=0.83, P=0.79, P>0.99, P=0.86, P>0.99, *Figure 3A-3F*; P=0.93, P=0.70, P=0.89, P=0.47, P=0.80, P=0.93, *Figure 4A-4F*). Table S4 and Table S5 show the results of univariate and multivariate analyses of affecting 5-year OS and CSS in patients with T1–3N0M0 RM after PSM. The age (P<0.001, P=0.002; Table S4) and regional nodes examined (P=0.04, P=0.02; Table S4) were independent prognostic factors for OS and CSS in T1–3N0M0 RM after preoperative chemotherapy. Additionally, age was an independent prognosis factor for OS and CSS in patients who had not received preoperative chemotherapy. The poor grade was associated with a worse CSS rather than OS (HR: 3.153, 95% CI: 1.564–6.358, P=0.001; HR: 1.583, 95% CI: 0.788–3.181, P=0.16; Table S5).

Discussion

AT is an important component of RC management to reduce recurrence and improve survival outcomes. However, the oncological benefits of AT for RM, a relatively rare subtype but with higher recurrence risk, have not been established. The individualized administration to RM patients is essential to improve survival outcomes. In this retrospective study, we demonstrated that RM is a poor prognostic factor for RC. Additionally, there were no survival benefits with AT in T1–3N0M0 RM patients.

Mucinous adenocarcinoma is a distinct form of RC, and its prognostic and clinical implications for therapy are currently subject to controversy. Tarantino *et al.* discovered that the pathological subtype of mucinous adenocarcinoma did not restrict the survival outcomes in patients with RC (15). Hugen *et al.*, based on data from the Netherlands Cancer Registry, showed that modern administration of therapy resulted in equal survival outcomes for RM and RA (14). Our study found that RM had a worse 5-year OS and CSS compared to RA, which is consistent with most current studies. The different metastasis modes and high risk of metastasis are important reasons for the poor prognosis (17,22,23). The mucus production under pressure may gain the chance of spreading tumor cells (23,24). In addition, molecular and biological distinctions between RM and RA lead to more aggressive biological behavior (25).

Due to the complexity of RC treatment, the current precise oncology benefits of AT remain unclear, especially after neoadjuvant chemotherapy or radiochemotherapy. Carvalho *et al.* showed that the data from the adjuvant RC trials over the past 30 years do not support the routine use of AT after preoperative chemoradiotherapy (8). Nevertheless, NCCN (National Comprehensive Cancer

Table 2 Univariate and multivariate analyses of the effects of prognostic factors on 5-year OS and CSS in patients with pT1–3N0M0 RM

Variable	Overall survival				Cancer-specific survival			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Age (years)		<0.001		<0.001		<0.001		<0.001
<70	Reference		Reference		Reference		Reference	
≥70	3.11 (2.437–3.968)		2.994 (2.369–3.784)		2.214 (1.612–3.043)		2.277 (1.689–3.071)	
Gender		0.10				0.03		0.02
Male	Reference				Reference		Reference	
Female	0.816 (0.646–1.029)				0.709 (0.522–0.962)		0.684 (0.495–0.945)	
Race		0.30				0.35		
White	Reference				Reference			
Black	1.147 (0.778–1.691)				1.047 (0.628–1.745)			
Other	0.676 (0.436–1.049)				0.603 (0.341–1.067)			
Marital status		0.002		0.03		0.06		
Single	Reference		Reference		Reference			
Married	0.716 (0.569–0.902)		0.776 (0.62–0.972)		0.744 (0.55–1.006)			
Household income		0.28				0.95		
< $60,000	Reference				Reference			
≥ $60,000	0.859 (0.678–1.088)				1.001 (0.734–1.366)			
Regional nodes examined		0.002		0.03		0.002		0.001
<12	Reference		Reference		Reference		Reference	
≥12	0.702 (0.56–0.88)		0.78 (0.623–0.977)		0.621 (0.462–0.835)		0.611 (0.451–0.828)	
Grade		0.32				0.23		
I/II	Reference				Reference			
III/IV	1.187 (0.863–1.633)				1.277 (0.838–1.947)			
Pathologic T		0.07				0.004		<0.001
pT1–2	Reference				Reference		Reference	
pT3	1.13 (0.921–1.347)				1.582 (1.17–2.139)		1.89 (1.36–2.626)	
Sphincter preservation		0.54				0.57		
No	Reference				Reference			
Yes	1.089 (0.8369–1.416)				1.109 (0.786–1.567)			
Preoperative chemotherapy		0.005		0.32		0.77		
No	Reference		Reference		Reference			
Yes	0.739 (0.59–0.927)		0.887 (0.701–1.122)		0.965 (0.717–1.299)			
AT		0.80				0.26		
No	Reference				Reference			
Yes	1.056 (0.81–1.378)				1.217 (0.859–1.723)			

OS, overall survival; CSS, cancer-specific survival; RM, rectal mucinous adenocarcinoma; HR, hazard ratio; CI, confidence interval; AT, adjuvant chemotherapy.

