

Research Article

The Role of High Intra-Abdominal Pressure During Hyperthermic Intraperitoneal Chemotherapy (HIPEC) in the Treatment of Spontaneously Ruptured Hepatocellular Carcinoma: A Multi-Center Retrospective Study

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Received: December 24, 2024; Accepted: January 09, 2025; Published: January 16, 2025

Abstract

Objectives: This study explores the clinical value of surgical resection combined with Hyperthermic Intraperitoneal Chemotherapy (HIPEC) under elevated Intra-Abdominal Pressure (IAP) in treating Spontaneous Rupture of Hepatocellular Carcinoma (srHCC).

Methods: The clinical data of 79 patients admitted to the Affiliated Hospital of Xuzhou Medical University, the Second Affiliated Hospital of Nanjing Medical University and the Affiliated Hospital of Soochow University from January 1, 2018 to January 1, 2023 for surgical treatment of ruptured hepatocellular carcinoma with hemorrhage were analyzed. Patients who received surgical resection combined with intraperitoneal hemoperfusion chemotherapy were included in the experimental group, which was further divided into Low-HIPEC group and High-HIPEC group based on the perfusion pressure. The control group (n-HIPEC group) included those who performed surgery alone. The clinical data, postoperative hospitalization time, complications, Postoperative Tumor-free Survival (PFS), Overall Survival (OS), and independent risk factors affecting prognosis were compared between the three groups. **Results:** There was no statistically significant difference in the number of complications and laboratory tests (before the treatment) between the three groups ($P>0.05$). The PFS was greater in the experimental group compared to the control group, with the High-HIPEC group exhibiting the highest rate, and this difference was statistically significant ($P<0.05$). However, the OS did not show a statistically significant difference among the three groups ($P>0.05$).

Conclusions: High IAP in HIPEC is well tolerated and significantly improves patient prognosis.

Keywords: Hepatocellular carcinoma (HCC); spontaneous rupture; hyperthermic intraperitoneal chemotherapy (HIPEC); Intra-abdominal pressure (IAP); High pressure

Introduction

HCC is the fifth most common cancer worldwide. Meanwhile, it is one of the most common causes of cancer-related deaths [1]. srHCC occurs in 3% to 15% of patients with HCC, which is one of the life-threatening complications [2]. Due to its sudden onset, rapid progression, and high rebleeding rate, the mortality rate is as high as 25%-75% [3,4]. Hepatectomy can be their first treatment choice for patients with srHCC in generally good condition. Because it can not only remove the lesion to control bleeding but also achieve the purpose of eradicating the tumor. It is considered to be the most effective measure at present [5-7]. However, patients with srHCC still have a high rate of postoperative tumor metastasis in the abdominal cavity, which influences their prognosis [8]. HIPEC can effectively remove or kill residual free cancer cells and subclinical lesions in the peritoneal cavity in the early postoperative period, maximizing macroscopic and microscopic co-cure, and can be a potential therapy to prevent postoperative abdominal metastasis in srHCC [9-12].

Several studies have shown that when HIPEC is applied at higher Intra-Abdominal Pressures (IAP), local drug uptake by tumor and peritoneal tissues is enhanced without increasing systemic absorption [28].

This effect proved to be most significant when combined with thermotherapy, suggesting a possible synergistic effect. In related animal experiments, high IAP was further shown to be associated with increased survival. The mechanism of action may be to facilitate the penetration of chemotherapeutic agents through a higher-pressure gradient. If it also proves its effectiveness in human trials, then high IAP may represent a strategy to augment the currently accepted HIPEC approach.

HIPEC using high IAP pressure facilitates full contact of the drug with the residual cancerous tissue, results in increased tissue penetration and has the potential to improve efficacy. We aimed to

study the efficacy of surgery combined with thermal perfusion after hepatocellular carcinoma rupture.

