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Survival Benefit of Primary Tumor Resection Combined With Chemotherapy in Patients With Unresectable Colorectal Mucinous Adenocarcinoma With Liver Metastasis

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Objective: To evaluate the survival benefit of combining primary tumor resection (PTR) and chemotherapy in patients with unresectable colorectal mucinous adenocarcinoma with liver metastasis (UCR-MAC-LM).

Methods: We obtained data from the surveillance, epidemiology, and end results database for patients with UCR-MAC-LM from 2010 to 2017. Clinicopathological characteristics were analyzed using the χ^2 test. Propensity score matching was performed to balance baseline characteristics. Kaplan-Meier analysis and log-rank tests were used to estimate and compare survival outcomes. Univariate and multivariate Cox regression analyses were conducted to identify the prognostic factors.

Results: A total of 10,178 patients with unresectable colorectal adenocarcinoma with liver metastasis were included, of whom 6.01% (n = 612) had UCR-MAC-LM. The UCR-MAC-LM group had a higher proportion of female patients, a greater number of elderly patients, an increased incidence of right colon localization, larger tumor size, and higher T and N staging than the unresectable colorectal non-mucinous adenocarcinoma with liver metastasis group ($P < 0.05$). Multivariate analysis identified several independent prognostic factors ($P < 0.05$). Patients with unresectable colorectal adenocarcinoma with liver metastasis who underwent PTR+C had superior survival rates compared with those who received PTR/C alone or no treatment (cancer-specific survival, $P < 0.05$; overall survival, $P < 0.05$). Subgroup analysis revealed that 17 of 22 groups of patients with UCR-MAC-LM who received PTR+C had significantly prolonged long-term survival compared with those who received PTR/C alone.

Conclusions: This surveillance, epidemiology, and end results-based study indicates that PTR+C may offer a survival advantage for a specific subgroup of patients with UCR-MAC-LM compared with PTR/C alone. Nonetheless, additional clinical trials are necessary to validate these findings.

Key Words: colorectal adenocarcinoma, mucinous adenocarcinoma, liver metastasis, chemotherapy, primary tumor resection

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Colorectal adenocarcinoma (CRC) is the fourth most common malignant tumor and ranks second in cancer death worldwide.[1] Distant metastasis is a critical risk factor associated with poor prognosis in CRC.[2] The liver is the most frequent metastatic site in CRC, with approximately 20% to 25% of patients presenting with synchronous liver metastasis at the time of diagnosis.[3]

Multidisciplinary treatment strategies, including adjuvant chemotherapy, complete resection of the primary tumors, and metastatic lesions, are recommended for the management of colorectal mucinous adenocarcinoma with liver metastasis (CR-MAC-LM).[4,5] Nevertheless, only ~20% of patients with colorectal adenocarcinoma with liver metastasis (CRLM) are classified as resectable, and >70% of patients with CRLM present with unresectable metastasis.[6–8] However, the necessity of primary tumor resection (PTR) for patients with unresectable colorectal adenocarcinoma with liver metastasis (UCRLM) is still a matter of discussion.[9–12] According to several guidelines, the standard management for patients with UCRLM is systemic chemotherapy, and PTR is not recommended unless there is perforation, bowel obstruction, or severe bleeding.[10,13,14] Oxaliplatin-based chemotherapy is preferentially recommended as the first-line treatment strategy for patients with UCRLM.[15,16] In addition, previous studies have shown that among patients with UCRLM, PTR+C provides better long-term outcomes than PTR/C alone.[17,18]

Mucinous adenocarcinoma (MAC) is a specific morphologic subtype of CRC that accounts for 10% to 15% of CRC patients.[19] MA is defined as >50% of tumor containing extracellular mucin.[20] It is generally recognized that MAC of CRC has distinct clinicopathological features and molecular pathways, which may contribute to higher advanced stages at diagnosis, different therapeutic responses, and poorer survival compared with non-mucinous adenocarcinoma (NOS).[21–28]

This study aimed to evaluate the therapeutic efficacy of PTR+C in patients with unresectable colorectal mucinous adenocarcinoma with liver metastasis (UCR-MAC-LM).

METHODS

Date Source

Information pertaining to all patients diagnosed with CRC was extracted from the surveillance, epidemiology, and end results (SEER) database, which encompasses comprehensive data on cancer incidence, prevalence, and survival, representing 28% of the US population. As the SEER database is freely available to the public, informed consent was deemed unnecessary.[29]

Patient Selection

We obtained data from patients diagnosed with UCRLM between 2010 and 2017 from the SEER database. All

participants were clinically staged according to the sixth edition of the American Joint Committee on Cancer. Patients with UCRLM were recruited based on the following inclusion criteria: (1) malignant ICD-O-3 behavior codes, (2) histologically confirmed diagnosis, (3) presence of PTR, and (4) vital status (alive or dead). Patients were excluded based on the following criteria: (1) unknown surgery information; (2) surgery for metastatic lesions was either performed or not reported; (3) nonhistologic diagnosis; (4) multiple primary cancer; (5) survival time <1 month or unknown; (6) PTR codes 10, 11, 12, 20, 22, 24, 26, 27, 28, and 29; (7) unknown surgery information; (8) unknown T/N stage; and (9) unknown radiotherapy information. Clinical variables of the patients, including age at diagnosis, sex, race, tumor grade, T/N stage, tumor size, and tumor location, were extracted from the SEER database. This study included 10178 patients with UCRLM diagnosed between 2010 and 2017 from the SEER database (Fig. 1).

Statistical Analysis

Differences between cancer-specific survival (CSS) and overall survival (OS) were analyzed using the log-rank test, and the Kaplan-Meier method was used to construct survival curves.[30,31] A multivariable Cox regression proportional hazards model was used to assess the impact of various factors on survival outcomes. χ^2 and Fisher exact probability tests were used to identify differences in baseline patient characteristics between treatment groups. In addition, univariate and multivariate Cox proportional hazard models with hazard ratios (HRs) and 95% CIs were used to investigate prognostic factors influencing survival outcomes. Only variables that were significantly associated with survival in univariate analysis were considered in multivariate analysis. To account for any disparities in baseline characteristics between the UCR-MAC-LM and unresectable colorectal nonmucinous adenocarcinoma with liver metastasis (UCR-NOS-LM) groups, propensity score matching (PSM) was performed using a multivariable logistic regression model based on age, sex, race, tumor location, tumor size, pathologic type, tumor differentiation, marital status, tumor T stage, tumor N stage, surgery, chemotherapy, and radiotherapy. A forest plot was used to compare the effects of PTR+C versus PTR/C alone in the different UCR-MAC-LM subgroups. Statistical significance was defined as a P-value of <0.05 (2-tailed), and all data analyses were performed using R software.

