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The prophylactic role of mitomycin C-based hyperthermic intraperitoneal chemotherapy (MMC-based HIPEC) on peritoneal metastasis of spontaneously ruptured hepatocellular carcinoma (srHCC): A pilot study

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Abstract: Hepatocellular carcinoma (HCC) was featured as spontaneous rupture hemorrhage under intratumoral overpressure. Spontaneous rupture hepatocellular carcinoma (srHCC) has a high propensity for peritoneal metastasis (PM). Although HIPEC has become standard treatment for malignancies with PM, it has been poorly described in srHCC. We conducted a single-arm, open-label, single-center, prospective study to explore the prophylactic role of MMC-based HIPEC on PM of srHCC. A total of 7 patients were collected from April 1, 2021 to April 30, 2022. HIPEC was conducted 3 times on the first, third and fifth postoperative days. 15 mg/m^2 of MMC was used with 60 minutes perfusion at 43°C. The primary end-point was local peritoneum recurrence free survival (RFS), whereas the secondary end-point was systemic RFS and overall survival (OS). The mean hepatectomy operation time was 232 minutes (SD: 124.08 minutes). The median bleeding loss was 200 mL (range 50–400 mL). The mean hospital stay was 13 days (SD: 3.42 days). Only mild abdominal distension was reported in 4 patients (57%). There were no patients who suffered from life-threatening intra-abdominal and extra-abdominal complications (EAC). At the data cut-off (April 30, 2023), one patient (14%) had died due to cachexia. Local peritoneal recurrence occurred in three patients (43%). Median follow-up was 16.1 months (IQR: 12.8–16.6 months). Median local peritoneum RFS was 12.3 months (95% CI: 7.0–17.5; 4 events) and median overall RFS was 7.5 months (95% CI: 4.2–10.8; 6 events). MMC-based HIPEC was safe and feasible in selected patients of srHCC. It showed a positive tendency in preventing PM, but large-scale research should be continued.

***Keywords*:** hyperthermic intraperitoneal chemotherapy, mitomycin-C, spontaneous rupture hepatocellular carcinoma

Introduction

Hepatocellular carcinoma (HCC), the most frequently occurring type of primary liver cancer, is the fourth most common cancer and the third most common cancer-related by mortality. The incidence of HCC is higher in East Asia, especially in China (*1*). HCC often develops as a result of chronic liver disease. In the case of cirrhosis and intratumoral overpressure, HCC can have characteristic spontaneous rupture and hemorrhage (*2*). Time has witnessed the increase of ruptured HCC in developing countries in recent years. However, spontaneous rupture HCC (srHCC) possesses higher acute mortality. Although the one-year overall survival rate could reach 57% after transcatheter arterial embolization (TAE) followed by staged surgical resection strategies, the delayed operation could cause postoperative peritoneal metastasis (PM) reached at 34.2% (*2*). In this regard, srHCC is regarded as an independent risk factor for PM of HCC (*3*).

Hyperthermic intraperitoneal chemotherapy (HIPEC) has shown considerable therapeutic efficacy in other tumors with PM, including gastrointestinal tumors, ovarian cancer, and peritoneal malignant tumors (*4*). Different chemotherapeutic drugs can be administrated in HIPEC. Traditionally, mitomycin C (MMC) and oxaliplatin (OX) were the most commonly used drugs in HIPEC. A meta-analysis, compared OX with MMC in HIPEC for PM from colorectal cancer (CRC), showed that MMC possessed comparable survival to OX but lower major complications (*5*). In this regard, could MMC-based HIPEC be applied in HCC? In fact, MMC could be commonly used as a chemotherapeutic agent in conventional transarterial chemoembolization (c-TACE) and hepatic arterial infusion chemotherapy (HAIC) (*6*) for HCC (*7,8*). C-TACE with MMC was effective and safe in a long-term follow-up study (*9*).