Materials and Methods

Patient Population

This retrospective study has been approved by the Medical Ethics Committee of Xuzhou Medical University Hospital, the First Affiliated Hospital of Soochow University, and The Second Affiliated Hospital of Nanjing Medical University, and informed consent was obtained from all members. The clinical data of 79 patients with srHCC who were hospitalized from January 1, 2018, to January 1, 2024, were selected for the retrospective study. Inclusion criteria: (1) The postoperative pathology was primary hepatocellular carcinoma; (2) No other treatment such as TACE or RFA was performed before the initial surgery; (3) Informed consent for surgery was completed prior to the surgery. Exclusion criteria: (1) Previously treated with TACE or RFA for HCC; (2) Pathological diagnosis was not hepatocellular carcinoma (e.g., metastatic hepatocellular carcinoma, intrahepatic cholangiocellular carcinoma, and hepatoportal cholangiocarcinoma); (3) No surgical treatment was performed during hospitalization; and (4) Incomplete demographics and clinical data prevented successful follow-up. 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.

Those who performed surgical resection combined with intraperitoneal hemoperfusion chemotherapy were included in the experimental group. In the experimental groups, Intra-Abdominal Pressure (IAP) between 10 and 11 mmHg was the Low-HIPEC group, and intra-abdominal pressure between 18 and 20 mmHg was the High-HIPEC group. (Intra-abdominal pressure was measured by transscystometry and monitored in real time using a pressure transducer. Maintain the target intra-abdominal pressure level by increasing or decreasing perfusion.) [24,25] And those who performed surgery alone were included in the n-HIPEC group. Seventy-nine cases had non-coagulable blood drawn by diagnostic laparotomy, and all cases were clinically diagnosed as hepatocellular carcinoma with ruptured hemorrhage.

Among them, there were 68 cases with tumors located in the right lobe of the liver 11 cases in the left lobe of the liver, tumor diameter 3.2 to 12.2 cm, average 8.1 cm. Liver function: Child A grade 61 cases, B grade 18 cases, C grade 0 cases.

HIPEC Procedures

The closed HIPEC technique was standardized across the three participating centers. After the surgical procedure, two drains were placed in the upper and lower abdomen, and the abdominal cavity was closed. Thermal perfusion was performed on postoperative days 1, 3, and 5 using the BR-TRG-I hyperthermic perfusion intraperitoneal treatment system (Bright Medical Tech, Guangzhou, China). The perfusion solution consisted of sterile injection water (3-5 L) and lobaplatin (50 mg). The perfusion temperature was maintained at (43±0.1)°C, the perfusion time was 60 minutes, and the circulation pump flow rate ranged from 200 to 600 mL/min. Intra-abdominal pressure was monitored using the Trauma Guard (TG) system.

Data Collection

Information collected included: (1) General information: age, gender, common comorbidities, liver function Child-Pugh grade, tumor size and tumor location. (2) Laboratory tests (the blood indices

were collected on the first day, one week and one month after the operation): □Prothrombin Time (PT), Hemoglobin (HGB), Platelets (PLT), Total Bilirubin (TBIL), Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), and albumin (ALB) (3). Treatment status: surgical procedure, HIPEC course, surgical complications, postoperative recurrence pattern, follow-up time, and outcome. Pre-treatment laboratory data and imaging data were based on the results of the most recent examination before treatment. Overall survival time and progression-free survival time from the first treatment (including preoperative treatment and surgery) to the last follow-up or death (intention-to-treat analysis) were calculated. Postoperative follow-up was performed for 1 year. Data were collected from the outpatients' visits or via telephone calls and letters for patients who could not attend regular hospital visits.

Statistical Methods

The data were processed by SPSS25.0 statistical software, and the count data and measurement data were expressed as (%) and ($x \pm s$), respectively, and recorded. Repeated measures of ANOVA and survival analysis were used to compare the above data categories □ and $\alpha = 0.05$ was used as the test level. $P < 0.05$ indicates that the difference is statistically significant.

Result

Basic data of patients who met the inclusion criteria were collected and listed in the table below.

35 cases were included in the n-HIPEC group, consisting of 28 males and 7 females, with an average age of (56.4±9.2) years. Low-HIPEC group included 24 cases, with 17 males and 7 females, and an average age of (53.9±11.4) years. High-HIPEC group also had 20 cases, with 17 males and 3 females, and an average age of (56.3±10.0) years.