RESULTS

Baseline Characteristics and Long-term Survival of UCR-MAC-LM and UCR-NOS-LM

During the period of 2010 to 2017, a total of 10,178 eligible patients were identified from the SEER database. The UCR-MAC-LM group comprised 612 (6.01%) patients, whereas the UCR-NOS-LM group comprised 9566 (93.99%) patients. Table 1 shows the characteristics of the eligible patients. In this patient cohort, a significantly greater proportion of female patients was diagnosed with UCR-MAC-LM (49.8%) than those with UCR-NOS-LM (42.5%) ($P < 0.001$). In addition, patients with UCR-MAC-LM had a significantly higher incidence of right-sided colon tumors than those with UCR-NOS-LM (54.4% vs. 33.0%, $P < 0.001$), indicating a higher predilection of UCR-MAC-LM to develop in the right colon. Furthermore, patients with UCR-MAC-LM were more likely to present with advanced stages of the disease, including T3-T4 (93.3% vs. 83.7%, $P < 0.001$) and lymph node involvement (77.0% vs. 72.4%, $P = 0.017$). Moreover, a significantly higher proportion of patients with UCR-MAC-LM underwent PTR than those with UCR-NOS-LM (85.9% vs. 69.8%, $P < 0.001$). However, a higher proportion of patients with UCR-NOS-LM opted for chemotherapy than those with UCR-MAC-LM (73.0% vs. 68.6%, $P = 0.02$). For further information on the patient cohort, please refer to Table 1. After PSM, the distribution of covariates, including sex, age, race, tumor differentiation, tumor T stage, tumor N stage, and marital status, was effectively balanced between the UCR-MAC-LM and UCR-NOS-LM groups. The PSM process achieved an optimal balance between covariates in the matched cohort, with a P-value > 0.05, as presented in Table 1.

We conducted Kaplan-Meier analysis and log-rank tests to compare the survival differences between UCR-MAC-LM and UCR-NOS-LM patients. The results indicated that patients with UCR-MAC-LM had significantly lower OS and CSS than patients with UCR-NOS-LM ($P = 0.011$ for OS, Fig. 2A; $P = 0.014$ for CSS, Figure 2B). The median OS was 16 months (95% CI: 14-17 months) for patients with UCR-MAC-LM and

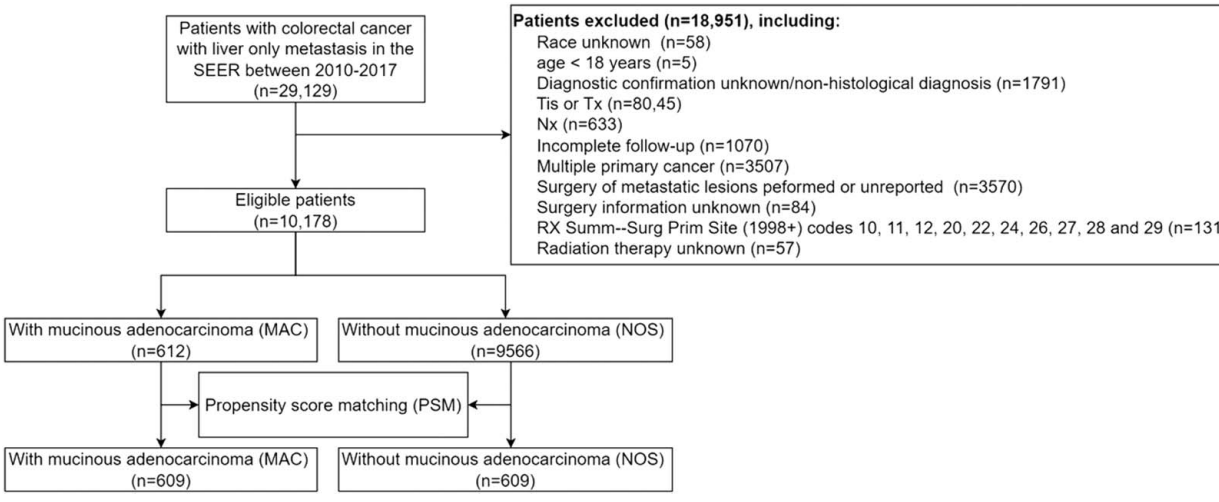

FIGURE 1. Flowchart of patient selection. SEER indicates surveillance, epidemiology, and end results.

TABLE 1. Clinicopathological Characteristics of MAC and NOS Patients

Variable	NOS n = 9566, n (%)	MAC n = 612, n (%)	*P*	MAC PSM n = 609, n (%)	NOS PSM n = 609, n (%)	*P*
Race						
White	7140 (74.6)	469 (76.6)	—	466 (76.5)	472 (77.5)	—
Black	1487 (15.5)	103 (16.8)	—	103 (16.9)	103 (16.9)	—
Others	939 (9.8)	40 (6.5)	0.025	40 (6.6)	34 (5.6)	0.769
Age (y)						
< 65	5428 (56.7)	318 (52.0)	—	316 (51.9)	314 (51.6)	—
≥ 65	4138 (43.3)	294 (48.0)	0.023	293 (48.1)	295 (48.4)	0.954
Sex						
Female	4066 (42.5)	305 (49.8)	—	303 (49.8)	309 (50.7)	—
Male	5500 (57.5)	307 (50.2)	< 0.001	306 (50.2)	300 (49.3)	0.774
CEA						
Borderline	29 (0.3)	0	—	—	—	—
Negative/Normal	1129 (11.8)	89 (14.5)	—	88 (14.5)	83 (13.6)	—
Positive/elevated	5641 (59.0)	355 (58.0)	—	353 (58.0)	354 (58.1)	—
Unknown	2767 (28.9)	168 (27.5)	0.112	168 (27.6)	172 (28.2)	0.907
Location						
Right colon	3152 (33.0)	333 (54.4)	—	333 (54.7)	323 (53.0)	—
Transverse colon	606 (6.3)	49 (8.0)	—	49 (8.0)	52 (8.5)	—
Left colon	5531 (57.8)	202 (33.0)	—	202 (33.2)	207 (34.0)	—
Overlapping	113 (1.2)	20 (3.3)	—	17 (2.8)	19 (3.1)	—
Colon NOS	164 (1.7)	8 (1.3)	< 0.001	8 (1.3)	8 (1.3)	0.981
Size (cm)						
≤ 5.0	4196 (43.9)	224 (36.6)	—	224 (36.8)	233 (38.3)	—
> 5.0	3756 (39.3)	317 (51.8)	—	315 (51.7)	312 (51.2)	—
Unknown	1614 (16.9)	71 (11.6)	< 0.001	70 (11.5)	64 (10.5)	0.794
Differentiation						
Grade I/II	6041 (63.2)	394 (64.4)	—	393 (64.5)	404 (66.3)	—
Grade III/IV	2278 (23.8)	147 (24.0)	—	146 (24.0)	136 (22.3)	—
Unknown	1247 (13.0)	71 (11.6)	0.588	70 (11.5)	69 (11.3)	0.774
T stage						
T0-T2	1559 (16.3)	41 (6.7)	—	41 (6.7)	31 (5.1)	—
T3-T4	8007 (83.7)	571 (93.3)	< 0.001	568 (93.3)	578 (94.9)	0.274
N stage						
N0	2636 (27.6)	141 (23.0)	—	140 (23.0)	116 (19.0)	—
N+	6930 (72.4)	471 (77.0)	0.017	469 (77.0)	493 (81.0)	0.106
Marital status						
Married	4978 (52.0)	306 (50.0)	—	304 (49.9)	303 (49.8)	—
Not married	4156 (43.4)	288 (47.1)	—	287 (47.1)	286 (47.0)	—
Unknown	432 (4.5)	18 (2.9)	0.067	18 (3.0)	20 (3.3)	0.947
Surgery						
Non-PTR	2885 (30.2)	86 (14.1)	—	86 (14.1)	81 (13.3)	—
PTR	6681 (69.8)	526 (85.9)	< 0.001	523 (85.9)	528 (86.7)	0.739
Radiotherapy						
No	8566 (89.5)	579 (94.6)	—	576 (94.6)	572 (93.9)	—
Yes	1000 (10.5)	33 (5.4)	< 0.001	33 (5.4)	37 (6.1)	0.712
Chemotherapy						
No	2580 (27.0)	192 (31.4)	—	190 (31.2)	183 (30.0)	
Yes	6986 (73.0)	420 (68.6)	0.020	419 (68.8)	426 (70.0)	0.709

