Original Article

The role of hyperthermic intraperitoneal chemotherapy in the treatment of spontaneously ruptured hepatocellular carcinoma: a pilot study

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Background: Spontaneous tumor rupture is a distinctive disease pattern in patients with hepatocellular carcinoma (HCC). The application of hyperthermic intraperitoneal chemotherapy (HIPEC) in spontaneously ruptured hepatocellular carcinoma (srHCC) is debatable. Our study aimed to compare the long-term outcomes of srHCC *vs.* nrHCC and to test the role of postoperative HIPEC in patients with srHCC after hepatectomy.

Methods: From 2014 to 2018, PSM was performed to compare 57 patients who performed liver resection for srHCC and met the research criteria with 57 nrHCC patients selected from 446 consecutive patients. Then patients with srHCC were divided into two groups according to whether they underwent HIPEC after hepatectomy.

Results: After 1:1 PSM, the clinical characteristics of the patients with srHCC and nrHCC were comparable. In terms of long-term outcomes, the nrHCC group had significantly longer OS (P=0.026) and DFS (P<0.001) than the srHCC group. Of the 57 srHCC patients, the HIPEC group showed added complications compared to the non-HIPEC group, including an increased length of hospital stay and higher in-hospital costs. However, there were no significant differences in the metastatic patterns of these recurrent patients, and there was no statistically significant difference in DFS (P=0.28) or OS (P=0.56) between the two groups.

Conclusions: The prognosis of ruptured HCC patients were worse than those of non-ruptured HCC patients. HIPEC may not be a robust treatment for srHCC now.

Keywords: Hyperthermic intraperitoneal chemotherapy (HIPEC); spontaneous rupture; hepatocellular carcinoma (HCC); propensity score matching

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Introduction

Liver cancer, ranking as the second-highest cause of cancer-related death, is one of the most common human malignancies around the world (1). In the last decades, advances in surgical techniques have made it possible for hepatocellular carcinoma (HCC) patients to live longer than in the past. However, the prognosis is still poor in patients who suffer from spontaneously ruptured HCC (srHCC) (2). Peritoneal and hepatic implantation metastasis, considered caused by exfoliated HCC cells, is the most often observed pattern of recurrence or metastasis in these patients (3). The more effective method to remove free HCC cells in the abdominal cavity deserves further exploration.

Peritoneal lavage with distilled water (DWPL), extensively applied for clearing bacteria and free tumor cells in the peritoneal cavity is a conventional technique developed to reduce the incidence of metastases. However, cancer cells can survive in a hypotonic condition, and the efficacy of this therapy is further affected by the contamination of the water *in vivo* and the "inoculum size" of exfoliated cancer cells (3-5).

Intraperitoneal chemotherapy can be conducted at an elevated temperature, defined as hyperthermic intraperitoneal chemotherapy (HIPEC). Hyperthermia can increase the permeability of chemotherapy on the peritoneal surface and enhance the sensitivity of the tumor to chemotherapy by interfering with DNA repair. It also induces apoptosis and activates heat-shock proteins that serve as receptors for natural killer cells, inhibits angiogenesis, and has a direct cytotoxic effect by promoting the denaturation of proteins (6-9). With women with advanced ovarian cancer, HIPEC resulted in more prolonged survival and could significantly improve their prognoses (10). Also, some randomized controlled trials (RCTs) support using this treatment in colorectal cancer (11,12). Moreover, some recent study suggested that cytoreductive surgery followed by HIPEC gives the patient a chance for a good relapse free and overall survival and might be considered as an option in highly patients (13-15). On this basis, we hypothesized HIPEC could improve the long-term outcomes of srHCC. Recent research from Chen suggested that fluorouracil implants can mitigate the risk of peritoneal and hepatic dissemination after HCC rupture (16). Therefore, our research aimed to estimate the safety and efficacy of using HIPEC in patients to treat srHCC. We present the following article in accordance with the STROBE reporting checklist. (available at http://dx.doi.org/10.21037/atm-20-5829).

Methods

Patients

Data collection was retrospective. Seven hundred seventy-four patients were found from a prospectively maintained database at the Guangdong Provincial People's Hospital in China between 2014 and 2018. A multidisciplinary team first assessed all patients. Then we operated on patients with excellent liver function. The inclusion criteria were Child's A or better liver disease and no clinical evidence of significant portal hypertension. After excluding patients according to the pre-specified criteria, among the remaining 503 patients, 446 nrHCC patients and 57 srHCC patients were eventually included for further analysis (*Figure 1*). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Institutional review board approval of our hospital was obtained for this study. This was a retrospective clinical study, which only analyzed the earlier clinical data. The data processed did not reveal the patient's identity information, so there was no need for ethical recognition and informed consent.

