Original Article

Prognostic significance of perioperative chemotherapy on resectable colorectal mucinous adenocarcinoma liver metastasis

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Background: Mucinous adenocarcinoma (MAC) is an uncommon subtype of colorectal cancer (CRC). For colorectal cancer liver metastasis (CRLM), perioperative chemotherapy (PCT) has been developed to improve the rate of resection and reduce the rate of early recurrence; however, its impact on long-term outcomes in MAC is unclear.

Methods: From 1999 to 2016, 442 patients with CRLM were retrospectively reviewed, all of whom underwent CRC resection and liver metastasis resection. Among them, 34 were MAC, and the others were non-MAC. A total of 102 non-MAC patients with CRLM who underwent surgery at the same period were matched with 34 MAC patients in a ratio of 3:1 by using a random number table for analysis.

Results: Clinicopathologic characteristics for the MAC group (n=34) and non-MAC group (n=102) had no statistical difference. Both recurrence free survival (RFS) and overall survival (OS) did not significantly differ between the two groups. Nevertheless, in the non-MAC group, OS was fundamentally prolonged in patients with PCT compared to those who didn't have PCT (P=0.031).

Conclusions: In this study, PCT had a survival benefit on non-MAC patients with CRLM while MAC patients with resectable CRLM do not benefit from PCT. When developing treatment like PCT or surgery alone for CRLM, mucinous histology should be considered as an important influence factor.

Keywords: Colorectal cancer (CRC); liver metastasis; mucinous adenocarcinoma (MAC); perioperative chemotherapy (PCT); prognosis

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Introduction

Colorectal cancer (CRC) is one of the main sources cancer-related mortality both in China and around the globe (1,2). The liver is the most well-known organ for metastasis in patients with CRC. Around a fourth of patients present with synchronous metastases at their diagnosis, and about 50% eventually develop metachronous metastases (3,4). For patients with colorectal cancer liver metastasis (CRLM), liver resection is the most efficient curative therapy with a 5-year survival rate of 40–50 percent (5). A percentage of chosen CRLM patients may be curable. A proportion of selected patients with CRLM are potentially curable. Aggressive locally surgical management, including liver resection and radiofrequency ablation, may prolong survival of patients with CRLM (6,7). For patients with potentially resectable CRLM, perioperative chemotherapy (PCT) has been investigated to improve

the rate of surgical resection and reduce the rate of early recurrence (8). However, despite several studies indicating the potential efficacy of PCT in prolonging the survival of CRLM, its benefits have not yet been confirmed in all histological subtypes of CRC (9,10). Particularly, to our knowledge, the value of PCT has not been reported for colorectal mucinous adenocarcinoma (MAC) patients who develop liver metastasis after complete resection.

MAC is a histological subtype of CRC, first described by Parham in 1923, accounting for about 1.6–25.4% of CRC (11,12). MAC is described as an adenocarcinoma in the World Health Organization (WHO) classification in which >50 percent of the lesion consists of extracellular mucin pools (13). Characterized by the extracellular deposition of mucus by the tumor cell population, MAC is an aggressive malignancy with a tendency of early intra-abdominal implantation metastases. Previously, due to the mucinous components being considered chemical barriers, MAC was thought to have poor response to chemotherapy (14). However, due to the low incidence, the characteristics of MAC in CRLM have not been clarified, and few studies have concerned themselves with its response to PCT or the prognostic impact of PCT for colorectal MAC with liver metastasis (15).

Therefore, there were two aims in this study: the primary endpoint was to explore the prognostic significance of MAC in resectable CRLM; the secondary endpoint was to investigate the value of PCT on long-term outcomes in MAC/non-MAC patients.