Fortunately, an increasing number of previous studies

have demonstrated that cytoreductive surgery (CRS) plus MMC-based HIPEC was a safe and effective approach in cases with PM of HCC (*10-12*). However, srHCC might possess a larger resected surface due to larger tumor size caused larger resection range, compared with PM of HCC. Postoperative HIPEC might increase the risk of hemorrhagic events. Furthermore, the dosage required for prevention purposes is possibly different from the dosage required for treatment purposes. The role of MMC-based HIPEC for srHCC remains unknown. We present cases with srHCC treated with MMC-based HIPEC followed by hepatectomy and evaluate the safety and feasibility of this procedure and the prophylactic role on PM.

Patients and Methods

This study was a single-arm, open-label, single-center, prospective study conducted with the approval of the Ethics Committee of West China Hospital, Sichuan University (2022-1163). The trial has been registered on *ClinicalTrials.gov* (NCT05544253).

Patients

Data collection was prospective. We selected the candidates at West China Hospital, who were diagnosed with srHCC and received emergency laparotomy or staged hepatectomy between April 1, 2021 and April 30, 2022.

Selections were eligible when meeting the criteria: *i*) Aged from 18–80; *ii*) Clinical diagnoses of srHCC – symptoms: acute abdominal pain and peritonitis; blood routine tests: decreased erythrocyte count; increased leucocyte count, especially the proportion of neutrophils; increased alpha-fetoprotein (AFP) and/or protein induced by vitamin K absence or antagonist-II (PIVKA-II); radiological features: contrast materials extravasation from lesions confirmed by abdominal contrast enhanced computed tomography or gadoxetic acid disodium (Gd-EOB-DTPA)-enhanced magnetic resonance imaging (MRI); intraoperative findings of tumor rupture and postoperative pathology are more confidently conclusive (*13*); *iii*) ECOG score of 0–2 points; *iv*) Child-Pugh class A-B liver function only; and *v*) Received emergency laparotomy or staged hepatectomy.

Exclusion criteria were: *i*) Contraindications of HIPEC, including intra-abdominal adhesions, intestinal obstruction, severe kidney insufficiency, myelosuppression, severe cardiovascular system disease, abdominal infection, bleeding tendency or coagulation dysfunction, severe pulmonary system disease, vital signs are unstable, cachexia; *ii*) Patients who refuse to accept clinical trials.

Intervention

After the written informed consent was given to the candidates, the specific procedures were conducted. All of the candidates have received liver resection and perfusion tubes had been placed at the end of the operation. After the operation, HIPEC was conducted 3 times on the first, third and fifth postoperative day. Intraperitoneal hyperthermic perfusion device (BR-TRG-II^{TM}, Bao Rui medical corporation, Guangdong, China) was used for HIPEC. 15 mg/m^2 of MMC served as chemotherapeutic agent for HIPEC. MMC possessed the inherent advantages of heat-stability and well-established pharmacokinetics in HIPEC. Furthermore, MMC has proved efficacy in c-TACE and HAIC for HCC. The perfusion volume was 2,000 cm^3 of normal saline with 15 mg/m^2 MMC. At the beginning of perfusion, it took 5 minutes to reach the target temperature of 43°C (109°F) using this device, and then adjusted the perfusion flow to 400ml/min. The abdominal temperature was maintained at 43°C for the 60 minute perfusion period (Figure 1). The candidate was monitored by electrocardiogram (ECG) and continuous low flow oxygen inhalation.