All patients underwent hepatic resection, and the surgical margins were free of tumors. Pathological examination confirmed the presence of hepatocellular carcinoma in the primary lesions. There were no deaths during the perioperative period. The average operative time was (185±45) minutes, The postoperative hospital stay lasted for (11±4) days.

Table 1: Basic conditions of patients in the three groups before surgery.

	nHIPEC N=35	Low-HIPEC N=24	High-HIPEC N=20	P Value
Age (Years)	56.4±9.2	53.9±11.4	56.3±10.0	0.61
Gender (%)				0.51
Male	28(80.0)	17(70.8)	17(85.0)	
Female	7(20.0)	7(29.2)	3(15.0)	
BMI (kg/m ²)	20.9±1.9	19.8±2.3	20.8±2.5	0.14
Hepatitis status (Positive)	22(77.1)	19(79.2)	16(80.0)	0.97
Cirrhosis (Yes)	18(51.4)	10(41.7)	11(55.0)	0.65
Solitary nodule (Yes)	27(77.1)	20(83.3)	15(75.0)	0.78
Portal hypertension (Yes)	6(17.1)	4(16.7)	4(20.0)	0.95
Tumor size (cm)	8.3±2.8	7.6±2.8	8.5±3.0	0.49
Right lobe of liver (Yes)	30(85.7)	20(83.3)	18(90.0)	0.82
Portal vein tumor thrombus (Yes)	3(8.6)	1(4.2)	1(5.0)	0.77
Vascular invasion (Yes)	12(34.3)	9(37.5)	8(40.0)	0.91
Icterus of skin and sclera (Yes)	5(14.3)	4(16.7)	2(10.0)	0.82
Child-Paugh				0.88
A	28(80.0)	18(75.0)	15(75.0)	
B	7(20.0)	6(25.0)	5(25.0)	
C	0(0)	0(0)	0(0)	

Note: BMI: Body Mass Index; The Child-Pugh grading scale, a quantitative assessment of liver reserve function proposed by Child in 1964, is categorized into A, B, and C levels.

Postoperative complications and recurrences are shown in Table 2. The vital signs of the patients remained stable during the intraperitoneal thermal perfusion chemotherapy. Common side effects after the perfusion period included Pleural effusion in 8 patients, Ascites in 11 patients, Lung infection in 11 patients, Abdominal infection in 8 patients, Postoperative bile leakage in 3 patient, Postoperative bleeding in 2 patients, Liver failure in 1 patient, Peritoneal implantation metastasis in 16 patients and Intrahepatic recurrence in 44 patients. There were no

Table 2: Postoperative complications and recurrence data.

	nHIPEC	Low-HIPEC	High-HIPEC	P value
Pleural effusion (n,%)	4 (11.4)	3 (12.5)	1 (5.0)	0.68
Ascites (n,%)	5 (14.3)	3 (12.5)	3 (15.0)	0.97
Lung infection (n,%)	6 (17.1)	3 (12.5)	2 (10.0)	0.75
Abdominal infection (n,%)	2 (5.7)	4 (11.4)	2 (10.0)	0.4
Abnormal liver function (n,%)	26 (74.3)	19 (79.2)	16 (80.0)	0.86
Postoperative bile leakage (n,%)	2 (5.7)	1 (4.7)	0 (0)	0.57
Postoperative bleeding (n,%)	2 (5.7)	0 (0)	0 (0)	0.28
Liver failure (n,%)	0 (0)	0 (0)	1 (5.0)	0.23
Reoperation (n,%)	0	0	0	Null
Intrahepatic recurrence (n,%)	20 (57.1)	13 (54.2)	11 (55.0)	0.97
Peritoneal implantation metastasis (n,%)	10 (28.6)	4 (16.7)	2 (10.0)	0.23
Lung metastasis (n,%)	2 (5.7)	0 (0)	0 (0)	0.28
Bone metastasis (n,%)	1 (2.9)	0 (0)	0 (0)	0.54

significant changes in the liver and kidney function biochemical markers before and after the perfusion. No intestinal obstruction or intestinal adhesions occurred in patients after intraperitoneal thermal perfusion chemotherapy. There was no significant difference in complications among the three groups(P>0.05).