Methods

Patients

The medical records of successive CRLM patients who experienced liver resection at the Sun Yat-sen Unviersity Cancer Center (Guangzhou, China) between December 1999 and January 2016 were assessed. Patients were enrolled who met the following requirements: (I) histologically confirmed CRC; (II) preoperative metastases limited to the liver; (III) R0 resection for both primary and metastatic tumors; and (IV) a follow-up time of at least 1 month. If patients had extrahepatic metastatic lesions, died during the perioperative era, or had palliative liver resection, the patients were excluded. MAC was defined according to the WHO classification as more than fifty percent of the tumor was comprised of pools of extracellular mucin. The staging of CRC was categorized by the 2010 American Joint Staging Committee on Cancer. The study was approved by institutional ethics committee of the Sun Yat-sen University Cancer Center. Prior to original treatment, written informed consent was received from all of the patients.

Treatments

The strategy management for patients with CRLM was determined by a multi-disciplinary team (MDT). Neoadjuvant chemotherapy and adjuvant chemotherapy regimens were determined according to evaluations by oncologists, and included FOLFOX [85 mg/m^2 intravenous (i.v.) oxaliplatin and 400 mg/m^2 i.v. leucovorin (LV) on Day 1; 400 mg/m^2 i.v. 5-fluorouracil (5-FU) on Day 1, and then 1,200 mg/m^2 i.v. 5-FU for Days 1–2 in a 2-week cycle], CAPOX [130 mg/m^2 i.v. oxaliplatin on Day 1 and 1,000 mg/m^2 oral capecitabine twice daily on Days 1–14 in a 3-week cycle], FOLFIRI (180 mg/m^2 i.v. irinotecan and 400 mg/m^2 i.v. LV on Day 1; 400 mg/m^2 i.v. 5-FU on Day 1 and then 1,200 mg/m^2 i.v. 5-FU for Days 1–2 in a 2-week cycle), and capecitabine (1,000 mg/m^2 oral capecitabine twice daily on Days 1–14 for a 3-week cycle). Tumor response was assessed using computerized tomography (CT) or magnetic resonance imaging (MRI) every 3 or 4 cycles. Patients underwent non-anatomical hepatectomy with R0 resection (tumor-free margin >1 mm). Among patients who underwent neoadjuvant chemotherapy, their adjuvant chemotherapy regimens were consistent with neoadjuvant chemotherapy and were recommended to begin 4 to 6 weeks after liver resection.

Follow-up

In the first 2 years, all patients were followed up every 3 months and then every 6 months until 5 years after resection of the liver. The follow-up evaluation included regular physical examination, assessment of carcinoembryonic antigen (CEA) and carbohydrate antigen19-9 (CA19-9), and CT scanning of the chest, abdomen and pelvis at 3, 6, 12, and 18 months, 2 years, and annually afterwards. Liver MRI was conducted to verify suspected lesions in CT or in patients with enhanced concentrations of CEA or CA19-9 but negative for the CT. June 2017 was the last follow-up time.

Statistical analysis

Categorical data were contrasted using the Fisher exact test or Chi-square test as shown. Recurrence-free survival

Table 1 Clinicopathologic characteristics of 380 patients with colorectal liver metastasis after curative liver resection

Characteristics	N (%)
Gender	
Male	256 (67.4)
Female	124 (32.6)
Age	
≤60 years	237 (62.4)
>60 years	143 (37.6)
Primary tumor location	
Colon	238 (62.6)
Rectum	142 (37.4)
T stage	
1–3	229 (60.3)
4	123 (32.4)
N stage	
0	137 (36.1)
1–2	208 (54.7)
Timing of metastasis	
Synchronous	118 (31.1)
Metachronous	262 (68.9)
Number of metastatic tumors	
1	158 (41.6)
2–3	113 (29.7)
4–5	29 (7.6)
Metastasis diameter (cm)	
≤3	249 (65.5)
>3	126 (33.2)
Preoperative CEA (ng/mL)	
≤50	290 (76.3)
>50	69 (18.2)
Perioperative chemotherapy	
No	69 (18.2)
Yes	311 (81.8)
Preoperative chemotherapy	
No	201 (52.9)
Yes	179 (47.1)
Adjuvant chemotherapy	
No	111 (29.2)
Yes	269 (70.8)
KRAS status	
Wild	59 (15.5)
Mutation	36 (9.5)
Histological grade	
Non-mucinous adenocairciniona	344 (90.5)
Aucinous adenocarcinoma	36 (9.5)

CEA, carcinoembryonic antigen.