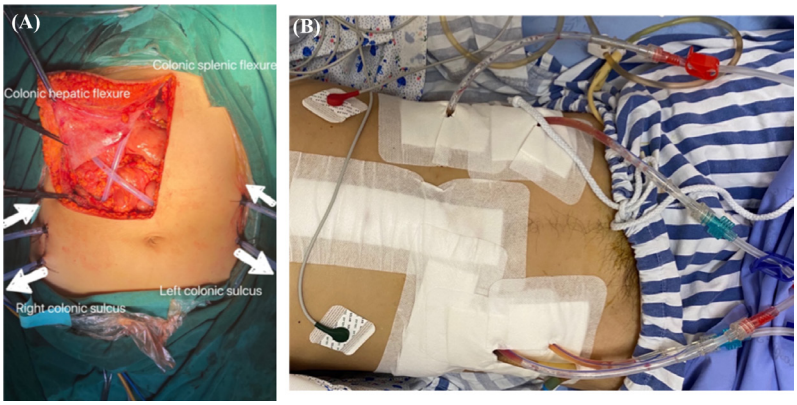

Figure 1. The position of HIPEC tubes in operation and HIPEC procedure. (A) Four perfusion drainage tubes were placed and fixed intraoperatively. Among them, 2 tubes were arranged from the left lower colonic sulcus to the right upper colonic hepatic flexure, whereas other 2 tubes were oppositely arranged from the right lower colonic sulcus to the left upper colonic splenic flexure. **(B)** The inflow tubes were connected to the red buttons, and the outflow tubes were connected to the blue buttons.

Simultaneously, the candidate also received balanced solution supplement during the process. HIPEC would be stopped immediately when the candidates were caught in life-threatening adverse events.

Follow-up and outcomes

We obtained follow-up data *via* outpatient service and telephone consultation. We followed the selections the first month after the hepatectomy and every 3 months after that. Peripheral blood tests, including routine blood, total biochemical items and tumor biomarkers (AFP and PIVKA-II) and full abdominal contrast-enhanced computed tomography (CECT) or magnetic resonance imaging (MRI) were conducted and administrated at every follow-up. The recurrence and metastasis were mainly assessed from the serum level of tumor markers and imaging evaluation.

The primary efficacy end-point was local peritoneum RFS, whereas the secondary efficacy end-point was systemic RFS and OS. Duration of progression of disease, including local peritoneum progression and systemic recurrence, was calculated from the first administration of MMC-based HIPEC. The definition of OS is the interval between the first administration of HIPEC and death for any reason or the last follow-up in the twelfth month. The censoring date of the present study was April 2023.

Morbidity was regarded as any complication detected during hospitalization or within 30 days after HIPEC. The categorization of postoperative complications were according to the Clavein-Dindo classification (*14*). Grade III or higher were considered as major morbidity (*15*). Specifically, postoperative hemorrhage, bile leakage, hepatic dysfunction, pulmonary infection and reoperation are included in the category of postoperative complications. In addition, National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v.4.03 for adverse events related to mitomycin C of HIPEC were monitored (*14*). Mortality is defined as the death within 30 days after surgery. Safety assessments included monitoring of morbidity and mortality of HIPEC. At a data cut-off of April 30, 2023, 7 patients were recruited to the study.

Statistics analysis

The measurement data of normal distribution was represented by mean (SD), the non-normal distribution data was represented by median (IQR), and the enumeration data was represented by frequency (%). Kaplan-Meier method was used to assess overall and progression survival rates and time. Safety was summarized descriptively. All analyses were performed using IBM SPSS statistics ver.26 (IBM, Armonk, NY). $P < 0.05$ was defined as statistically significant in this study.

Results

Patient Characteristics

During the study period, 15 patients underwent hepatectomy due to liver cancer peritoneum related diseases in West China Hospital, Sichuan University between April 1, 2021 and April 30, 2022. All of the selections received postoperative clinical pathological diagnoses. Only 10 of them were diagnosed as spontaneously ruptured hepatocellular carcinoma. At a data cut-off of April 2023, 7 patients were recruited to the study. They received eligibly assessment and received MMC-based HIPEC after hepatectomy. Figure 2 demonstrates patient enrollment.