Procedure and HIPEC outcome measure

Then, the patients with srHCC were divided into two groups according to whether they underwent HIPEC after hepatectomy. In the HIPEC group, the silicon perfusion catheters were placed at the end of the laparoscopic hepatectomy or open radical surgery. HIPEC was administered 2 times on the 3rd and 5th days after the operation in 30 patients (17-23). The detailed information concerning the HIPEC process can be found in the protocol, uploaded as a supplementary file. The temperature in the abdominal cavity was supported at 43 ℃ (109 °F) by circulating the heated saline. Perfusion with 5-fluorouracil (1,000 mg/m^2) (24,25) or lobaplatin (50 mg/m^2) (26-30) was then started at a flow rate of 300 to 600 milliliters per minute to cause the entire abdomen to be filled with the perfusate. The treatment supported 90 minutes holding the 60-minute perfusion period. At the end of the procedure, perfusion catheters were used to drain the perfusion as thoroughly as possible.

Follow-up

Follow-up data were obtained by outpatient service and telephone consultation for patients and reviewing the medical record from the database. The patients

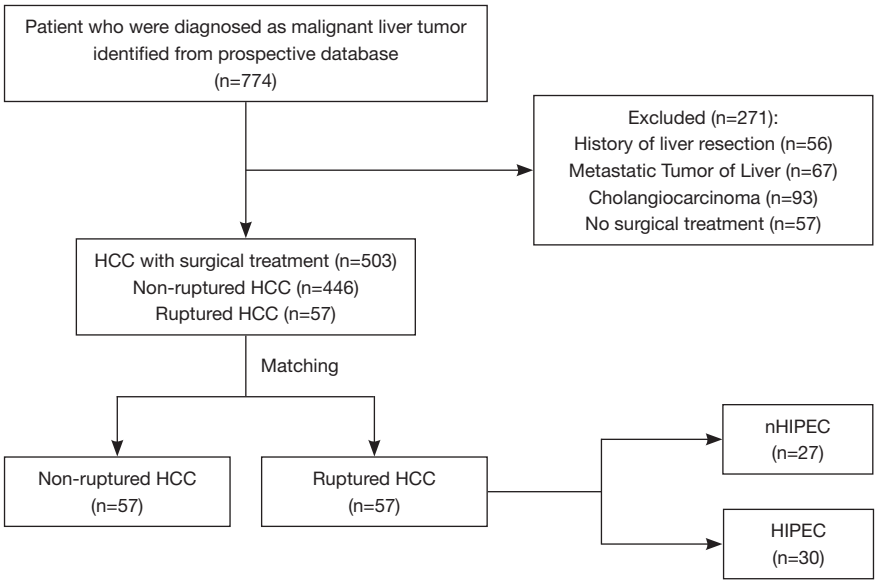

Figure 1 Flow chart showing patient enrollment and surgical treatment strategies. HCC, hepatocellular carcinoma; HIPEC, hyperthermic intraperitoneal chemotherapy.

were followed up every 3 months in the first year after hepatectomy and every 3 to 6 months after that. The recurrence and metastasis of patients were estimated by analyzing their AFP levels and the results of ultrasonography, contrast-enhanced CT, or MRI. Overall survival (OS) is defined as the interval between the surgery date and death for any reason. Disease-free survival (DFS) time was regarded as the time after surgery, during which the patient survived with no evidence of HCC. Patients who had no documented evidence of events were censored at the date of the last follow-up. The censoring date of the present study was May 30, 2019.

Morbidity was defined as any complication observed during hospitalization or within 30 days after the procedure. On the Clavien-Dindo classification, the details of postoperative complications are categorized (31). The following postoperative outcomes were tested: postoperative bleeding, bile leakage, hepatic dysfunction, pulmonary complications, reoperation, and mortality within 30 days of the surgery. The definition of the postoperative complications is according to current evidence (32-34).

Propensity score matching

Propensity-score matching is a statistical method that can find a group of cases with similar baseline features. The propensity score, estimated using a non-parsimonious multivariable logistic-regression model, is a conditional probability of having a particular exposure (HCC with ruptured versus non-ruptured HCC) given a set of measured baseline measured covariates (35-37). We performed matching by a 1:1 matching protocol without replacement, with a caliper width equal to 0.2. Equilibrium is assessed for all the baseline variables to estimate the prematch imbalance and postmatch balance. A P value that is greater than 0.05 for a variable after matching shows a slight imbalance.