(RFS) has been described as the interval between the date of resection of the liver the date of recurrence, death, or last follow-up. Overall survival (OS) has been described as the period from the date of resection of the liver to the date of death or final follow-up. RFS and OS rates were estimated with the Kaplan-Meier method. Differences between groups were compared by using the log-rank test. Parameters in multivariate Cox models of which P<0.10 for OS was included in the univariate analysis. Subsequently, the hazard rations (HRs) and confidence intervals (CIs) of 95% were calculated. Statistically significant was regarded as a two-side P value of <0.05. SPSS statistical software (version 22.0, Chicago, IL, USA) was used to perform all the statistical analysis.

Results

Patient characteristics

We studied information from 442 CRLM patients who had resections of the liver. After removing patients with extrahepatic metastasis (n=25) or incomplete resections (n=16), and 21 patients without complete medical records, 380 patients meeting the criteria were identified for further review. As shown in *Table 1*, 256 (67.4%) men and 124 (32.6%) women were included, with a median age of 57 years (range, 20–82 years). In total, 238 (62.6%) and 142 (37.4%) of the primary tumors were located in the colon and rectum, respectively. Meanwhile, 118 (31.1%) patients had synchronous metastases at the time of diagnosis. MAC accounted for 9.5% (n=34) of cases, while

Table 2 Comparison in clinicopathologic characteristics of colorectal mucinous adenocarcinoma and 1:3-matched non-mucinous adenocarcinoma liver metastasis after curative liver resection

Characteristics	Mucinous adenocarcinoma	Non-mucinous adenocarcinoma	P value
Gender			0.304
Male	19	68	
Female	15	34	
Age			0.107
≤60 years	16	65	
>60 years	18	37	
Primary tumor location			0.837
Colon	23	66	
Rectum	11	36	
T stage			0.066
1–3	16	64	
4	18	33	
N stage			0.415
0	11	40	
1–2	23	56	
Timing of metastasis			0.527
Synchronous	22	72	
Metachronous	12	30	
Number of metastatic tumors			0.123
1	18	36	
2–3	8	37	
4–5	0	3	
Metastasis diameter (cm)			0.299
≤3	20	69	
>3	14	31	
Preoperative CEA (ng/mL)			0.280
≤50	24	83	
>50	7	14	
Perioperative chemotherapy			0.904
No	7	22	
Yes	27	80	
Preoperative chemotherapy			0.920
No	19	58	
Yes	15	44	
Adjuvant chemotherapy			0.834
No	11	35	
Yes	23	67	

CEA, carcinoembryonic antigen.

non-MAC accounted for 90.5% (n=344). A total of 122 (46.2%) patients received PCT, including 47 (38.5%) who received FOLFOX, 32 (26.2%) who received XELOX, 36 (29.5%) who received FOLFIRI, and 7 (5.7%) who received capecitabine. Furthermore, 200 (75.8%) patients received adjuvant chemotherapy, including 57 (28.5%) who received FOLFOX, 82 (41.0%) who received XELOX, 46 (23.0%) who received FOLFIRI, and 15 (7.5%) who received capecitabine. The median duration of adjuvant chemotherapy was 3.0 months (range, 1.0–6.0 months).