Baseline characteristics of enrolled patients are shown in Table 1. The mean age of enrolled patients was 51 years and mean BMI was 23.46. Most patients had slightly higher transaminases than normal, but liver

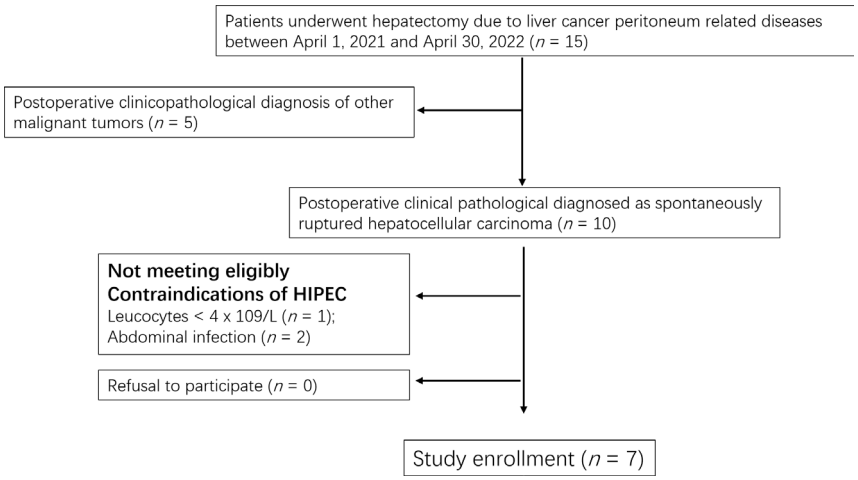

Figure 2. Flow of study participants.

Table 1. Characteristics of enrolled patients

Case Number	Age	Sex	BMI	Background Liver Disease	Viral load	PLT 10^9/L	ALT /IU/L	AST /IU/L	TB umol/L	PT /s	INR	Alb/g/L	AFP ng/mL	PIVKA-II mAU/mL
1	38	M	24.06	HBV	<1.00E + 02	237	324	86	6.1	12.9	1.18	42.4	13,605.0	8,051
2	41	M	20.76	HBV	2.03E + 02	209	124	129	21.5	12.5	1.15	39.9	8,998.0	750,000
3	56	M	25.14	HBV	1.72E + 05	235	31	34	15.5	11	0.98	45.8	36.5	40,709
4	46	F	21.36	HBV	6.07E + 05	262	66	50	25.2	12.5	1.11	32.2	49,334.0	4,398
5	75	F	27.64	Primary biliary cirrhosis	-	46	14	27	21.6	12.7	1.15	33.2	43.7	74
6	36	F	22.76	HBV	<1.00E + 02	97	16	19	6.5	11.3	1.01	37.3	10,649	1,466
7	68	M	21.80	HBV	<1.00E + 02	127	37	32	10.5	13.5	1.24	38.5	1,210	18,894
Median/Mean (range)	51 ± 15	-	23.36 ± 2.43	-	-	173.29 ± 82.84	87.43 ± 111.04	53.86 ± 39.80	15.27 ± 7.76	12.34 ± 0.89	1.12 ± 0.09	38.47 ± 4.83	8,998 (43.7–13,605.0)	8,051 (1,466–40,709)

M, male; F, female; HBV, hepatitis B virus.

Table 2. Perioperative Parameters

Case Number	Initial Treatment (TAE/Systemic treatment/Emergency Resection/Selective resection)	Duration from initial treatment to resection (month)	Operation time (minutes)	Bleeding loss (mL)	Blood Transfusion (mL)	Hospital Stay (day)	In-hospital costs (dollar)	Perioperative morbidity Clavien-Dindo	Post-operative treatment (TACE/ Huaier Granule/ Targeted agent + immune therapy)
1	TAE + Sorafenib	6	290	100	-	10	10,812.64	II	Huaier Granule + Sorafenib
2	TAE	0.25	270	1400	-	17	16,345.63	II	Donafenib
3	Emergency Resection	-	360	400	Fresh Frozen Plasma: 400 mL	9	14,564.53	II	TACE + Donafenib
4	Emergency Resection	-	167	50	-	10	14,294.42	I	Huaier Granule + Sorafenib
5	Emergency Resection	-	120	20	-	17	11,581.78	I	Sorafenib
6	TAE + Camrelizumab + lenvatinib	4	381	200	-	15	16,181.86	II	TACE + Camrelizumab + lenvatinib
7	Emergency Resection	-	136	200	-	13	9,158.15	II	TACE + Dnoafenib
Median/Mean (range)	-	-	232.00 ± 124.08	200 (50–400)	-	13.00 ± 3.42	13,277.00 ± 2,782.66	-	-