MAC indicates mucinous adenocarcinoma; NOS, non-MAC unresectable colorectal mucinous adenocarcinoma with liver metastases; PSM, propensity score matching; PTR, primary tumor resection.

19 months (95% CI: 18-19 months) for patients with UCR-NOS-LM. Similarly, the median CSS was 16 months (95% CI: 14-18 months) for patients with UCR-MAC-LM and 19 months (95% CI: 19-20 months) for those with UCR-NOS-LM. After PSM, the OS and CSS of patients with UCR-MAC-LM remained significantly lower than those of patients with UCR-NOS-LM (Figs. 3A, B).

Patient Characteristics of UCR-MAC-LM With Different Treatment

After finding that patients with UCR-MAC-LM had a lower survival rate than those with UCR-NOS-LM, we conducted a more extensive analysis of patients who underwent various treatment modalities, including PTR+C, PTR/C, and no treatment. Table 2 presents the detailed information regarding the 3 groups. Our findings suggest that a greater proportion of patients aged below 65 years and married were observed in the PTR+C (56.1%; 57.5%) and PTR/C groups (48.3%; 40.3%), respectively, compared with the no-treatment group (23.8% and 33.3%) ($P = 0.006$, $P < 0.001$). In addition, we found that a higher proportion of patients with UCR-MAC-LM who had well or moderately differentiated tumors and tumors located in the right colon were represented in the PTR+C (69.9%; 55.5%) and PTR/C (58.9%; 54.2%) groups than in the no treatment group (33.3%; 38.1%) ($P < 0.001$, $P < 0.001$). Furthermore, our analysis revealed that a higher proportion of patients with T3-

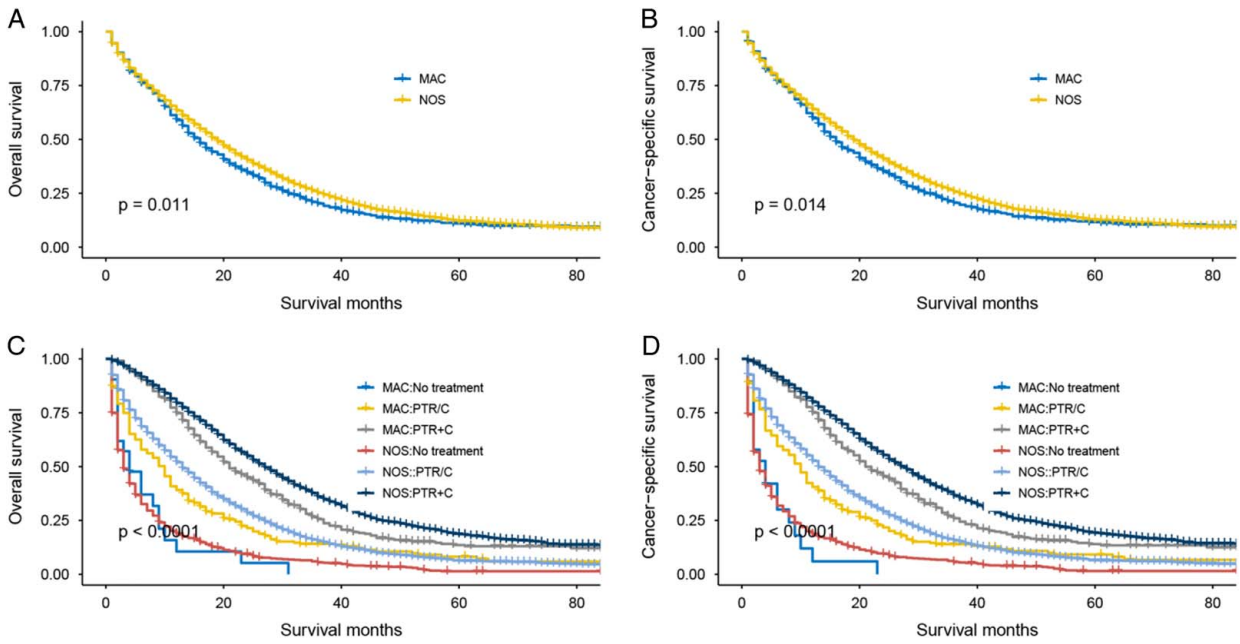

FIGURE 2. (A), Overall survival among patients with unresectable colorectal mucinous adenocarcinoma with liver metastasis (UCR-MAC-LM) and nonmucinous adenocarcinoma with liver metastasis (UCR-NOS-LM), $P < 0.05$; CSS among patients with UCR-MAC-LM and UCR-NOS-LM, $P < 0.05$ (B); Overall survival among patients with UCR-MAC-LM and UCR-NOS-LM who received PTR + C, PTR/C, or with no treatment, $P < 0.05$ (C); CSS among patients with UCR-MAC-LM and UCR-NOS-LM who received PTR + C, PTR/C, or with no treatment, $P < 0.05$ (D). CSS indicates cancer-specific survival; MAC, mucinous adenocarcinoma; NOS, non-mucinous adenocarcinoma; PTR, primary tumor resection. full color online

T4 stage and lymph node involvement were treated with PTR +C (96.6%, 82.5%) compared with patients treated with PTR/C (90.3%, 71.2%) or no treatment (71.4%, 47.6%) ($P < 0.001$). These results suggest that PTR + C may represent a superior therapeutic strategy for advanced tumor stages in patients with UCR-MAC-LM.