Due to the number of MAC patients being so small compared to the number of non-MAC patients (9.5% *vs.* 90.5%), we selected 102 patients from the 344 patients without a mucinous component as the non-MAC group by random number table for matching with the MAC group in a 3:1 ratio. We then compared the clinicopathologic characteristics between the two groups. As shown in *Table 2*, the MAC and non-MAC groups did not significantly differ in clinicopathologic characteristics in terms of age, gender, timing of metastasis, primary tumor location, T stage, N stage, number of metastases, preoperative CEA level, and proportion of PCT. After adjuvant chemotherapy lasting 3 or 6 months, CT, MRI, or physical examination follow-up demonstrated that 6 of 34 (17.6%) patients in the MAC group and 8 of 102 (7.8%) patients in the non-MAC group had progression disease (P<0.05). Finally, we used these two groups for further survival analysis.

Survival outcomes

All individuals were followed up for a total of 58 months (range 2–124 months) after the original liver resection. The median follow-up time between the MAC group (58 months) was not significantly different; range (2.0–123.0 months) and the non-MAC group (64 months; range, 2.2–124.0 months; P=0.687). Overall, 85 of 136 (62.5%) patients developed tumor recurrence after liver resection, and 57 of 136 (41.9%) patients died of disease progression. Both RFS and OS did not significantly differ between the MAC and the non-MAC groups (median OS: 64 *vs.* 59 months, respectively, P=0.677, *Figure 1A*; median RFS: 19 *vs.* 35 months, respectively, P=0.902, *Figure 1B*). Among patients in the MAC group, OS time was not significantly different between those who received PCT and those who did not receive PCT (median OS: 38 *vs.* 78 months, respectively, P=0.290, *Figure 2A*). Nevertheless, in the non-MAC group, OS time was significantly longer in patients with PCT than those without PCT (median OS: 59 *vs.* 40 months, respectively, P=0.031, *Figure 2B*).

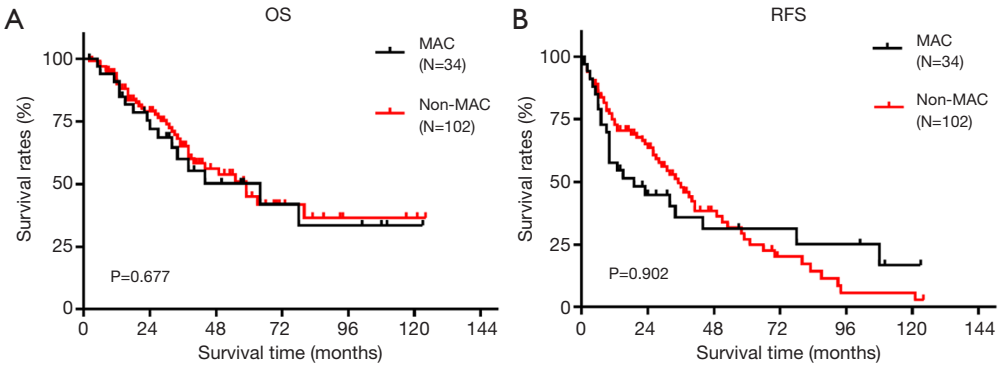

Figure 1 Kaplan-Meier survival curves comparing. (A) Overall survival (OS) and (B) recurrence-free survival (RFS) rates in patients of mucinous adenocarcinoma (MAC) and non-MAC who develop colorectal liver metastases after curative liver resection.