Statistical analysis

Paired comparisons were conducted by using McNemar's tests for binary variables expressed as the number and percentage of subjects, and a paired Student's *t*-tests or paired-sample tests were performed for continuous variables described as the mean values and standard deviation. The Kaplan-Meier survival analysis was conducted to estimate differences in patient OS and DFS between the two groups. Cox proportional hazard regression analysis was used to find independent prognostic factors. R 3.6.1 software conducted all statistical analyses for Windows.

Table 1 Characteristics before and after propensity score matching

Variables	Before matching			After matching		
	srHCC (n=57), n (%)	nrHCC (n=446), n (%)	P value	srHCC (n=57), n (%)	nrHCC (n=57), n (%)	P value
Male	48 (84.2)	392 (87.9)	0.429	48 (84.2)	43 (75.4)	0.243
Age (mean ± SD)	50.7±13.9	53.9±11.5	0.019	50.7±13.9	53.3±13.0	0.301
CAHB	29 (50.9)	267 (59.9)	0.194	29 (51.8)	22 (38.6)	0.187
AFP	22 (38.6)	143 (32.1)	0.322	22 (38.6)	20 (35.1)	0.698
Solitary nodule	50 (87.7)	360 (80.7)	0.199	50 (87.7)	56 (98.2)	0.061
LLR	22 (38.6)	194 (43.5)	0.456	22 (38.6)	24 (42.1)	0.698
Serum ALT (mean ± SD)	45.6±40.7	50.6±54.1	0.403	45.6±40.7	49.0±45.2	0.666
Serum AST (mean ± SD)	54.2±45.5	56.4±57.5	0.423	54.2±45.5	62.1±57.5	0.418
Bilirubin (mean ± SD)	18.3±10.2	18.7±23.3	0.560	18.3±10.2	17.7±7.5	0.753
PT (mean ± SD)	14.4±1.2	14.5±1.6	0.492	14.4±1.2	15.5±11.7	0.461
ALB (mean ± SD)	36.4±5.7	38.3±17.3	0.819	36.4±5.7	37.7±5.5	0.189
PVTT	5 (8.8)	19 (4.3)	0.132	52 (91.2)	54 (94.7)	0.716
MVI	23 (40.1)	134 (30.0)	0.122	23 (40.4)	21 (36.8)	0.700
Tumor size (mean ± SD)	8.1±4.4	5.4±3.6	0.025	8.1±4.4	7.1±4.4	0.242

All demographic and pathological variables with P<0.2 are included in the logistic model. srHCC, spontaneously ruptured hepatocellular carcinoma; CAHB, chronic active hepatitis B; AFP, alpha-fetoprotein; LLR, laparoscopic liver resection; PVTT, portal vein, tumor thrombus; MVI, microvascular invasion; PT, prothrombin time; SD, standard deviation.

Results

Propensity-score matching analysis to compare srHCC versus non-ruptured HCC groups

We obtained a 1:1 paired cohort (57 patients in each group) for the srHCC versus nrHCC comparison. The patient demographics and clinical characteristics before and after PSM are presented in *Table 1*. These groups were well-matched for crucial confounders—i.e., age, chronic activated hepatitis B (CAHB), solitary nodule, portal vein, tumor thrombus (PVTT), microvascular invasion, and tumor size. After matching, there are still slight differences for some variables not contained in the PSM analysis (*Table 1*). However, the balance test revealed that the selected patients in the two cohorts were matched well. *Figure 2* shows the density curve of the propensity scores in both groups before and after matching.

The 1-, 2- and 3-year DFS rates in the nrHCC patient were 66.0%, 63.5% and 55.6%, respectively, and were 33.5%, 31.0%, and 18.6%, respectively, in the srHCC patient. The 1-, 2- and 3-year OS rates in the nrHCC group were 84.4%, 76.7% and 76.7%, respectively, and were 72.7%, 58.2% and 38.3%, respectively, in the srHCC group. The outcomes of OS and DFS were significantly better for patients without spontaneous rupture than for those with rupture after liver resection (P=0.029 and P<0.001, respectively; *Figure 2*).