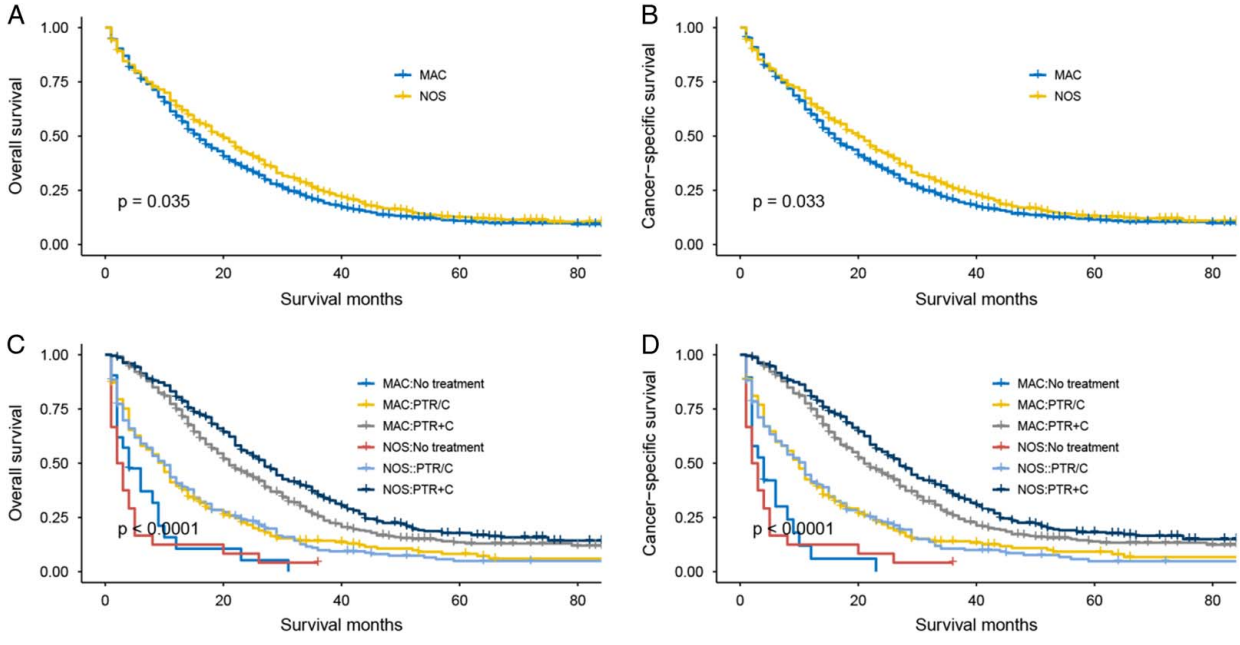

FIGURE 3. (A), Overall survival among patients with unresectable colorectal mucinous adenocarcinoma with liver metastasis (UCR-MAC-LM) and nonmucinous adenocarcinoma with liver metastasis (UCR-NOS-LM), $P < 0.05$; CSS among patients with UCR-MAC-LM and UCR-NOS-LM, $P < 0.05$ (B); overall survival among patients with UCR-MAC-LM and UCR-NOS-LM who received PTR + C, PTR/C, or with no treatment, $P < 0.05$ (C); CSS among patients with UCR-MAC-LM and UCR-NOS-LM who received PTR + C, PTR/C, or with no treatment, $P < 0.05$ (D). CSS indicates cancer-specific survival; MAC, mucinous adenocarcinoma; NOS, non-mucinous adenocarcinoma; PTR, primary tumor resection. full color online

TABLE 2. Clinicopathological Characteristics of Patients With Unresectable Colorectal Mucinous Adenocarcinoma With Liver Metastasis Who Received PTR + C, PTR/C, or With No Treatment

Variable	PTR+C n = 355, n (%)	PTR/C n = 236, n (%)	No treatment n = 21, n (%)	*P*
Race	—	—	—	0.522
White	278 (78.3)	176 (74.6)	15 (71.4)	—
Black	59 (16.6)	40 (16.9)	4 (19.0)	—
Others	18 (5.1)	20 (8.5)	2 (9.5)	—
Age (y)	—	—	—	0.006
< 65	199 (56.1)	114 (48.3)	5 (23.8)	—
≥ 65	156 (43.9)	122 (51.7)	16 (76.2)	—
Sex	—	—	—	0.430
Female	169 (47.6)	125 (53.0)	11 (52.4)	—
Male	186 (52.4)	111 (47.0)	10 (47.6)	—
CEA	—	—	—	0.053
Negative/ normal	61 (17.2)	27 (11.4)	1 (4.8)	—
Positive/ elevated	206 (58.0)	133 (56.4)	16 (76.2)	—
Unknown	88 (24.8)	76 (32.2)	4 (19.0)	—
Location	—	—	—	< 0.001
Right colon	197 (55.5)	128 (54.2)	8 (38.1)	—
Transverse colon	29 (8.2)	19 (8.1)	1 (4.8)	—
Left colon	119 (33.5)	75 (31.8)	8 (38.1)	—
Overlapping	8 (2.3)	11 (4.7)	1 (4.8)	—
Colon NOS	2 (0.6)	3 (1.3)	3 (14.3)	—
Size (cm)	—	—	—	< 0.001
> 5.0	176 (49.6)	135 (57.2)	6 (28.6)	—
≤ 5.0	153 (43.1)	67 (28.4)	4 (19.0)	—
Unknown	26 (7.3)	34 (14.4)	11 (52.4)	—
Differentiation	—	—	—	< 0.001
Grade I/II	248 (69.9)	139 (58.9)	7 (33.3)	—
Grade III/IV	90 (25.4)	56 (23.7)	1 (4.8)	—
Unknown	17 (4.8)	41 (17.4)	13 (61.9)	—
T stage	—	—	—	< 0.001
T0-T2	12 (3.4)	23 (9.7)	6 (28.6)	—
T3-T4	343 (96.6)	213 (90.3)	15 (71.4)	—
N stage	—	—	—	< 0.001
N0	62 (17.5)	68 (28.8)	11 (52.4)	—
N+	293 (82.5)	168 (71.2%)	10 (47.6%)	—
Marital status	—	—	—	< 0.001
Married	204 (57.5)	95 (40.3)	7 (33.3)	—
Not married	140 (39.4)	135 (57.2)	13 (61.9)	—
Unknown	11 (3.1)	6 (2.5)	1 (4.8)	—
Radiotherapy	—	—	—	0.161
No	331 (93.2)	227 (96.2)	21 (100)	—
Yes	24 (6.8)	9 (3.8)	0	—

CEA indicates carcinoembryonic antigen; NOS, non-mucinous adenocarcinoma; PTR, primary tumor resection.

Prognostic Risk Factors for OS in UCR-MAC-LM

To further explore the factors that affect the OS of patients with UCR-MAC-LM, we used Cox proportional hazards regression models to validate the protective or adverse prognostic factors (Table 3). Univariate analysis revealed that age (HR = 1.43, $P < 0.001$), carcinoembryonic antigen (CEA) levels (HR = 1.76, $P < 0.001$), tumor grade (HR = 1.32, $P = 0.007$), tumor N stage (HR = 0.66, $P < 0.001$), marital status (HR = 1.31, $P = 0.003$), PTR (HR = 0.67, $P = 0.002$), radiotherapy (HR = 0.50, $P = 0.001$), and chemotherapy (HR = 0.47, $P < 0.001$) were all significantly associated with OS in UCR-MAC-LM. To overcome the limitations of univariate analysis, we conducted multivariable Cox analysis to identify independent factors related to OS. Our multivariate analysis demonstrated that age, CEA level, tumor grade, tumor N stage, PTR, radiotherapy, and chemotherapy were all statistically significant independent factors for OS among patients with UCR-MAC-LM (Table 3).