Table 3 Univariate and multivariate analyses of the effects of prognostic factors on 5-year OS and CSS in patients with ypT1–3N0 RM after preoperative chemotherapy and surgery

Variable	Overall survival				Cancer-specific survival			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Age (years)		<0.001		<0.001		0.001		0.003
<70	Reference		Reference		Reference		Reference	
≥70	2.968 (1.914–4.602)		2.829 (1.954–4.096)		2.131 (1.254–3.619)		1.992 (1.257–3.159)	
Gender		0.006		0.01		0.04		0.06
Male	Reference		Reference		Reference		Reference	
Female	0.55 (0.376–0.805)		0.581 (0.377–0.895)		0.589 (0.37–0.937)		0.606 (0.361–1.018)	
Race		0.65				0.74		
White	Reference				Reference			
Black	1.226 (0.655–2.297)				1.115 (0.518–2.4)			
Other	0.826 (0.424–1.608)				0.735 (0.341–1.698)			
Marital status		0.16				0.12		
Single	Reference				Reference			
Married	0.771 (0.53–1.122)				0.705 (0.446–1.12)			
Household income		0.16				0.34		
< $60,000	Reference				Reference			
≥ $60,000	0.768 (0.524–1.127)				0.802 (0.503–1.279)			
Regional nodes examined		0.01		0.03		0.004		0.008
<12	Reference		Reference		Reference		Reference	
≥12	0.622 (0.432–0.897)		0.657 (0.454–0.95)		0.52 (0.333–0.811)		0.537 (0.339–0.848)	
Grade		0.36				0.67		
I/II	Reference				Reference			
III/IV	1.246 (0.749–2.073)				1.137 (0.61–2.119)			
Pathologic T		0.66				0.71		
pT1–2	Reference				Reference			
pT3	1.108 (0.712–1.726)				0.905 (0.526–1.555)			
Sphincter preservation		0.34				0.73		
No	Reference				Reference			
Yes	0.826 (0.549–1.244)				1.095 (0.666–1.8)			
AT		0.49				0.88		
No	Reference				Reference			
Yes	0.859 (0.567–1.299)				0.961 (0.581–1.59)			

OS, overall survival; CSS, cancer-specific survival; RM, rectal mucinous adenocarcinoma; HR, hazard ratio; CI, confidence interval; AT, adjuvant chemotherapy.

Table 4 The clinicopathological characteristics of the patients between AT (+) and AT (–) groups after propensity score matching

Variable	Preoperative chemotherapy			No preoperative chemotherapy		
	AT (–) group	AT (+) group	P	AT (–) group	AT (+) group	P
Age (years)			0.65			0.30
<70	79	47		91	44	
≥70	26	13		73	26	
Gender			0.70			0.06
Male	74	44		91	48	
Female	31	16		73	22	
Race			0.68			0.46
White	86	52		155	63	
Black	11	4		4	3	
Other	8	4		5	4	
Marital status			0.15			0.76
Single	47	20		62	25	
Married	58	40		102	45	
Household income			0.60			0.26
< $60,000	35	22		42	23	
≥ $60,000	70	38		122	47	
Regional nodes examined			0.95			0.57
<12	53	30		91	34	
≥12	52	30		73	36	
Grade			0.80			0.31
I/II	95	55		150	61	
III/IV	10	5		14	9	
Pathologic T			0.72			0.38
ypT1–2/pT1–2	18	9		90	34	
ypT3/pT3	87	51		74	36	
Sphincter preservation			0.58			0.16
No	34	22		23	15	
Yes	71	38		141	55	

AT, adjuvant chemotherapy.