Hepatectomy versus hepatectomy combined with HIPEC for patients with srHCC

Clinicopathological characteristics

The clinicopathological features and demographic and baseline disease characteristics of 57 patients for the two groups are shown in *Table 2*, and no statistical differences were attained between the HIPEC and non-HIPEC patients. No death occurred during the perioperative period. The mean operative time was 285.33±104.03 minutes in the HIPEC group and 280.37±98.30 minutes in the surgery only group, and 52.63% of patients required perioperative blood transfusion. The median total duration of hospitalization was 11.26±3.6 days in the non-HIPEC

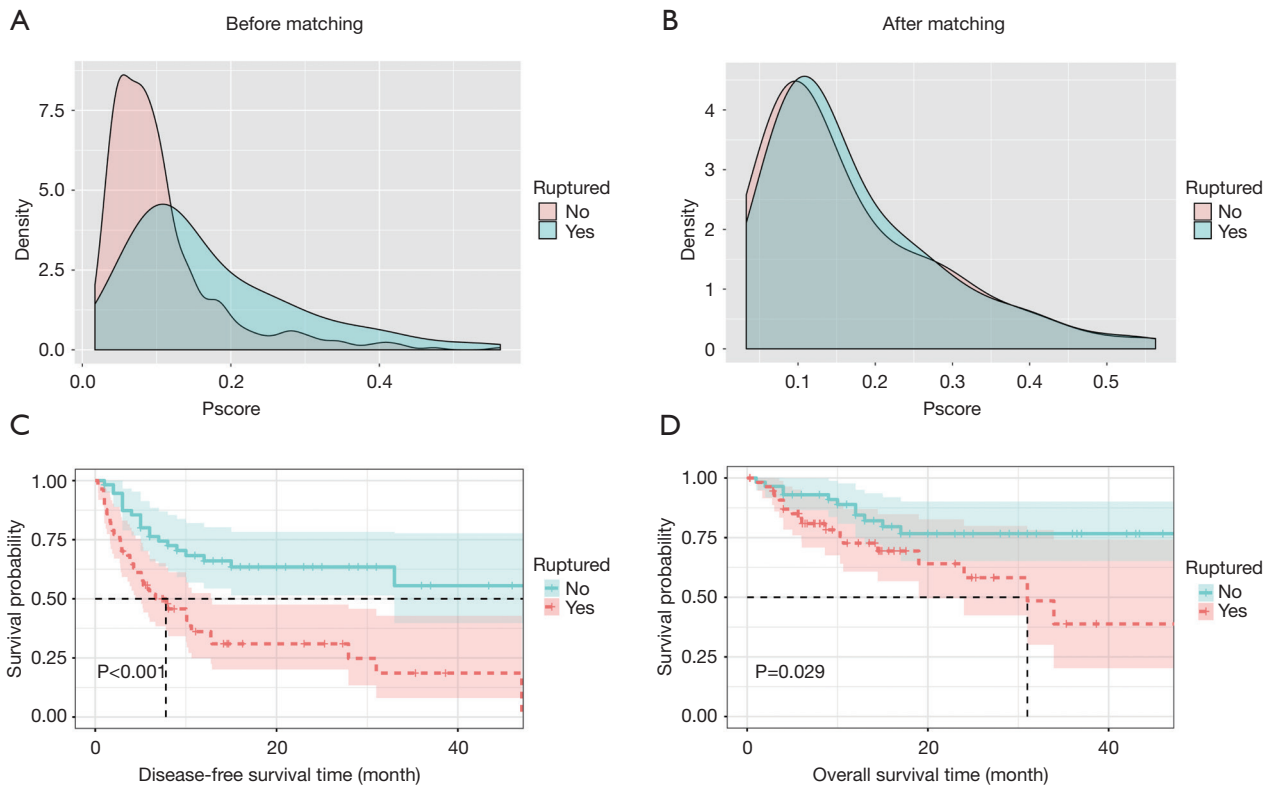

Figure 2 The overall balance test showed that the selected patients in the two groups matched well (A,B). Comparison of survival rates between the ruptured and non-ruptured groups. (C,D) Cumulative DFS and OS, measured before propensity matching and after propensity matching. OS, overall survival; DFS, disease-free survival.

group and 16.42±7.8 days in the HIPEC group.

Clavien-Dindo grade I–II complications occurred in 14 cases, and grade III-IV morbidity occurred in 1 case among the 30 patients in the HIPEC group. Among the 27 patients in the non-HIPEC group, grade I–II complications occurred in 12 cases; grade III–IV morbidity occurred in 2 cases. The incidence of postoperative bleeding, peritoneal infection, hepatic dysfunction, and pulmonary complications is similar in the two groups. Patients who undergo HIPEC had a higher incidence of other complications than those having no HIPEC (50.0% versus 11.1%; P=0.002); the difference was statistical significance. No significant differences were observed in the incidence rate of morbidity between the HIPEC and non-HIPEC groups (P=0.889). The mean hospitalization expenses were higher in the HIPEC patient than in the non-HIPEC patient ($16,946.82 versus $8,934.29, respectively; P<0.001). There were no postoperative deaths or reoperations in both groups (*Table 2*).