Prognostic Risk Factors for CSS in UCR-MAC-LM

To identify the factors associated with CSS in patients with UCR-MAC-LM, we employed Cox proportional hazards regression models. Univariate analysis revealed that several variables were significantly associated with CSS, including age (HR = 1.43, $P < 0.001$), CEA level (HR = 1.70, $P < 0.001$), tumor grade (HR = 1.40, $P = 0.002$), tumor N stage (HR = 0.64, $P < 0.001$), marital status (HR = 1.33, $P = 0.002$), PTR (HR = 0.66, $P = 0.001$), radiotherapy (HR = 0.51, $P = 0.001$), and chemotherapy (HR = 0.47, $P < 0.001$) (Table 4). All of these variables were included in the multivariate analysis. Our multivariate analysis demonstrated that PTR and chemotherapy were independent protective factors for CSS in patients with UCR-MAC-LM. In addition, we found that age, CEA level, tumor grade, and tumor N stage were independent risk factors or protective factors (Table 4).

Survival Benefit of PTR+C for Patients With UCR-MAC-LM

To investigate the potential benefits of different treatment modalities for long-term survival in patients with UCR-MAC-LM, we conducted additional analyses of the treatment effects. Treatment strategies were divided into 3 groups: PTR + C (n = 355), PTR/C (n = 236), and no treatment (n = 21). However, the sample size of patients who received radiotherapy was too small for meaningful analysis (n = 33; Table 1). Our findings revealed the following:

Our analysis showed that patients with UCR-MAC-LM who received PTR+C had significantly improved OS and CSS rates than those who received PTR/C alone ($P < 0.0001$, as illustrated in Figs. 1A, B, respectively). The median OS was 21 months (95% CI: 19-25 months) for patients undergoing PTR + C compared with 10 months (95% CI: 8-11 months) for those receiving PTR/C alone. The median CSS was also significantly better in the PTR + C group (21 months, 95% CI: 20-25 months) than in the PTR/C group (10 months, 95% CI: 8-11 months). Furthermore, the PTR + C group exhibited better OS and CSS rates than the PTR/C group in patients with UCR-MAC-LM ($P < 0.0001$, as illustrated in Figs. 3C, D, respectively). The median OS was 27 months (95% CI: 24-30 months) for patients undergoing PTR + C compared with 10 months (95% CI: 8-12 months) for those receiving PTR/C alone. The median CSS for patients undergoing PTR + C was 27 months (95% CI: 25-30 months) and 11 months (95% CI: 8-12 months) for those receiving PTR/C alone.

Our results demonstrated that PTR + C was associated with prolonged long-term survival in both UCR-MAC-LM and UCR-NOS-LM patients compared with PTR/C alone. Notably, patients with UCR-MAC-LM who underwent PTR + C had a better prognosis than those with UCR-NOS-LM who received PTR/C alone (median OS:21 vs. 10 months, $P < 0.001$; median CSS:21 VS 11 months, $P < 0.001$, as shown in Figs. 3C, D, respectively). In light of the poorer clinical outcomes observed in UCR-MAC-LM than in UCR-NOS-LM, our research underscores the crucial role of PTR + C as a therapeutic option in managing UCR-MAC-LM.

TABLE 3. Univariate and Multivariate Analyses of Overall Survival for Patients With Unresectable Colorectal Mucinous Adenocarcinoma With Liver Metastasis

	Univariable			Multivariable		
Variable	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
Race						
Black	Reference	—	—	—	—	—
White	0.82	0.65-1.04	0.102	—	—	—
Others	0.93	0.63-1.39	0.736	—	—	—
Age (y)						
<65	Reference	—	—	Reference	—	—
≥65	1.43	1.20-1.70	<0.001	1.34	1.11-1.62	0.002
Sex						
Female	Reference	—	—	—	—	—
Male	0.94	0.79-1.12	0.46	—	—	—
CEA						
Negative/normal	Reference	—	—	Reference	—	—
Positive/elevated	1.76	1.34-2.33	<0.001	1.52	1.14-2.02	0.004
Unknown	1.67	1.23-2.26	<0.001	1.41	1.03-1.93	0.031
Location						
Right colon	Reference	—	—	Reference	—	—
Transverse colon	1.34	0.97-1.83	0.074	1.29	0.93-1.79	0.122
Left colon	1.02	0.84-1.24	0.847	1.10	0.90-1.34	0.377
Overlapping	2.43	1.52-3.88	<0.001	2.25	1.39-3.62	<0.001
Colon NOS	2.37	1.17-4.81	0.016	1.73	0.82-3.65	0.150
Size (cm)						
>5.0	Reference	—	—	Reference	—	—
≤5.0	0.81	0.67-0.98	0.03	0.95	0.78-1.16	0.619
Unknown	0.80	0.60-1.07	0.137	0.76	0.54-1.06	0.104
Differentiation						
Grade I/II	Reference	—	—	Reference	—	—
Grade III/IV	1.32	1.08-1.62	0.007	1.32	1.07-1.62	0.009
Unknown	1.12	0.85-1.48	0.43	0.81	0.56-1.16	0.245
T stage						
T0-T2	Reference	—	—	—	—	—
T3-T4	0.94	0.67-1.34	0.746	—	—	—
N stage						
N+	Reference	—	—	Reference	—	—
N0	0.66	0.53-0.83	<0.001	0.55	0.43-0.69	<0.001
Marital status						
Married	Reference	—	—	Reference	—	—
Not married	1.31	1.10-1.56	0.003	1.12	0.93-1.35	0.237
Unknown	1.22	0.73-2.06	0.450	1.30	0.76-2.22	0.338
PTR						
No	Reference	—	—	Reference	—	—
Yes	0.67	0.528-0.860	0.002	0.40	0.28-0.56	<0.001
Chemotherapy						
No/unknown	Reference	—	—	Reference	—	—
Yes	0.47	0.39-0.57	<0.001	0.47	0.38-0.58	<0.001
Radiotherapy						
No/unknown	Reference	—	—	Reference	—	—
Yes	0.50	0.33-0.76	0.001	0.58	0.38-0.88	0.011

CEA indicates carcinoembryonic antigen; HR, hazard ratio; NOS, non-mucinous adenocarcinoma; PTR, primary tumor resection.

Subgroup Analysis of Patients With UCR-MAC-LM

To investigate the impact of different treatment modalities on the prognosis of patients with UCR-MAC-LM, we categorized the patient cohort into 22 subgroups based on clinicopathological characteristics, as outlined in the accompanying table. We used Cox's regression model in each subgroup to estimate the HR and 95% CI, as depicted in Figure 4. Our analysis revealed significant statistical differences in the majority of subgroups when comparing the efficacy of PTR + C with that of PTR/C alone ($P < 0.05$ in 17 subgroups). However, no significant differences were observed in the other subgroups (Fig. 4).

DISCUSSION

In this study, we conducted a comprehensive analysis of data from a cohort of 10,178 patients who had been diagnosed with UCRLM, among whom 612 patients had been diagnosed with MAC. To our knowledge, this is the first population-based study to assess the prognostic value of PTR + C in patients with UCR-MAC-LM. Our study revealed that PTR + C was significantly associated with a survival benefit in patients with UCR-MAC-LM compared with treatment with PTR/C alone. The substantial survival advantage observed in this large cohort of SEER patients emphasizes the crucial importance of implementing PTR + C in the management of patients with UCR-MAC-LM.