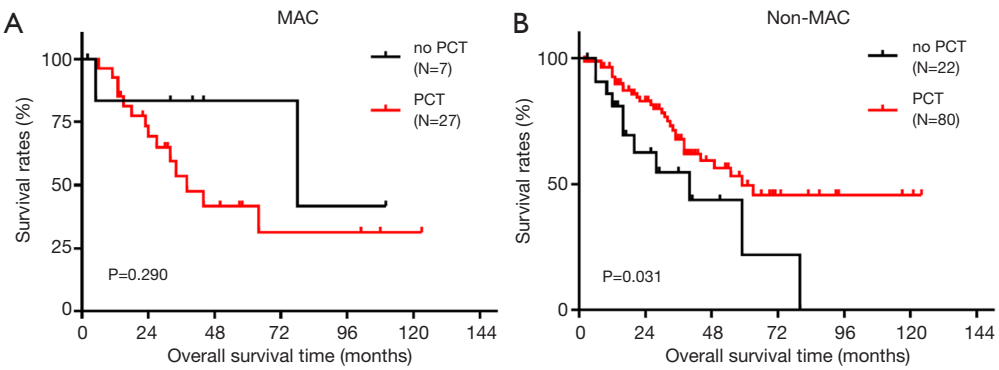

Figure 2 Kaplan-Meier survival curves comparing overall survival rates, based on administration of perioperative chemotherapy (PCT), in (A) the mucinous adenocarcinoma (MAC) group and (B) the non-MAC group patients who develop colorectal liver metastases after curative liver resection.

Univariate and multivariate analysis

In patients with non-MAC, univariate analysis showed that male sex, number of liver metastasis not more than 1, and PCT, were independent factors found to be significant for higher OS rate (P<0.05); multivariate analysis showed that PCT was the only independent predictor of higher OS rate (P=0.044). Among patients in the MAC group, multivariate analysis showed that number of liver metastases more than 1 was an independent predictor of poorer OS rate (P=0.04; *Table 3*).

Discussion

The prognostic impact of MAC in CRLM

MAC is an uncommon histologic subtype of CRC and characterized by the formation of a tumor comprised of at least 50 percent mucin according to WHO definition. Mucins are proteins with a high molecular weight and are heavily glycosylated. The mucinous component is believed to function as a chemical barrier that may prevent chemotherapy medications from effectively penetrating cancer cells (16,17).

Mucinous differentiation is associated with several molecular and genetic features. Mucinous tumors show overexpression of the mucin gene MUC2, which might be caused by hypomethylation of the MUC2 promotor (18,19). MAC is connected with enhanced microsatellite instability (MSI) status, CpG island methylation phenotype, reduced expression of P53, APC mutation rate, and expression of p21 (20-23) compared to non-mucinous CRC. Regarding K-ras mutation rate in colorectal MAC, conflicting results have been reported (20,24).

MAC has been considered a prognostic factor in few studies of CRLM (25,26). Lupinacci *et al.* reported that, in

Table 3 Univariate and multivariate analyses of prognostic factors for overall survival in patients with mucinous adenocarcinoma and non-mucinous adenocarcinoma

Variables	Mucinous adenocarcinoma				Non-mucinous adenocarcinoma			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Age (≤60 *vs.* >60 years)	1.370 (0.492–3.812)	0.547			0.740 (0.394–1.388)	0.35		
Sex (male *vs.* female)	0.548 (0.190–1.581)	0.266			0.454 (0.210–0.985)	<0.05		
Primary tumor location (rectum *vs.* colon)	1.316 (0.473–3.666)	0.599			1.559 (0.839–2.896)	0.16		
T stage (4 *vs.* 1–3)	2.002 (0.715–5.606)	0.186			0.891 (0.456–1.741)	0.74		
N stage (positive *vs.* negative)	2.033 (0.646–6.398)	0.225			1.947 (0.980–3.870)	0.06		
Timing of metastasis (synchronous *vs.* metachronous)	1.694 (0.582–4.931)	0.333			1.298 (0.650–2.595)	0.46		
Number of metastatic tumors (>1 *vs.* 1)	1.638 (0.614–4.372)	0.324	0.358 (0.123–1.044)	0.04	2.123 (1.109–4.063)	0.02		
Metastases diameter (>3 *vs.* ≤3 cm)	0.477 (0.153–1.493)	0.204			1.860 (0.972–3.558)	0.06		
Preoperative CEA (>50 *vs.* ≤50 ng/mL)	2.367 (0.740–7.570)	0.146			1.673 (0.744–3.764)	0.21		
Preoperative chemotherapy (yes *vs.* no)	2.111 (0.771–5.781)	0.146			1.532 (0.826–2.842)	0.18		
Peri-operative chemotherapy (yes *vs.* no)	0.455 (0.102–2.028)	0.455			2.086 (1.040–4.184)	0.04	4.14 (1.040–16.475)	0.044