Long-term outcomes

Of the 57 patients found in the study, 30 (53.4%) underwent HIPEC, and 27 (46.6%) underwent surgery alone. After a median follow-up of 9.43 months, 44 of the 57 patients (77.19%) had experienced a disease recurrence, and 17 of the 57 patients (29.82%) died. The median DFS was longer in patients that underwent HIPEC after liver resection than in patients that had operation alone (10.07 versus 6.00 months, P=0.28, *Figure 3*), but no statistically significant difference was attained. The long-term outcomes were not significantly improved in the HIPEC group compared to the non-HIPEC group after hepatectomy of srHCC.

The postoperative 3-month, 6-month, and 12-month DFS rates were 69.0%, 53.33%, and 46.67%, respectively, in the HIPEC group and were 77.78%, 48.15%, and 33.33%, respectively, in the non-HIPEC patients. The DFS rate in the HIPEC patient was higher than that in the non-HIPEC patient. No significant difference was observed for DFS between the two treatment arms (P=0.56; *Figure 3*).

Table 2 Baseline clinical characteristics data of patients with srHCC undergoing operation or operation-HIPEC

Variables	HIPEC (n=30), N (%)	nHIPEC (n=27), N (%)	P value
Gender (male)	27 (90.0)	21 (78.8)	0.283
Age* (year)	53.47±12.70	47.67±14.69	0.116
BMI* (kg/m^2)	23.47±2.53	21.9±3.05	0.038
Hepatitis status (positive)	25 (83.3)	25 (67.6)	0.427
CAHB (yes)	16 (53.3)	13 (48.1)	0.696
Cirrhosis (yes)	17 (56.7)	11 (40.7)	0.284
Serum ALT* (U/L)	44.50±46.62	46.74±33.73	0.838
Serum AST* (U/L)	47.53±28.82	61.56±58.44	0.248
Albumin* (g/L)	36.75±5.79	35.92±5.61	0.591
Creatinine* (μmol/L)	85.56±27.09	73.4±17.64	0.052
Bilirubin* (mmol/L)	20.69±12.61	15.55±5.59	0.057
Prothrombin time* (sec)	14.67±1.14	14.09±1.27	0.075
Platelet* (10^9)	235.77±132.78	249.89±94.51	0.647
HGB* (g/L)	120.90±33.28	125.11±27.86	0.608
AFP (ng/mL, ≥400)	11 (36.7)	11 (40.7)	0.752
Satellite lesions (yes)	4 (13.3)	2 (7.4)	0.673
Solitary nodule	25 (83.3)	25 (67.6)	1.000
Operation way (min)			0.051
LLR	8 (26.7)	14 (51.9)	
OLR	22 (73.3)	13 (48.1)	
Operation time* (min)	280.69±102.66	280.37±98.3	0.991
Tumor size* (cm)	7.42±4.97	8.83±3.7	0.235
PVTT (yes)	3 (10.0)	2 (7.4)	1.000
High grade (grade 2 or 4)			0.464
Grade 2	11 (36.7)	6 (22.2)	
Grade 3	17 (56.7)	20 (74.1)	
Grade 4	1 (3.3)	1 (3.7)	
MVI (yes)	13 (43.3)	10 (37.0)	0.299
Postoperation stay* (day)	16.17±7.78	11.26±3.6	0.004
In-hospital costs*,$ (dollar)	16,946.82±4,465.37	8,934.29±2,920.03	<0.001
Perioperative mortality	0	0	NA
Postoperative outcomes‡			
Overall morbidity	15 (50.0)	14 (51.9)	0.889

Table 2 (*continued*)

Table 2 (*continued*)

Variables	HIPEC (n=30), N (%)	nHIPEC (n=27), N (%)	P value
Clavien-Dindo grade			0.789
I–II	14 (46.7)	12 (44.4)	
III–IV	1 (3.3)	2 (7.4)	
V (death)	0	0	
Bleeding	5 (16.7)	4 (14.8)	1.000
Bile leakage	0	0	1.000
Peritoneal infection	5 (16.7)	5 (18.5)	1.000
Hepatic dysfunction	13 (43.3)	8 (29.6)	0.284
Pulmonary complications	8 (26.7)	5 (18.5)	0.464
Other complications[¶]	15 (50.0)	3 (11.1)	0.002
Reoperation	0	0	1.000
Recurrence			
Intrahepatic	13 (43.3)	14 (51.9)	0.696
Peritoneal dissemination	3 (10.0)	3 (11.1)	0.892
Lung	2 (6.7)	1 (3.7)	0.617
Bone	0	0	NA
Brain	0	0	NA