TABLE 4. Univariate and Multivariate Analyses of CSS for Patients With UCR-MAC-LM

	Univariable			Multivariable		
Variable	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
Race						
Black	Reference	—	—	—	—	—
White	0.82	0.65-1.04	0.105	—	—	—
Others	0.98	0.65-1.48	0.932	—	—	—
Age (y)						
< 65	Reference	—	—	Reference	—	—
≥ 65	1.43	1.19-1.70	< 0.001	1.39	1.14-1.69	< 0.001
Sex						
Female	Reference	—	—	—	—	—
Male	0.95	0.79-1.13	0.543	—	—	—
CEA						
Negative/normal	Reference	—	—	Reference	—	—
Positive/elevated	1.79	1.35-2.38	< 0.001	1.53	1.14-2.06	0.004
Unknown	1.67	1.22-2.28	0.001	1.42	1.03-1.95	0.033
Location						
Right colon	Reference	—	—	Reference	—	—
Transverse colon	1.42	1.03-1.97	0.033	1.47	1.05-2.05	0.026
Left colon	1.05	0.86-1.27	0.658	1.15	0.93-1.41	0.189
Overlapping	2.37	1.45-3.88	< 0.001	2.33	1.41-3.85	< 0.001
Colon NOS	2.47	1.22-5.00	0.012	1.81	0.86-3.82	0.121
Size (cm)						
> 5.0	Reference	—	—	Reference	—	—
≤ 5.0	0.79	0.65-0.96	0.019	0.93	0.76-1.13	0.463
Unknown	0.80	0.60-1.08	0.141	0.74	0.53-1.04	0.081
Differentiation						
Grade I/II	Reference	—	—	Reference	—	—
Grade III/IV	1.40	1.13-1.72	0.002	1.42	1.15-1.76	0.001
Unknown	1.14	0.86-1.52	0.357	0.79	0.54-1.15	0.223
T stage						
T0-T2	Reference	—	—	—	—	—
T3-T4	0.99	0.69-1.44	0.973	—	—	—
N stage						
N+	Reference	—	—	Reference	—	—
N0	0.64	0.51-0.81	< 0.001	0.55	0.44-0.70	< 0.001
Marital status						
Married	Reference	—	—	Reference	—	—
Not married	1.33	1.11-1.59	0.002	1.15	0.95-1.39	0.156
Unknown	1.33	0.78-2.29	0.296	1.63	0.93-2.85	0.088
PTR						
No	Reference	—	—	Reference	—	—
Yes	0.66	0.51-0.85	0.001	0.38	0.26-0.54	< 0.001
Chemotherapy						
No/unknown	Reference	—	—	Reference	—	—
Yes	0.47	0.39-0.57	< 0.001	0.46	0.37-0.57	< 0.001
Radiotherapy						
No/unknown	Reference	—	—	Reference	—	—
Yes	0.51	0.34-0.77	0.001	0.59	0.38-0.90	0.014

CEA indicates carcinoembryonic antigen; HR, hazard ratio; NOS, non-mucinous adenocarcinoma; PTR, primary tumor resection.

Numerous studies have consistently demonstrated that colorectal mucinous adenocarcinoma is associated with a worse prognosis compared with other histologic subtypes.[32–34] In our investigation, we also found that patients with UCR-MAC-LM had lower OS and CSS rates than patients with UCR-NOS-LM. Patients with UCR-MAC-LM had a higher proportion of females, advanced T and N stages, larger tumor size, and right-sided colon localization, which is consistent with previous studies.[35–38] There is a lack of reliable guidelines regarding the optimal management of CRCLM, leading to controversy surrounding its management.

Chemotherapy is recommended for patients with metastatic colorectal cancer.[28,39] However, the efficacy of PTR in patients with UCRCLM remains controversial. While some studies have revealed a significant improvement in OS associated with PTR,[10,18,40–42] others have not found any survival benefit.[43,44] Furthermore, several studies have demonstrated that patients with CR-MAC-LM who underwent PTR+C may experience better survival outcomes than those who underwent PTR/C alone.[17,45]

Our study demonstrated that PTR was an independent favorable prognostic factor for patients with UCR-MAC-LM. Subgroup analysis showed that among the 22 subgroups of patients with UCR-MAC-LM, 17 subgroups exhibited a survival benefit from PTR + C compared with PTR alone. A previous study by Budd et al[46] highlighted that PTR + C was associated with enhanced survival, potentially due to heightened chemosensitivity after reduction of the systemic tumor burden. However, MAC has been shown to be less