HR, hazard ration; CI, confidence intervals.

patients with a CRLM, presence of mucinous content >50% was an independent negative prognostic factor compared with those who had tumors with mucinous content <50% (P=0.011) (25). Verhulst *et al.* reviewed papers using the WHO definition of MAC, and defined cohort studies, case-control studies or cross-sectional studies comparing survival in MAC and adenocarcinoma patients; the meta-analysis showed enhanced risk of death in MAC patients. In that review, mucinous differentiation resulted in a 2–8% increased hazard of death, but a difference in the proportion of stage IV patients at presentation was not identified (14). Likewise, in the present study, our results do not demonstrate that MAC, compared with non-MAC patients, is associated with long-term survival in resectable CRLM patients (P>0.05).

The prognostic impact of PCT in CRLM

Although liver resection is the main treatment strategy which confers the best prognosis for long-term survival for patients with resectable CRLM, after liver resection, the majority of patients will develop recurrence (6,27,28). PCT, including neoadjuvant chemotherapy and adjuvant chemotherapy, is supposed to decrease recurrence rates after surgery (10,29). Neoadjuvant chemotherapy has an extra benefit in enabling the evaluation of tumor chemo-responsiveness, while adjuvant chemotherapy after liver resection is indented to decrease CRLM recurrence. Chemo-responsiveness can help differentiate patients benefiting from liver resection or adjuvant chemotherapy from these with aggressive biological conduct who may not be efficient in further therapy. However, the PCT survival effects in patients with resectable CRLM remains controversial (9). First, the EORTC study 40983 showed that PCT with FOLFOX (folinic acid, fluorouracil, and oxaliplatin) improved progression-free survival (PFS) in patients with initially resectable CRLM undergoing liver resection compared to surgery alone (8,30). In that cohort, no difference was found in OS in patients receiving additional PCT compared with surgery alone (30). Apart from that trial, several retrospective and

prospective studies have shown that PCT could not transfer improved PFS to OS, particularly for longer-term survival when compared to liver resection alone (10,29). In our study, the results show that, compared to surgery alone, PCT does not improve RFS or OS rates for the entire cohort (P>0.05). However, in the non-MAC group, PCT significantly prolonged OS time for CRLM (P=0.031). Conversely, in the MAC group, PCT showed no difference in OS rate. Therefore, besides the chemotherapeutic agents or the variability of regimens, different biological behavior in histologic subtypes of CRC might be one of the causes of discrepancies in benefits on survival outcomes from PCT. Furthermore, our results also indicate that it might be the poor chemo-responsiveness that causes the MAC patients with resectable liver metastasis not have long-term survival benefit from PCT. Taking into account that the response to chemotherapy may be poor, MAC patients with liver metastases need to be carefully considered for PCT.

Limitations

The retrospective nature of this research and the tiny number of patients limits this study. In a prospective study with a bigger sample size, these results need to be validated. Furthermore, the different PCT regimens could have had particular prognostic impacts that were not evaluated in the present research. Moreover, the effect of MSI status, and biomarkers like KRAS, NRAS, and BRAF mutations, on the efficacy of PCT was not assessed in this study. These biomarkers should be examined, and the genetic mechanism should be investigated in future studies.

Conclusions

In conclusion, PCT has a positive survival benefit on non-MAC patients with CRLM, while MAC patients with CRLM do not benefit from PCT. When developing a treatment strategy like PCT or surgery alone for CRLM, mucinous histology should be considered as one of the prognostic factors. Due to the retrospective nature and the small number of patients, these conclusions need to be validated by further research.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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. The study was approved by institutional ethics committee of the Sun Yat-sen University Cancer Center (No. 2019-99-86). Prior to original treatment, written informed consent was received from all of the patients.

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