function of all enrolled patients conformed to Child-Pugh class A. Except for patient No.5, who suffered from srHCC caused by autoimmune hepatitis, other patients were HBV-related srHCC. Among the patients with HBV-related srHCC, 4 of them (57%) had low viral load, only No.3 and No.4 showed 10^5 higher viral load. The median AFP was 8,998 ng/mL (range: 43.7–13,605.0 ng/mL). The median PIVKA-II was 8,051 mAU/mL (range: 1,466–40,709 mAU/mL). The tumor markers AFP and PIVKA-II in all patients were significantly higher than normal values ($p < 0.05$).

Perioperative parameters

Perioperative parameters are shown in Table 2. All of the selections received laparotomy. Figure 3 shows the preoperative CECT images and intraoperative specimens of No.4. Three cases (43%) had initially received emergency transcatheter arterial embolization (TAE) and subsequently staged hepatectomy, and 4 (57%) underwent emergency laparotomy. The mean hepatectomy operation time was 232.00 minutes (SD: 124.08 minutes). The median bleeding loss was 200 mL (range: 50–400 mL). Only 1 (14%) had received intraoperative transfusion of fresh frozen plasma 400 mL. The postoperative complications of surgery of all selections were classified as Clavien-Dindo I-II. Five (71%) were Clavien-Dindo II, whereas the other 2 (29%) were Clavien-Dindo I. Specifically, No.1, 6, and 7 had postoperative fever caused by pulmonary infection, and received total parenteral nutrition for support treatment. No. 2 and No.3 received 2 units of red blood cell suspension. No patients died or underwent reoperations during the perioperative period. The mean hospital stay was 13 days (SD: 3.42 days). The mean hospitalization expenses reached $13,277.00 (SD: 2,782.66). All selections were treated with postoperative targeted therapy, including Sorafenib, Donafenib, and lenvatinib. Patients with microvascular invasion (MVI), one of high-risk factors of recurrence, also received TACE after surgery.

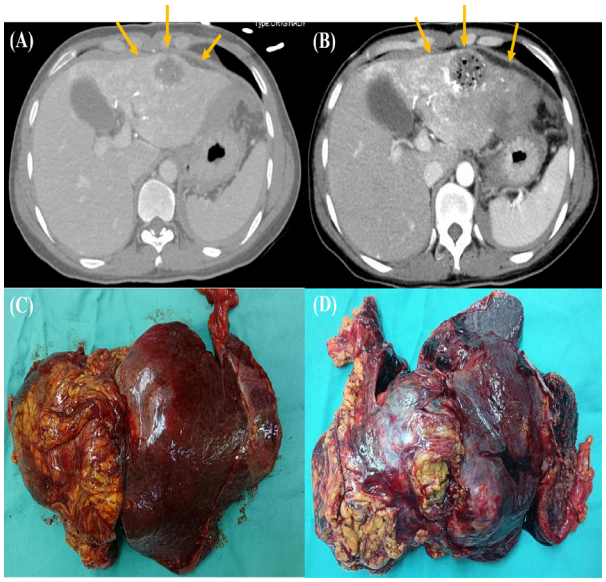

Figure 3. (A) and (B) CT image of No.4 patient. The CT image showed the targeted tumor was located in the left hemiliver. **(C) and (D)** the intraoperative specimen of No.4 patient.