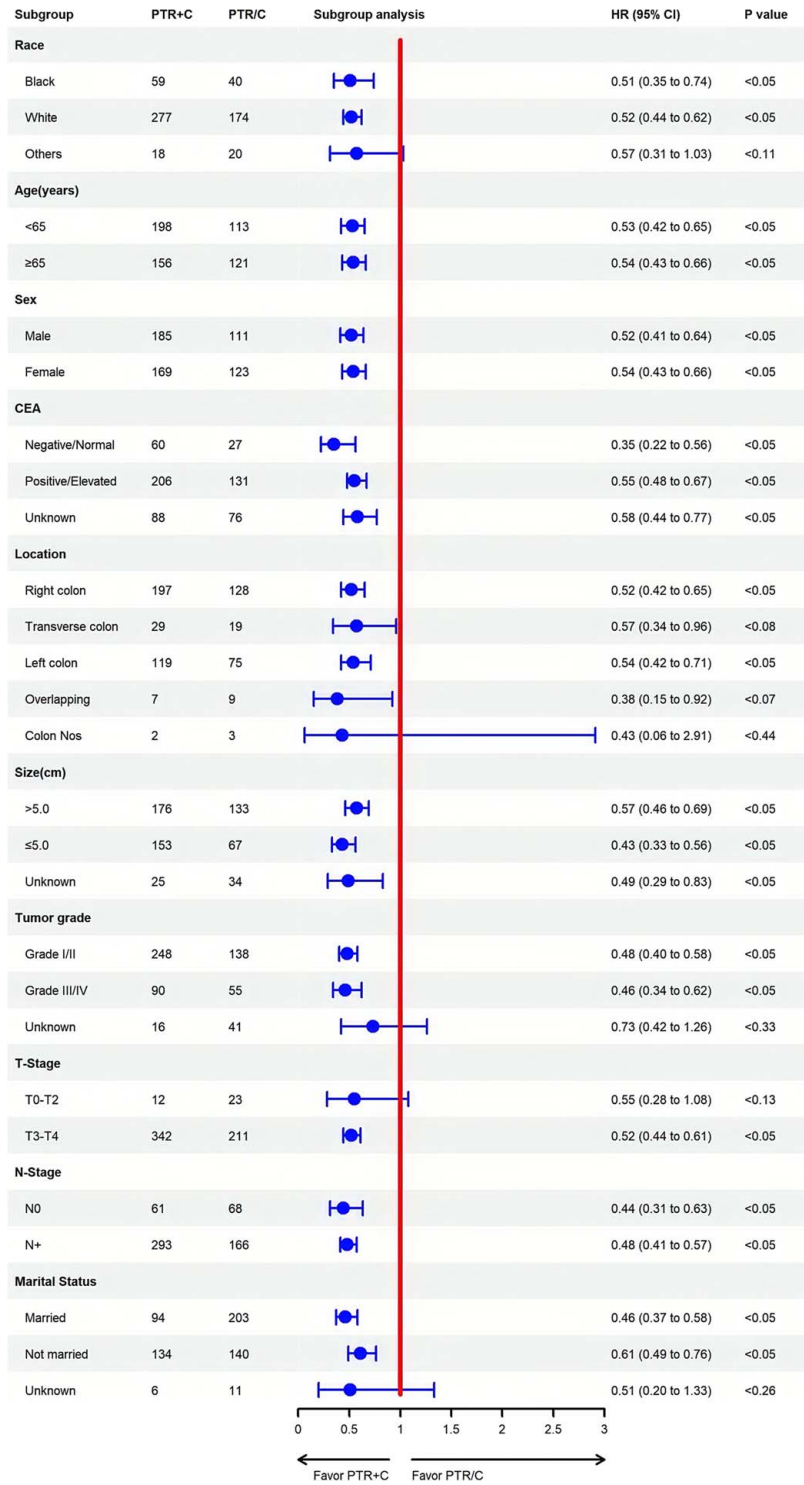

FIGURE 4. Subgroup analysis of PTR+C and PTR/C among patients with unresectable colorectal mucinous adenocarcinoma with liver metastasis. CEA indicates carcinoembryonic antigen; PTR, primary tumor resection. full color online

chemosensitive than NOS,[27,39,47] suggesting that PTR + C may have even greater therapeutic value in the management of UCR-MAC-LM despite the associated high risk of recurrence. In addition, PTR + C has the potential to render initially unresectable liver metastasis resectable, enabling curative resection of the liver metastasis and ultimately improving the long-term survival of patients. This underscores the potential therapeutic value of PTR strategies in the management of UCR-MAC-LM. Patients with UCR-MAC-LM who meet the eligibility criteria for PTR may exhibit superior clinical and pathologic features compared with other patients with metastatic colorectal cancer, which could explain the significant

enhancement in OS observed in these individuals after PTR. On the basis of our study findings, we strongly recommend the implementation of PTR + C as a therapeutic strategy for appropriate surgical candidates with UCR-MAC-LM to improve OS.

Although this study's findings display promise, it is important to acknowledge several inherent limitations. First, the SEER database lacks vital information on peritoneal metastasis, a commonly observed phenomenon in patients with UCR-MAC-LM. Addressing this concern necessitates future investigations with larger sample sizes and supplementary data sources. Second, a limitation of this study lies in the limited details available regarding the specific chemotherapeutic regimens used by the patients. To achieve a more precise assessment of PTR+C efficacy in UCR-MAC-LM patients, future research should incorporate comprehensive data on chemotherapeutic agents, dosages, and treatment durations. Third, it is imperative to acknowledge that appendiceal mucinous adenocarcinoma is associated with poor differentiation and an unfavorable prognosis. However, due to data limitations within the SEER database, definitive determination of its inclusion in the final patient selection is precluded, potentially influencing study outcomes. Fourth, as a retrospective study, our investigation is susceptible to inherent selective bias. Factors such as patients' functional status, clinical manifestations, extent of metastasis, related complications, and other pertinent considerations may have influenced the decision to proceed with PTR. Lastly, it is crucial to recognize that inherent bias remains a concern in observational studies, even with the adjustment of multiple confounding variables. Consequently, future prospective randomized controlled trials are of utmost importance to corroborate these findings and explore the therapeutic potential of PTR+C in UCR-MAC-LM patients.

CONCLUSIONS

UCR-MAC-LM is a distinct solid entity of colorectal cancer with an OS rate inferior to that of non-MAC. Our research findings suggest that at least one identifiable cohort of patients with UCR-MAC-LM may benefit more from PTR + C than from PTR/C alone. Therefore, we recommend PTR for eligible patients with UCR-MAC-LMs. However, further prospective investigations are needed to accurately evaluate the impact of PTR + C on the survival of patients with UCR-MAC-LM, particularly in light of potential publication bias.

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REFERENCES

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *Ca-Cancer J Clin*. 2021;71:209–249.
2. Miyoshi N, Ohue M, Yasui M, et al. Novel prognostic prediction models for patients with stage IV colorectal cancer after concurrent curative resection. *Esmo Open*. 2016;1:e000052.
3. de Mestier L, Neuzillet C, Pozet A, et al. Is primary tumor resection associated with a longer survival in colon cancer and unresectable synchronous metastases? A 4-year multicentre experience. *Ejso-eur J Surg Onc*. 2014;40:685–691.
4. Luo D, Liu Q, Yu W, et al. Prognostic value of distant metastases sites and surgery in stage IV colorectal cancer: a population-based study. *Int J Colorectal Dis*. 2018;33:1241–1249.
5. Nordlinger B, Van Cutsem E, Gruenberger T, et al. Combination of surgery and chemotherapy and the role of targeted agents in the treatment of patients with colorectal liver metastases: recommendations from an expert panel. *Ann Oncol*. 2009;20:985–992.
6. Choti MA, Sitzmann JV, Tiburi MF, et al. Trends in long-term survival following liver resection for hepatic colorectal metastases. *Ann Surg*. 2002;235:759–766.
7. Line PD, Hagness M, Dueland S. The potential role of liver transplantation as a treatment option in colorectal liver metastases. *Can J Gastroenterol*. 2018;2018:8547940.
8. de Mestier L, Manceau G, Neuzillet C, et al. Primary tumor resection in colorectal cancer with unresectable synchronous metastases: a review. *World J Gastro Oncol*. 2014;6:156–169.
9. Bouviez N, Lakkis Z, Lubrano J, et al. Liver resection for colorectal metastases: results and prognostic factors with 10-year follow-up. *Langenbeck's Arch Surg*. 2014;399:1031–1038.
10. Faron M, Pignon JP, Malka D, et al. Is primary tumour resection associated with survival improvement in patients with colorectal cancer and unresectable synchronous metastases? A pooled analysis of individual data from four randomised trials. *Eur J Cancer*. 2015;51:166–176.
11. Zhang RX, Ma WJ, Gu YT, et al. Primary tumor location as a predictor of the benefit of palliative resection for colorectal cancer with unresectable metastasis. *World J Surg Oncol*. 2017; 15:138.
12. Anwar S, Peter MB, Dent J, et al. Palliative excisional surgery for primary colorectal cancer in patients with incurable metastatic disease. Is there a survival benefit? A systematic review. *Colorectal Dis*. 2012;14:920–930.
13. Benson AB, Venook AP, Al-Hawary MM, et al. NCCN Guidelines insights: colon cancer, version 22018. *J Natl Compr Canc Ne*. 2018;16:359–369.
14. Kallini JR, Gabr A, Abouchaleh N, et al. New developments in interventional oncology: liver metastases from colorectal cancer. *Cancer J*. 2016;22:373–380.
15. Simmonds PC. Palliative chemotherapy for advanced colorectal cancer: systematic review and meta-analysis. Colorectal Cancer Collaborative Group. *Bmj Open*. 2000;321:531–535.
16. Seium Y, Stupp R, Ruhstaller T, et al. Oxaliplatin combined with irinotecan and 5-fluorouracil/leucovorin (OCFL) in metastatic colorectal cancer: a phase I-II study. *Ann Oncol*. 2005; 16:762–766.
17. Xu Z, Becerra AZ, Fleming FJ, et al. Treatments for stage IV colon cancer and overall survival. *J Surg Re*. 2019;242:47–54.
18. Gulack BC, Nussbaum DP, Keenan JE, et al. Surgical resection of the primary tumor in stage IV colorectal cancer without metastasectomy is associated with improved overall survival compared with chemotherapy/radiation therapy alone. *Dis Colon Rectum*. 2016;59:299–305.
19. Viganò L, Russolillo N, Ferrero A, et al. Resection of liver metastases from colorectal mucinous adenocarcinoma: is this a different disease? Results of a case-control study. *Ann Surg*. 2014; 260:878–884; discussion 884-5.
20. Luo C, Cen S, Ding G, et al. Mucinous colorectal adenocarcinoma: clinical pathology and treatment options. *Cancer Commun*. 2019; 39:13.
21. Jivapaisarnpong P, Boonthongtho K. Clinicopathological characteristics of mucinous and non-mucinous adenocarcinoma in the colon and rectum in Rajavithi Hospital, Thailand. *J Med Assoc Thailand*. 2011;94(suppl 2):S41–S45.
22. Hugen N, Verhoeven RH, Radema SA, et al. Prognosis and value of adjuvant chemotherapy in stage III mucinous colorectal carcinoma. *Ann Oncol*. 2013;24:2819–2824.
23. Safaee A, Moghimi-Dehkordi B, Fatemi SR, et al. Characteristics of colorectal mucinous adenocarcinoma in Iran. *Asian Pac J Cancer Prev*. 2010;11:1373–1375.
24. Lupinacci RM, Mello ES, Coelho FF, et al. Prognostic implication of mucinous histology in resected colorectal cancer liver metastases. *Surgery*. 2014;155:1062–1068.