Network) guidelines recommend AT to all patients with pathological stage II/III RC if they did not receive neoadjuvant chemotherapy regardless of the surgical pathology results (3). In UK guidelines, pathological high-risk factors, such as tumor grade and peripheral nerve invasion, are essential to guide AT (9). However, the value of histological classification, which has a poor prognosis, in guiding the administration of AT is unclear. Additionally, the infrequent occurrence of RM relative to RA limits the availability of reliable evidence on the benefits of AT for this histologic type. As a result, developing a safe, specified, and efficient AT strategy is essential to directing care and

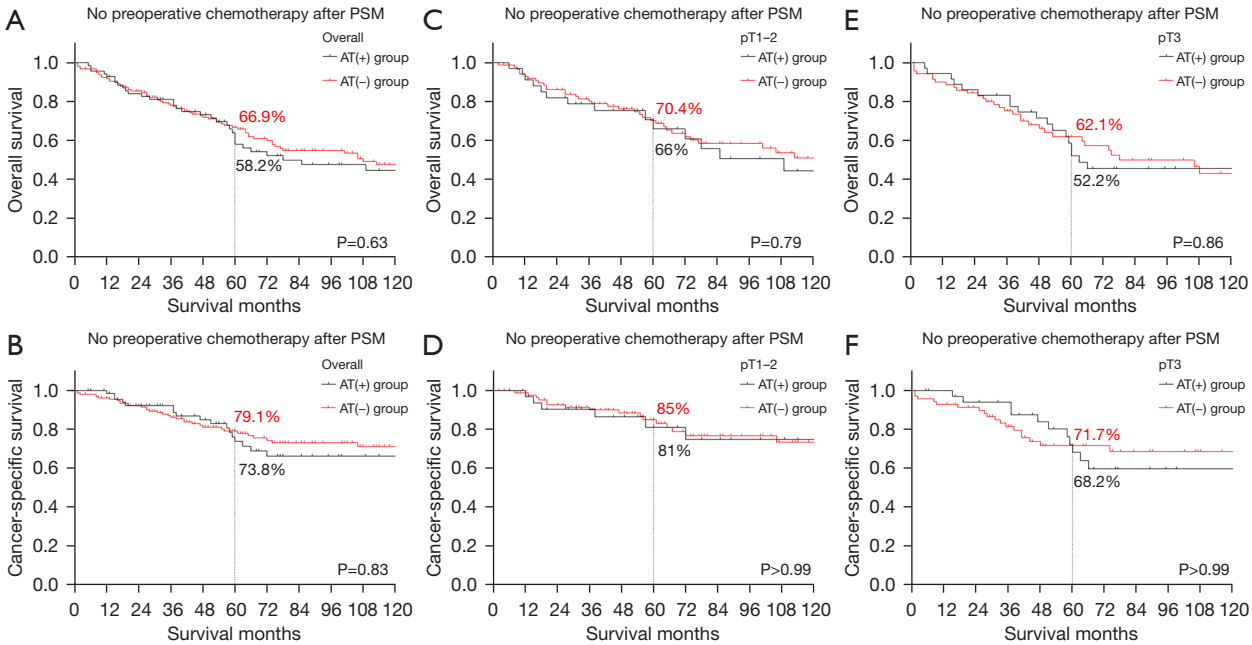

Figure 3 After PSM, Kaplan-Meier curves for the RM patients who did not receive preoperative chemotherapy and the subtype analysis based on the T stage. AT, adjuvant chemotherapy; PSM, propensity score matching; RM, rectal mucinous adenocarcinoma.