Postoperative clinicopathological characteristics

All of selections received postoperative pathological examination. The clinicopathological features of 7 patients are shown in Table 3. The median maximum tumor diameter was 11.0 cm (range: 6.0–12.0). All surgical margins reached R0. The mean incisal edge was 1.46 ± 1.26 cm. No satellite lesions were found in all specimens. Three (42,86%) specimens had MVI, but the number is less than or equal to 5, and the distance from the adjacent liver tissue is less than 1cm. Five (71.43%) were medium differentiation, whereas two (28.57%) were medium to low differentiation.

Table 3. Postoperative clinicopathological characteristics

Case number	Maximum tumor diameter (cm)	Incisal Edge (cm)	Satellite lesions	MVI	Degree of Differentiation
1	10.5	1.0	None	None	Medium to low differentiation
2	12.5	0.5	None	None	Medium differentiation
3	12.0	1.2	None	Yes, the number is less than or equal to 5, and the distance from the adjacent liver tissue is less than 1 cm	Medium differentiation
4	11.8	4.0	None	None	Medium differentiation
5	5.0	2.0	None	None	Medium differentiation
6	11.0	0.2	None	Yes, the number is less than or equal to 5, and the distance from the adjacent liver tissue is less than 1 cm	Medium to low differentiation
7	6.0	1.3	None	Yes, the number is less than or equal to 5, and the distance from the adjacent liver tissue is less than 1 cm	Medium differentiation
Median/Mean (range)	11.0 (6.0–12.0)	1.46 ± 1.26	None	-	-

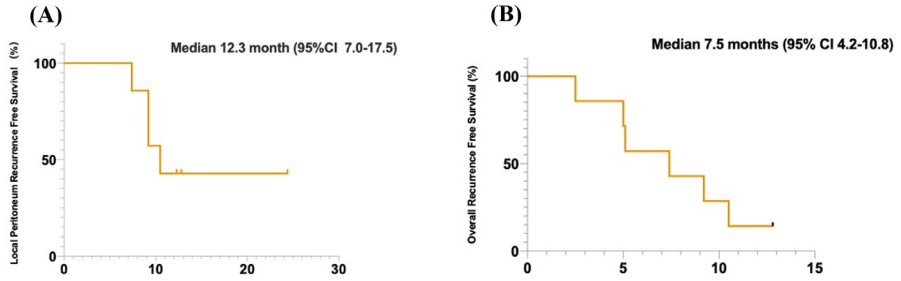

Figure 4. (A) Local peritoneum RFS and (B) overall RFS for all study patients who underwent postoperative MMC-based HIPEC. RFS, recurrence free survival; MMC-based HIPEC, mitomycin C-based hyperthermic intraperitoneal chemotherapy.

Safety and adverse events

There were no postoperative 30-day mortalities in this study. Postoperative complications of MMC-based HIPEC occurred in 4 patients (57%). Specifically, they developed mild abdominal distension after HIPEC, which could be relieved after symptomatic treatment. There were no patients who suffered from life-threatening intra-abdominal complications (IAC), including anastomotic leakage, abdominal bleeding, and pleural effusion. The previous study showed that MMC had higher incidence of extra-abdominal complications (EAC), including liver function damage, neutropenia, and leucopenia (*16*). Fortunately, no patients developed EAC due to lower MMC dosage.

Long-term outcomes

At the data cut-off (April 30, 2023), six patients (86%) still survived, and one patient (14%) had died due to cachexia caused by HCC. Recurrence occurred in six patients (86%). The median follow-up was 16.1 months (IQR: 12.8–16.6). Median local peritoneum RFS was 12.3 months (95% CI: 7.0–17.5; 4 events) and median overall RFS was 7.5 months (95% CI: 4.2–10.8; 6 events). The postoperative 3-month, 6-month, 9-month and 1-year local peritoneum RFS rate was 100%, 100%, 57.1% and 42.9%, respectively (Figure 4A).