25. Nozoe T, Anai H, Nasu S, et al. Clinicopathological characteristics of mucinous carcinoma of the colon and rectum. *J Surg Oncol*. 2000;75:103–107.
26. Khan M, Loree JM, Advani SM, et al. Prognostic implications of mucinous differentiation in metastatic colorectal carcinoma can be explained by distinct molecular and clinicopathologic characteristics. *Clin Colorectal Canc*. 2018;17:e699–e709.
27. Maisano R, Azzarello D, Maisano M, et al. Mucinous histology of colon cancer predicts poor outcomes with FOLFOX regimen in metastatic colon cancer. *J Chemotherapy*. 2012;24:212–216.
28. Mekenkamp LJ, Heesterbeek KJ, Koopman M, et al. Mucinous adenocarcinomas: poor prognosis in metastatic colorectal cancer. *Eur J Cancer*. 2012;48:501–509.
29. Hankey BF, Ries LA, Edwards BK. The surveillance, epidemiology, and end results program: a national resource. *Cancer Epidem Biomar*. 1999;8:1117–1121.
30. Peto R, Pike MC, Armitage P, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. analysis and examples. *Br J Cancer*. 1977;35:1–39.
31. Dinse GE, Lagakos SW. Nonparametric estimation of lifetime and disease onset distributions from incomplete observations. *Biometrics*. 1982;38:921–932.
32. Kanemitsu Y, Kato T, Hirai T, et al. Survival after curative resection for mucinous adenocarcinoma of the colorectum. *Dis Colon Rectum*. 2003;46:160–167.
33. Verhulst J, Ferdinande L, Demetter P, et al. Mucinous subtype as prognostic factor in colorectal cancer: a systematic review and meta-analysis. *J Clin Pathol*. 2012;65:381–388.
34. Wang L, Hirano Y, Heng G, et al. Mucinous adenocarcinoma as a high-risk factor in stage II colorectal cancer: a propensity score-matched study from Japan. *Anticancer Res*. 2020;40:1651–1659.
35. Okuno M, Ikehara T, Nagayama M, et al. Mucinous colorectal carcinoma: clinical pathology and prognosis. *Am Surgeon*. 1988; 54:681–685.
36. Hyngstrom JR, Hu CY, Xing Y, et al. Clinicopathology and outcomes for mucinous and signet ring colorectal adenocarcinoma: analysis from the National Cancer Data Base. *Ann Surg Oncol*. 2012;19:2814–2821.
37. Du W, Mah JT, Lee J, et al. Incidence and survival of mucinous adenocarcinoma of the colorectum: a population-based study from an Asian country. *Dis Colon Rectum*. 2004;47:78–85.
38. Nozoe T, Anai H, Nasu S, et al. Clinicopathological characteristics of mucinous carcinoma of the colon and rectum. *J Surg Oncol*. 2000;75:103–107.
39. Ott C, Gerken M, Hirsch D, et al. Advanced mucinous colorectal cancer: epidemiology, prognosis and efficacy of chemotherapeutic treatment. *Digestion*. 2018;98:143–152.
40. Tarantino I, Warschkow R, Worni M, et al. Prognostic relevance of palliative primary tumor removal in 37,793 metastatic colorectal cancer patients: a population-based, propensity score-adjusted trend analysis. *Ann Surg*. 2015;262:112–120.
41. Li CL, Tang DR, Ji J, et al. Colorectal adenocarcinoma patients with M1a diseases gain more clinical benefits from palliative primary tumor resection than those with M1b diseases: a propensity score matching analysis. *World J Clin Cases*. 2020;8: 3230–3239.
42. Xu J, Ma T, Ye Y, et al. Surgery on primary tumor shows survival benefit in selected stage IV colon cancer patients: a real-world study based on SEER database. *J Cancer*. 2020;11:3567–3579.
43. Ha GW, Kim JH, Lee MR. Meta-analysis of oncologic effect of primary tumor resection in patients with unresectable stage IV colorectal cancer in the era of modern systemic chemotherapy. *Ann Surg Treat Res*. 2018;95:64–72.
44. Hu CY, Bailey CE, You YN, et al. Time trend analysis of primary tumor resection for stage IV colorectal cancer: less surgery, improved survival. *JAMA Surg*. 2015;150:245–251.
45. Simillis C, Kalakouti E, Afxentiou T, et al. Primary tumor resection in patients with incurable localized or metastatic colorectal cancer: a systematic review and meta-analysis. *World J Surg*. 2019;43:1829–1840.
46. Budd GT, Cristofanilli M, Ellis MJ, et al. Circulating tumor cells versus imaging—predicting overall survival in metastatic breast cancer. *Clin Cancer Res*. 2006;12:6403–6409.
47. McCawley N, Clancy C, O'Neill BD, et al. Mucinous rectal adenocarcinoma is associated with a poor response to neoadjuvant chemoradiotherapy: a systematic review and meta-analysis. *Dis Colon Rectum*. 2016;59:1200–1208.