The 79 cases that met the inclusion criteria were divided into three groups, and the blood indices were collected on the first day, one week and one month after the operation, and were analyzed by ANOVA with repeated measurements. Plot the data as a scatter plot (Figure 1).

Survival analysis using death and tumor recurrence as the observed outcomes resulted in the following survival curves High-HIPEC group had a higher PFS rate than Low-HIPEC group, while Low-HIPEC group had a higher rate than n-HIPEC group (P<0.05) (Figure 3). However, the OS did not show a statistically significant difference among the three groups (P>0.05).

COX multifactorial regression analysis of disease-free survival showed that Whether the tumor was solitary or not was associated with postoperative recurrence of spontaneously ruptured hepatocellular carcinoma (p=0.03). The risk of recurrence of srHCC was 2.34 times higher in patients with multiple tumors than in those with solitary tumor, with a Hazard Ratio (HR) 95% interval of 0.195-4.38. The remaining factors were not associated with postoperative recurrence (P > 0.05).

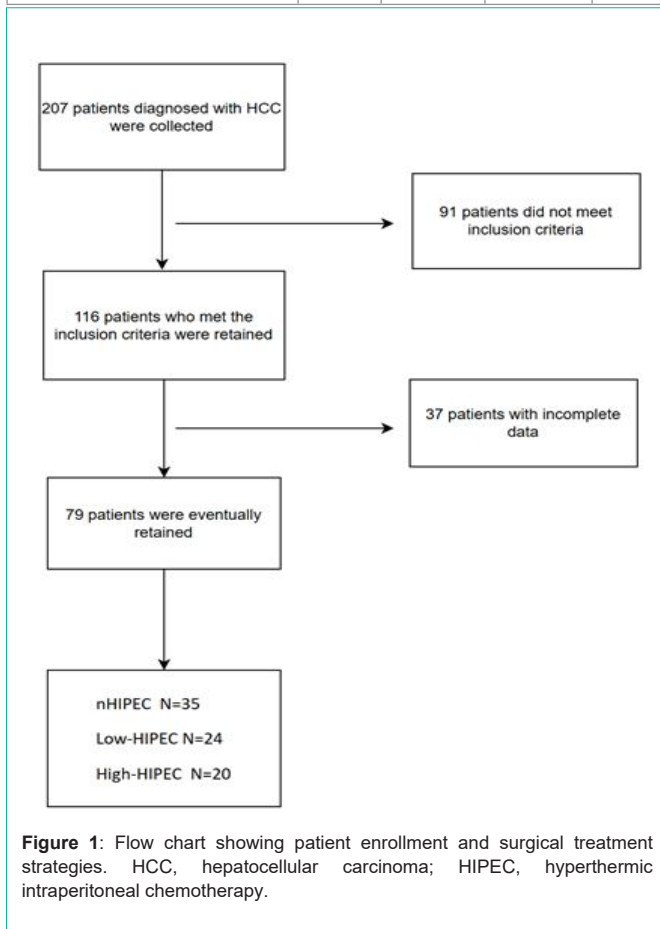


Figure 1: Flow chart showing patient enrollment and surgical treatment strategies. HCC, hepatocellular carcinoma; HIPEC, hyperthermic intraperitoneal chemotherapy.