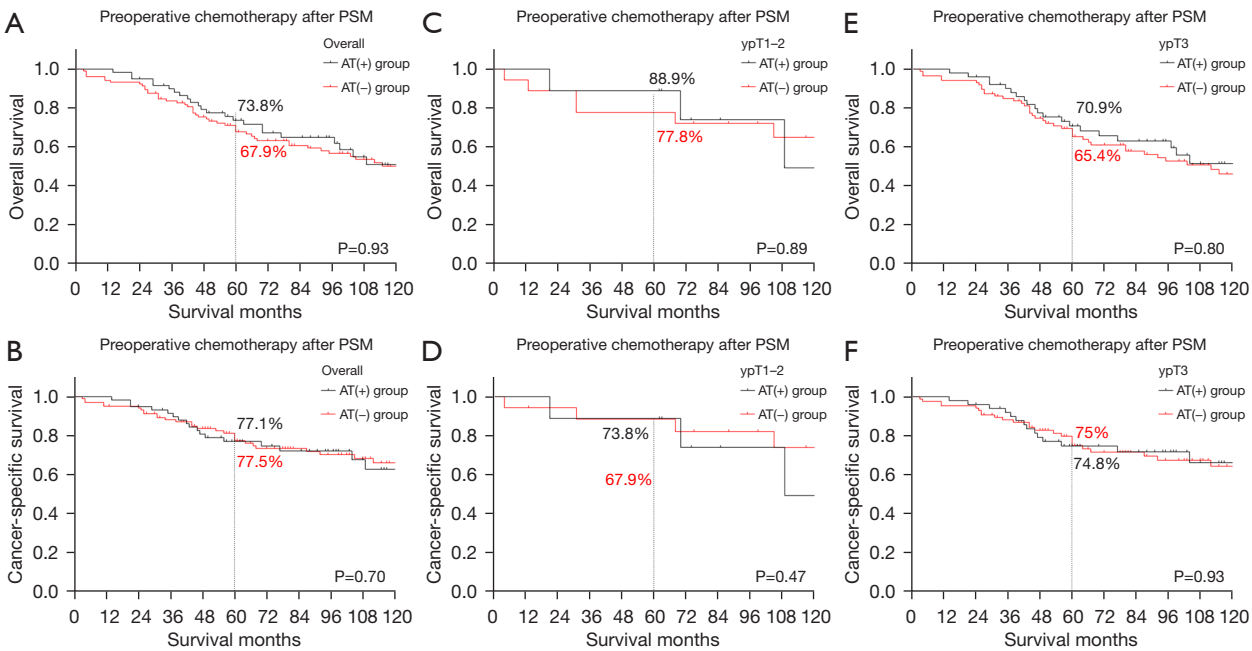

Figure 4 After PSM, Kaplan-Meier curves for the RM patients after preoperative chemotherapy and the subtype analysis based on the T stage. AT, adjuvant chemotherapy; RM, rectal mucinous adenocarcinoma; PSM, propensity score matching.

enhancing the prognosis of RM. Our previous study showed AT did not provide a survival benefit in patients with stage ypI RC undergoing preoperative chemotherapy (26), and it was unclear whether this result applied to RM with more aggressive behavior. In this population-based study, we found that there were no survival benefits with AT in T1–3N0M0 RM patients, which may be related to RM having higher chemotherapy resistance. Resistance to chemotherapy is a significant challenge in the treatment of mucinous adenocarcinoma. The mucin produced by the cancer cells can form a physical barrier that hinders the penetration of chemotherapy drugs into the tumor (27,28), which makes it more difficult for the drugs to reach and effectively target the cancer cells. Furthermore, Glasgow *et al.* found that known molecular markers for response to chemotherapy, such as TYMS and GSTP1, were significantly overexpressed in mucinous tumors compared to non-mucinous adenocarcinomas (29). Genetic alterations lead to the activation of pro-survival signals and the inhibition of signals that induce cell death in response to chemotherapy (11,30,31). Our studies demonstrated that AT had not provided survival benefits to pathological T1–3N0M0 RM patients, regardless of the status of preoperative chemotherapy. Thus, AT's side effects and expected benefits should be carefully evaluated. In this study, we observed a high proportion of patients with less than 12 lymph nodes examined, which may be associated with several factors, including earlier TNM stage, tumor location in the rectum, and patients who underwent preoperative neoadjuvant therapy (32,33). Additionally, we found that there were differences in marital status between the AT (–) and AT (+) groups, but it is not generally considered a prognostic factor in biological research.

There are some limitations to our research. First, we did not obtain the clinical stage of preoperative treatment from the database, which limits our ability to directly assess the effect of preoperative chemotherapy on pathological staging. The differences of stage migration to preoperative chemotherapy may affect survival outcomes and the accurate assessment of the efficacy of AT treatment. Second, although the SEER database based on a large population contains information about chemotherapy, it does not provide detailed treatment regimens such as the types of chemotherapy drugs, dosages, and duration of treatment, which is an important to exploring the benefits of AT. This may be a limitation in studying the effectiveness of AT. Third, there was a lack of data related to radiotherapy in the study. Radiotherapy is an important component of RC treatment, which has been associated with decreased rates of LR of RC. Fourth, the lack of information on patients' microsatellite instability (MSI) status in our study is a limitation. Mucinous adenocarcinoma shows a relatively high frequency of MSI as a marker of a deficient mismatch repair (dMMR) system, which is important from a prognostic and therapeutic perspective, as MSI-high status confers improved survival in mucinous adenocarcinoma and may qualify a patient for anti-programmed death 1 (PD-1) therapy. Finally, our study did not obtain information about the circumferential margin of the rectal, which is important for decision-making for AT.

Conclusions

Our study found that RM is a poor prognosis factor in pathological T1–3N0M0 RC. However, AT does not appear necessary to improve survival outcomes of pathological T1–3N0M0 RM.

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Footnote

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