*, mean ± standard deviation; [‡], multiple parameters per patient possible; [¶], including abdominal distension, fever, vomiting; [$], overall hospital costs for the inpatient episode were calculated initially in the Chinese yuan renminbi and converted to dollars at an exchange rate of 1 to 6.9298. srHCC, spontaneously ruptured hepatocellular carcinoma; HIPEC, hyperthermic intraperitoneal chemotherapy; BMI, body mass index; CAHB, chronic active hepatitis B; HGB, hemoglobin; AFP, alpha-fetoprotein; LLR, laparoscopic liver resection; OLR, open liver resection; PVTT, portal vein, tumor thrombus; MVI, microvascular invasion.

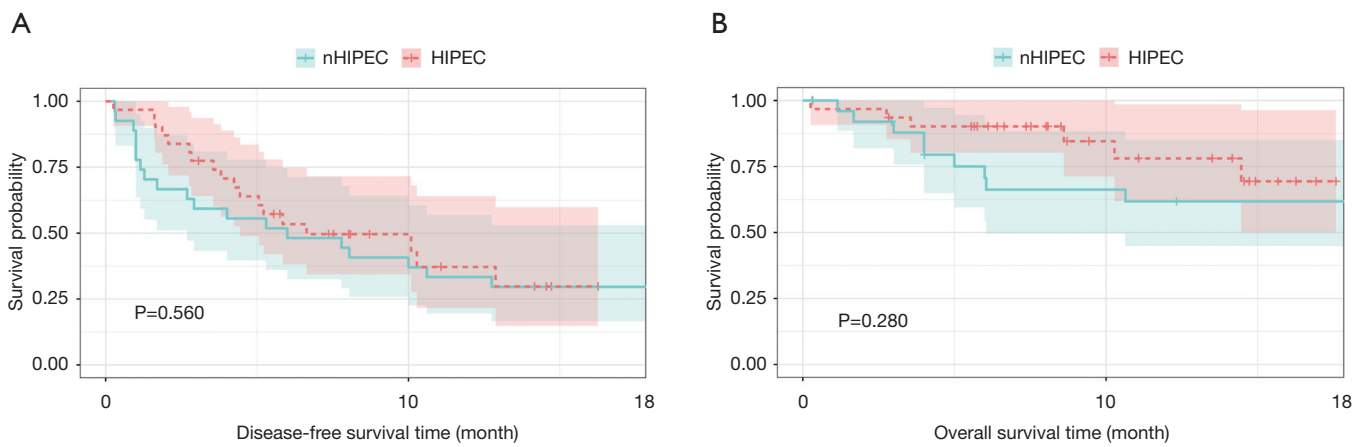

Figure 3 Comparison of survival rates between the HIPEC and nHIPEC groups (A,B). HIPEC, hyperthermic intraperitoneal chemotherapy.

The pattern of recurrence included lung, peritoneal cavity, bone, and brain metastasis. The incidence of intraperitoneal implant metastasis was not significantly different between the HIPEC and the non-HIPEC patient (P=0.892). The intrahepatic recurrence rate in the HIPEC patient and the non-HIPEC patient was 43.3% and 51.9%, respectively (P=0.696).

Univariate analysis showed that CAHB, ALT, AST, AFP, satellite lesions, number of tumors, and tumor size were associated with recurrence. Sex, AFP, and tumor size were correlated with OS. Multivariate Cox regression analyses did not find better clinical outcomes for patients treated with HIPEC, and HIPEC cannot be served as an independent predictor of clinical prognosis (*Table 3*).

Discussion

With the advance in operative techniques, the apparatus for hepatectomy, and perioperative management, surgical therapy has been proved to be a safe and effective method to treat HCC and has achieved encouraging survival prognosis. Tumor rupture is still a formidable clinical challenge for surgeons. The prognosis of patients with srHCC is abysmal, and the median survival time is 7 weeks to 11 months (38,39). A Japanese study showed the 1-, 3-, and 5-year survival rates for all patients undergoing hepatectomy for liver cancer were 87.8%, 69.2%, and 53.4%, respectively (40). Rupture of HCC means a later tumor stage, reflected by the tumor size, number of tumors, portal vein tumor thrombus, and microvascular invasion. A previous study showed that tumors on or protruding from the liver surface are more prone to rupture (41), but the present studies cannot test this issue, as detailed clinical data concerning the location and shape of the ruptured tumors was not obtained.