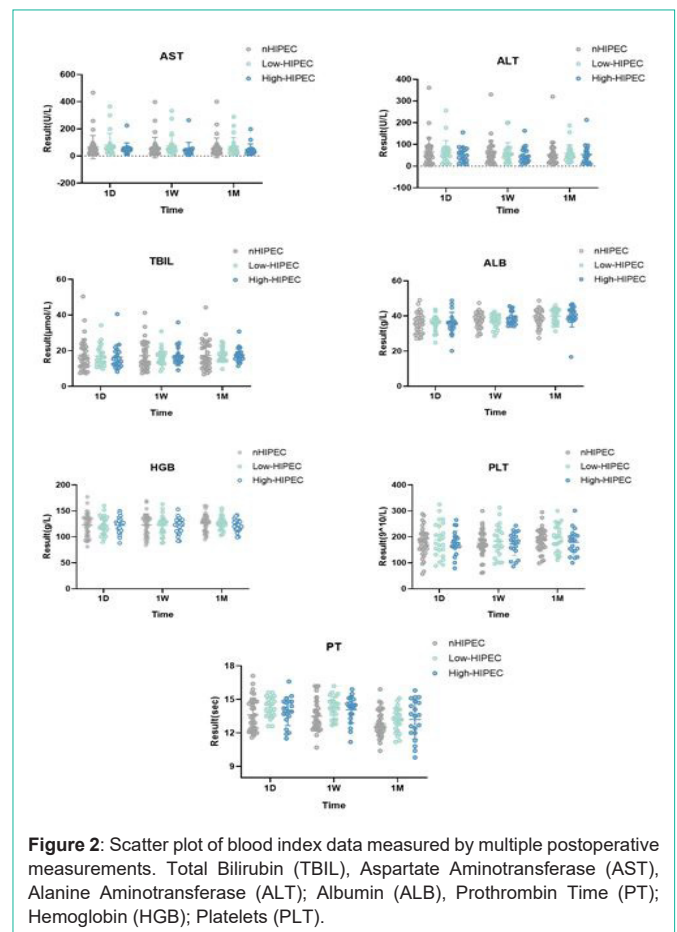


Figure 2: Scatter plot of blood index data measured by multiple postoperative measurements. Total Bilirubin (TBIL), Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT); Albumin (ALB), Prothrombin Time (PT); Hemoglobin (HGB); Platelets (PLT).

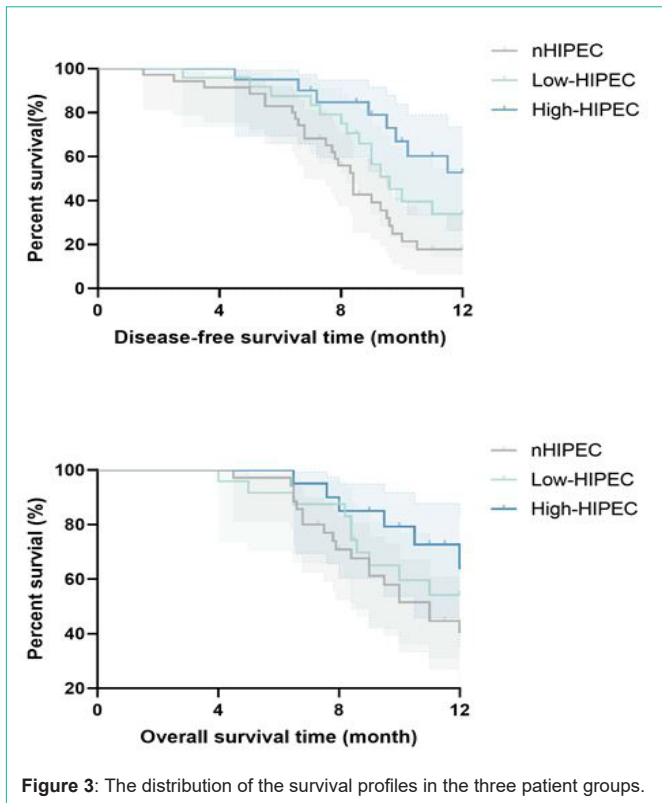


Figure 3: The distribution of the survival profiles in the three patient groups.

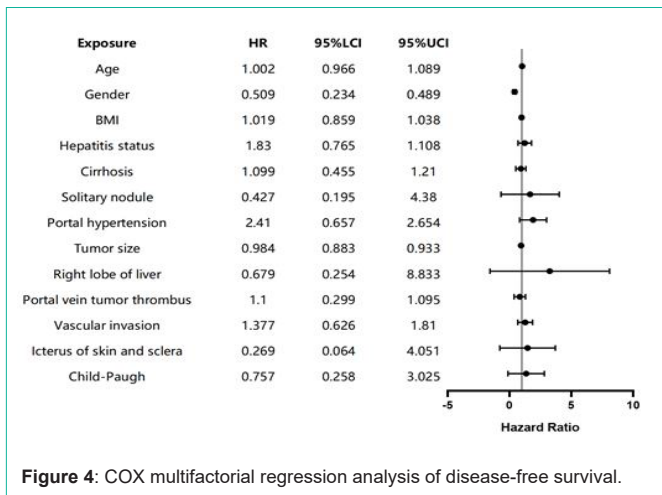


Figure 4: COX multifactorial regression analysis of disease-free survival.