The postoperative 3-month, 6-month, 9-month and 1-year RFS rate was 85.7%, 57.1%, 42.9% and 14.3% (Figure 4B). The pattern of recurrence included intrahepatic recurrence, lung, and peritoneal cavity metastasis. Specifically, two patients (29%) suffered from intrahepatic recurrence, four patients (57%) suffered from peritoneum recurrence, and one patient (14%) suffered from lung metastasis. The post-recurrence treatment included targeted strategy plus immune therapy, transarterial chemoembolization (TACE), hepatic arterial infusion chemotherapy (HAIC), and reoperation according to the HCC treatment guideline of our institution.

Discussion

Unlike other tumors, hepatocellular carcinoma is featured by spontaneous rupture under intratumoral overpressure (*17*). It has been regarded as a terminal event with a drastically poor prognosis, despite the morbidity of srHCC was low (*17*). Although previous studies demonstrated that standard TAE followed by staged surgical resection strategy improved one-year OS reached at 57% (*3*), the delayed hepatectomy boosted postoperative PM by 34.2% as well (*2*). EVOCAPE-1 (Evolution of Peritoneal Carcinomatosis study 1) elucidated that untreated PM rapidly lead to developed symptoms, including small-bowel obstruction, ascites, tumor-related pain, and malnutrition (*18-20*), which severely impacted survival of patients with liver cancer under chronic liver disease background. However, that did not mean that emergency hepatectomy should be considered predominately to reduce the rate of PM as a result of higher in-hospital mortality rate based on the latest meta-analysis (*21*). Therefore, it is paramount to present a measure to reduce both the risk of perioperative mortality and the risk of peritoneal recurrence.

Sugarbaker *et al.* (*18*) first demonstrated that selected patients with PM could benefit from HIPEC, which provided the foundation (*22-25*). After that, Blake Cady's first-order principle elaborated which tumor types and chemotherapeutic agents were suitable for HIPEC (*18*). Time has witnessed substantial progress of HIPEC in selected patients with PM of colorectal, gastric, appendiceal and ovarian primary tumor. Historically, hepatobiliary organs as part of foregut organs have a high propensity for early metastatic progression. Although they were of the opinion that these tumors subordinated to gastrointestinal tumor have limited response to HIPEC, they showed potential with a condition of valid response to chemotherapeutic agents (*18,26*). Although clinical trials related to application of HIPEC in preventing PM after srHCC were rare, previous researchers were optimistic towards CRS plus HIPEC for PM of HCC (*10,12,27*). A multicenter study conducted by Sanket *et al*. demonstrated that it was a safe and effective approach especially for patients who underwent CCR 0-1 resections. The median OS could reach 46.7 months, whereas the projected RFS could reach more than 3 years (*12*). Tabrizian *et al.* counted CRS with or without HIPEC in patients with PM of HCC (*11*). However, they concluded that the median OS was only 35.6 months even in CCR0-1 group. After that, Hung *et al.* (*10*) also

confirmed the safety and effectiveness of HIPEC. These clinical trials formed the basis of application of HIPEC in HCC. In the present study, we collected candidates with srHCC with high risk of PM. Our findings are also complementary to previous studies. In the 16 months of median follow-up, only one patient died, attributed to cachexia. We highlighted median local peritoneum RFS was 12.3 months. Most studies of srHCC have shown the PM rate from 20–50% (*28,29*). Since our study was small-scale and selected for high risk of PM after srHCC, it showed a modest result in MMC-based HIPEC. As we all know, a small sample size can easily induce type II errors and result in false negative results. However, this study identified the feasibility and safety of MMC-based HIPEC procedure for srHCC, which can potentially be widely adopted in clinical practice. Larger scale research could be sponsored to further explore the real role of MMC-based HIPEC on srHCC.