An earlier report showed that long-term survival could be expected if the patient can tolerate the liver resection of the ruptured tumor in selected cases. However, the recurrence rate of survival patients is as high as 67% to 100%, with extrahepatic recurrence occurring in about half of these patients (39,42-44). A ruptured HCC is regarded as a T4 tumor, in the light of the TNM staging system, and is correlated with poor clinical outcomes, with tumor cell implanting in the abdominal cavity increasing the recurrence rate of cancer (45,46). Distilled water lavages during surgery have been accepted as an established technique to prevent tumor cells disseminating after liver resection and have been proved to yield positive outcomes (47,48). However, this approach has limitations (3-5).

HIPEC has been widely applied after surgery for various abdominal malignant tumors with proven safety and feasibility. Since Spratt and others first reported the treatment mode of HIPEC in 1980, it has gradually become a mature treatment mode through continuous improvement by clinicians and scholars (8). However, in the present study in patients with srHCC, the comparison between the HPIEC group and the non-HIPEC group could not prove significant differences in OS and DFS. There is no sufficient evidence that intraperitoneal hyperthermic perfusion chemotherapy leads to added survival benefits for patients with srHCC, and HIPEC did not present a lower risk of abdominal metastasis. Although the incidence of postoperative complications has no statistical difference between the HIPEC group and the non-HIPEC group, additional treatment may reduce the quality of life of patients, and some patients experienced increased abdominal distension (32.3%), fever (29.0%), vomiting (19.3%) and other additional complications after HIPEC. HIPEC increases the financial burden of patients and the length of hospitalization after the operation. There are still many problems with HIPEC treatment itself, including how to select the patients, a drug used in the treatment and specific operation (treatment, temperature, and time), and the corresponding complications and risk of death caused by the treatment (49).

There are still some questions about how HIPEC works inside the body. The mechanisms considered are: first, a nuclear mechanism mediates hyperthermia that inhibits DNA replication, transcription, and repair. After an hour of 43 ℃ hyperthermia, the tumor cells can be irreversibly killed (50). Second, under elevated temperature, the absorption rate and activity of chemotherapeutic drugs in the abdominal cavity is enhanced, and the anticancer effect is improved (51). Then, mechanical irrigation and the chemotherapy drugs act directly on free cancer cells (FCCs), which may be planted in the peritoneum and form nodules, in the abdominal cavity. Through intraperitoneal washing and direct action of chemotherapy drugs, HIPEC could reduce the risk of recurrence caused by FCCs (51). The HIPEC treatment in our study was lobaplatin or 5-fluorouracil, and the treatment time was 60 minutes. Whether specific changes to other drugs and in treatment time and improvements to HIPEC operation will continue to improve the survival of these patients still needs to be further explored. Getting robust clinical data on whether different genotypes, primary tumor sites, and other factors

Table 3 Univariate and multivariate analysis of factors associated with OS and DFS in patients with srHCC