Discussion

Although the prognosis of liver cancer has improved over the years, survival remains poor in patients with ruptured Hepatocellular Carcinoma (HCC). The prognosis of ruptured HCC is poor, with a tumor recurrence rate as high as 80.29% even two years after surgery—significantly higher than that for patients with unruptured tumors. This is particularly true for exophytic ruptured hepatocellular carcinoma, which frequently leads to intra-abdominal dissemination and implantation [13-15] posing a challenge for treatment.

The spontaneous rupture of HCC represents a poor prognostic event. Treatment options include hepatic artery interventional embolization and surgical resection. Among them, hepatic artery

interventional embolization can rapidly achieve hemostasis and induce ischemic necrosis of the tumor [16], offering a swift therapeutic effect with less damage to the body compared to surgical resection. However, this approach has limitations, including the difficulty in embolizing some hepatic collateral arteries [17,18]. Additionally, this treatment cannot completely cure ruptured hepatocellular carcinoma bleeding, leading a higher risk of rebleeding [19]. Surgical resection, although a long-established treatment for ruptured HCC, has gradually shown some drawbacks in long-term clinical treatment practice. For older patients or patients with severely impaired liver function because of long-term chronic liver disease, the risks associated with surgery are significantly elevated. Furthermore, clinical studies have shown that surgical resection may increase the risk of metastatic tumor implantation in the abdominal cavity [20], which is detrimental to the long-term prognosis of patients.

Prior research has substantiated the distinctive efficacy of HIPEC in the management of peritoneal carcinoma and the complications associated with malignant ascites resulting from peritoneal metastases from malignant abdominal cavity tumors, including gastric cancer, colorectal cancer, and ovarian cancer [21,22,23]. There is a long-standing lack of research on the use of HIPEC after surgery for ruptured hepatocellular carcinoma. This research suggests that the application of hepatic resection combined with intraperitoneal hemoperfusion chemotherapy is expected to improve the long-term outcomes of patients with spontaneous rupture and bleeding of hepatocellular carcinoma. Meanwhile, increasing perfusion pressure is expected to improve the efficacy of HIPEC. However, further studies are needed to establish specific and standardized ranges of perfusion pressure for optimal clinical outcomes.

Despite the fact that this study has included a larger number of influencing factors, there are still limitations. For example, there are differences in the skill level of the attending surgeon, the financial situation of the patient, and the medical conditions in the operating room, all of which may affect the results of the study. Meanwhile, the results of this study showed that HIPEC did not significantly reduce the probability of abdominal implant metastasis. We still need more and more scientifically rigorous studies to validate the efficacy and safety of increasing the intra-abdominal pressure of HIPEC.

Nowadays, while partial resection of liver cancer has been standardized, there remains ongoing debate about how best to optimize HIPEC technology, including drug regimen, duration, temperature and IAP [26,27]. Although early evidence suggests that increased IAP may be related to increased local drug uptake and efficacy, its impact on key intraoperative and postoperative parameters and outcomes remains unclear. In the study by Louis Choon Kit Wong et al., an IAP of approximately 20 mmHg during HIPEC was well tolerated, but intraoperative and postoperative outcomes were not significantly different from normal conditions [28]. Nevertheless, it remains crucial to address the potential adverse effects associated with HIPEC.

Summary

The combination of hepatic resection and intraperitoneal hemoperfusion chemotherapy in patients with spontaneous rupture and bleeding of hepatocellular carcinoma has been shown to be both safe and effective, providing the benefits of reliable hemostasis. Additionally, high perfusion pressure can enhance the efficacy of HIPEC, which is anticipated to improve the long-term prognosis of patients with spontaneous rupture and bleeding of hepatocellular carcinoma for these patients.

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