In addition to the widespread concern of tumor types in the application of HIPEC, rational chemotherapeutic agent selection has been explored as well. Traditional MMC-based HIPEC regiment had proven efficacy in a Netherland's trail (*30*). In addition, OX short time perfusion has also been developed in the PRODIGE 7 trial (*ClinicalTrials.gov* identifier NCT00769405) (*31*). Notably, lower agent activity of OX in the peritoneal cavity was found (*30,32*). Further recent study also highlighted the limitation of OX-based HIPEC and superiority of MMC (*33*). The recent meta-analysis compared the efficacy of OX and MMC-based HIPEC in colorectal cancer (*5*). They concluded that OX and MMC possessed comparable survival, but OX had higher morbidity with major complications (*5*). Furthermore, several publications demonstrated that OX might have a higher risk of postoperative hemorrhage (*15*), which could cause major and even life-threatening complication for major hepatectomy. MMC was time-consuming compared with OX. However, recently, a trial, HIPECT4 (*ClinicalTrials.gov* identifier NCT02614534), will explore the efficacy of 60-minute MMC-based HIPEC in a prophylactic setting (*34*). The previous research showed that complications of HIPEC included anastomotic leakage, abdominal bleeding, pleural effusion, abdominal abscess, and fistula formation (*5*). The process of HIPEC would be disturbed with these complications, leading to limited therapeutic effect. Compared with HIPEC for colorectal tumor, the incidence of complications of HIPEC for srHCC was lower. In the present study, no adverse reactions of Clavien-Dindo Grade III or IV were encountered. On the one hand, absence of intestinal anastomosis operation prevented the incidence of anastomotic leakage, which was the main complication of HIPEC. On the other hand, drug choice of MMC conferred more safety properties. Fortunately, there were no patients with observed abdominal bleeding. Abdominal bleeding was life-threatening for srHCC patients with low levels of hemoglobin, which was thought to be related to the coverage of raw surface (*5*). Hompes *et al.* (*16*) indicated that MMC had a high propensity for EAC, including neutropenia and leucopenia. They showed that up to 39% of patients could suffer from neutropenia (*35*). Melissa *et al*. demonstrated that MMC could also cause interstitial lung disease and acute respiratory distress syndrome (ARDS) (*35*). Fortunately, in the present study, we have not found any adverse reactions related to the above, so far.

MMC, alkylating chemotherapeutic agent, interfered with DNA-synthesis and non-cycle dependent (*36,37*). MMC could reach a high intraperitoneal concentration with low systemic absorption due to large molecular weight (334.3 Da). The cytotoxicity could be amplified by hyperthermia (*38*). In addition, MMC was popular in locoregional treatment of HCC, namely c-TACE and HAIC (*8*). Historically, Gruber-Rouh *et al.* (*39*) and Achenbach *et al*. (*40*) performed TACE using mitomycin and lipiodol. A recent systemic review showed of the 52 articles on TACE, 8% used MMC (*41*). MMC could serve as the most popular component in double and triple chemotherapeutic strategy in TACE. However, some research declared that TAE had comparable efficacy with TACE in 3 recent randomized control trials. Among those, Chang *et al*. used cisplatin (*42*), whereas Kawai *et al.* used doxorubicin (*43*). In this regard, there has been no evidence to prove a limitation of MMC in TACE. Additionally, it has been shown that MMC is preferentially stimulated by hypoxic tumor cells to produce cytotoxic metabolites (*44*).

Of note, as far as we know, it was the first trial focused on MMC-based HIPEC in srHCC. Historically, there was only one retrospective study that highlighted use of HIPEC in srHCC (*45*). However, they concluded negative results. This is possibly caused by 5-fluorouracil administrated in the HIPEC process. 5-FU is a nucleoside metabolism inhibitor and cell cycle specific aimed at S phase (*46,47*). Theoretically, cell cycle-specific agents are modestly suitable to limited duration of HIPEC (30–120 min) (*38,47-49*).

In conclusion, MMC-based HIPEC showed safety and feasibility for srHCCs, although it was limited by the modest result since it's a small-scale sample and the absence of a comparator group. Larger scale research should be continued. Therefore, we would conduct a randomized clinical trial (NCT05544253) highlighted by the prophylactic role of MMC-based HIPEC on PM of srHCCs. We believe that the results of this study could support further investigations.

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Conflict of Interest: The authors have no conflicts of interest to disclose.

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