Variable	Disease-free survival				Overall survival			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Gender (F or M))	0.674 (0.294–1.540)	0.349	–	–	0.309 (0.106–0.892)	0.029	1.845 (0.381–8.951)	0.447
Age (≤47.0 *vs.* >47.0)	0.442 (0.184–1.066)	0.069	0.176 (0.022–1.400)	0.101	0.017 (0.026–1.301)	0.088	0.134 (0.015–1.193)	0.072
BMI, kg/m^2	0.927 (0.386–2.226)	0.866	–	–	0.219 (0.029–1.677)	0.143	0.140 (0.016–1.197)	0.073
Hepatitis (N *vs.* Y)	6.842 (0.938–49.93)	0.058	0.153 (0.151–15.44)	0.720	2.458 (0.325–18.61)	0.384	–	–
CAHB (N *vs.* Y)	1.068 (1.445–5.857)	0.003	1.256 (0.394–4.019)	0.699	2.009 (0.771–5.235)	0.153	2.226 (0.655–7.567)	0.200
Cirrhosis (N or Y)	1.169 (0.615–2.223)	0.633	–	–	1.082 (0.427–2.741)	0.868	–	–
ALT, IU/mL (≤40 *vs.* >40)	1.964 (1.031–3.740)	0.040	2.321 (0.573–9.394)	0.238	2.312 (0.885–6.034)	0.087	1.388 (0.404–4.767)	0.602
AST, IU/mL (≤35 *vs.* >35)	1.894 (0.963–3.725)	0.064	0.992 (0.255–3.850)	0.990	1.667 (0.614–4.552)	0.317	–	–
PLT, 10^9/L	0.925 (0.405–2.112)	0.853	–	–	1.453 (0.465–4.543)	0.520	–	–
Albumin, g/L	0.646 (0.319–1.309)	0.225	–	–	0.663 (0.234–1.878)	0.439	–	–
Creatinine, μmol/L	0.749 (0.389–1.440)	0.387	–	–	0.447 (0.158–1.266)	0.130	0.748 (0.191–2.936)	0.677
TBIL, μmol/L (≤21 *vs.* >21)	1.075 (0.846–1.336)	0.553	–	–	0.925 (0.534–1.604)	0.782	–	–
PT, sec (≤14.6 *vs.* >14.6)	1.170 (0.579–2.365)	0.662	–	–	1.114 (0.394–3.145)	0.838	–	–
HGB, g/L (≤115 *vs.* >115)	1.338 (0.699–2.563)	0.379	–	–	0.663 (0.234–1.878)	0.439	–	–
AFP, IU/mL (≤400 *vs.* >400)	3.034 (1.558–5.909)	0.001	2.603 (0.832–8.134)	0.100	3.148 (1.153–8.598)	0.025	3.642 (0.959–13.82)	0.058
Satellite lesions (N or Y)	2.805 (1.057–7.448)	0.038	1.380 (0.149–12.73)	0.776	2.722 (0.572–12.96)	0.208	–	–
Num of tumor (S or M)	0.484 (0.199–1.171)	0.107	0.646 (0.141–2.964)	0.574	0.456 (0.128–1.628)	0.226	–	–
Operation way (LLR *vs.* OR)	0.816 (0.417–1.600)	0.555	–	–	0.756 (0.289–1.981)	0.570	–	–
Tumor size (<10 *vs.* ≥10 cm)	2.969 (1.424–6.190)	0.003	1.530 (0.376–6.221)	0.552	3.343 (1.200–9.310)	0.021	1.574 (0.381–6.505)	0.531
PVTT (N or Y)	1.097 (0.387–3.114)	0.861	–	–	1.126 (0.256–4.961)	0.875	–	–
MVI (N or Y)	1.237 (0.684–2.361)	0.518	–	–	1.187 (0.461–3.055)	0.772	–	–
HIPEC (Y or N)	0.773 (0.399–1.498)	0.446	–	–	0.469 (0.156–1.410)	0.178	0.409 (0.116–1.445)	0.165

Variables were adopted for their multivariable analysis by univariate analysis P<0.2. OS, overall survival; DFS, disease-free survival; srHCC, spontaneously ruptured hepatocellular carcinoma; F, female; M, male; S, solitary nodule; M, multiple nodules; BMI, body mass index; CAHB, chronic active hepatitis B; PT, prothrombin time; TBIL, total bilirubin; PLT, platelet; HGB, hemoglobin; AFP, alpha-fetoprotein; LLR, laparoscopic liver resection; OR, open resection; PVTT, portal vein tumor thrombus; MVI, microvascular invasion; HIPEC, hyperthermic intraperitoneal chemotherapy.

impact the therapeutic efficacy, we will provide a precise and effective treatment plan for patients with the peritoneal spread.

Finally, several limitations of our study should be mentioned. First, this is a retrospective study, and potential confounders and biases could not be avoided. A RCT can better reduce the selection biases in observational studies. However, considering that srHCC is a relatively rare event, it is critical to perform an RCT here; also, the setting of srHCC means patients usually need urgent treatment, and the process of identification, recruitment, and randomization may lead to clinically unacceptable treatment delays. Second, the occurrence of srHCC is rare, and this is a single-center study, so the sample size of this study is small, which may cause type 2 errors. In order to eliminate selection bias, PSM was performed in this research. Processed with the combination of clinical and pathological covariates, the propensity score matching made a comparable distribution of the clinicopathological characteristics between the cohorts, thus bringing about a result that was similar to random allocation. Third, given some cases, might be clinically silent because of how much rupture and bleeding, it is challenging to explain the complete spectrum of srHCC fully.

Conclusions

The prognosis of ruptured HCC patients was reduced compared with those of non-ruptured HCC patients. The addition of HIPEC after surgery did not influence the OS of DFS; there were more postoperative hospitalizations, more hospital expenses, and even more postoperative complications with HIPEC. The curative management of srHCC by surgery alone leads to a better quality of life. These results suggest HIPEC may not be a robust treatment for srHCC. More prospective and randomized data are needed to determine whether some selected patients with srHCC still receive help from HIPEC.

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Footnote

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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 conducted in accordance with the Declaration of Helsinki (as revised in 2013). Institutional review board approval of our hospital was obtained for this study. This was a retrospective clinical study, which only analyzed the earlier clinical data. The data processed did not reveal the patient's identity information, so there was no need for ethical recognition and informed consent.

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