Research

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The Role of Elevated Intra-Abdominal Pressure During Hyperthermic Intraperitoneal Chemotherapy (HIPEC) in the Management of Spontaneously Ruptured Hepatocellular Carcinoma: A Multicenter Retrospective Study

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1. Abstract

1.1. Objectives: This study aimed to evaluate the clinical effectiveness of combining surgical resection with hyperthermic intraperitoneal chemotherapy (HIPEC) performed under elevated intra-abdominal pressure (IAP) in patients with spontaneously ruptured hepatocellular carcinoma (srHCC).

1.2. Methods: Clinical records of 79 patients who underwent surgical treatment for ruptured hepatocellular carcinoma with hemorrhage between January 2018 and January 2023 at three medical centers were retrospectively reviewed. Patients who received surgical resection followed by intraperitoneal perfusion chemotherapy were assigned to the experimental group, which was further divided according to perfusion pressure into a low-pressure HIPEC group and a high-pressure HIPEC group. Patients who underwent surgical treatment without HIPEC constituted the control group. Clinical characteristics, postoperative hospital stay, complications, progression-free survival (PFS), overall survival (OS), and prognostic factors were compared among the groups.

1.3. Results: No significant differences were observed among the groups regarding baseline laboratory values or postoperative complication rates. Patients who received HIPEC demonstrated improved progression-free survival compared with those who underwent surgery alone. Among the HIPEC-treated patients, those receiving treatment under higher intra-abdominal pressure exhibited the most favorable outcomes. Elevated pressure during HIPEC was well tolerated and did not increase adverse events.

1.4. Conclusions: The application of HIPEC under higher intra-abdominal pressure appears to be safe and may significantly improve the prognosis of patients with spontaneously ruptured hepatocellular carcinoma.

2. Keywords: Hepatocellular carcinoma; spontaneous rupture; hyperthermic intraperitoneal chemotherapy; intra-abdominal pressure; high-pressure perfusion

3. Introduction

Hepatocellular carcinoma (HCC) ranks among the most prevalent malignancies worldwide and represents a leading cause of cancer-related mortality. Spontaneous rupture of hepatocellular carcinoma occurs in approximately 3–15% of affected patients and is considered a severe and potentially fatal complication. Due to its abrupt onset, rapid progression, and high likelihood of recurrent bleeding, mortality rates can range between 25% and 75%.

For patients with adequate physiological status, hepatectomy is generally considered the preferred therapeutic option. Surgical resection can effectively control hemorrhage while simultaneously removing the tumor, making it one of the most effective treatment strategies currently available. Despite this, patients with ruptured HCC frequently experience postoperative recurrence and peritoneal metastasis, which significantly worsens their long-term prognosis.

Hyperthermic intraperitoneal chemotherapy has been increasingly explored as an adjuvant treatment strategy. HIPEC delivers heated chemotherapeutic agents directly into the abdominal cavity, allowing elimination of microscopic residual tumor cells and free cancer cells that may remain after surgery. This approach can potentially reduce the risk of peritoneal dissemination and improve postoperative outcomes.

Previous research suggests that administering HIPEC under increased intra-abdominal pressure may enhance the penetration of chemotherapeutic drugs into tumor and peritoneal tissues while not significantly increasing systemic drug absorption. When combined

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with hyperthermia, this pressure-dependent effect may further improve the therapeutic efficacy of intraperitoneal chemotherapy. Animal studies have demonstrated that higher intra-abdominal pressure during HIPEC can lead to increased drug penetration and improved survival outcomes.

Based on these findings, the present study aimed to investigate the effectiveness and safety of combining hepatic resection with HIPEC performed under elevated intra-abdominal pressure in patients with spontaneously ruptured hepatocellular carcinoma.

4. Materials and Methods

4.1. Patient Population

This retrospective study was approved by the ethics committees of the participating medical institutions. Clinical data from 79 patients diagnosed with spontaneously ruptured hepatocellular carcinoma between January 2018 and January 2024 were collected and analyzed.

Eligible patients met the following criteria: postoperative pathological confirmation of primary hepatocellular carcinoma, absence of prior treatments such as transarterial chemoembolization or radiofrequency ablation before surgery, and completion of informed consent procedures for surgery. Patients were excluded if they had received previous interventional therapies for HCC, had a different pathological diagnosis such as metastatic liver cancer or cholangiocarcinoma, did not undergo surgical treatment during hospitalization, or had incomplete clinical records preventing adequate follow-up.

The study followed the principles of the Declaration of Helsinki. Because the research relied on previously collected clinical data and patient identifiers were removed during analysis, additional ethical consent was not required.

Patients who underwent hepatic resection combined with intraperitoneal perfusion chemotherapy were included in the experimental group. Within this group, individuals receiving HIPEC at intra-abdominal pressures of 10–11 mmHg were categorized as the low-pressure HIPEC group, while those treated at pressures of 18–20 mmHg were classified as the high-pressure HIPEC group. Intra-abdominal pressure was continuously monitored through bladder pressure measurement using a pressure transducer and adjusted by modifying the perfusion volume.

Patients who underwent surgery without HIPEC were included in the control group. Among all cases, the majority of tumors were located in the right hepatic lobe, while a smaller number occurred in the left lobe. Tumor diameters ranged from approximately 3 to 12 cm. Most patients had preserved liver function corresponding to Child-Pugh class A, with the remainder classified as class B.

4.2. HIPEC Procedure

The closed HIPEC technique was standardized across all participating centers. After completion of the surgical resection, drainage tubes were placed in the abdominal cavity, and the incision was closed.

Intraperitoneal hyperthermic chemotherapy was performed on postoperative days 1, 3, and 5 using a dedicated perfusion system. The perfusion solution consisted of sterile water combined with lobaplatin. The temperature of the circulating solution was maintained at approximately 43°C. Each treatment session lasted 60 minutes, and the perfusion flow rate ranged between 200 and 600 mL per minute.

During treatment, intra-abdominal pressure was monitored continuously using a dedicated monitoring system to ensure that the target pressure level was maintained throughout the procedure.

4.3. Data Collection

Clinical data were collected from hospital records and included patient demographics, comorbid conditions, liver function status, tumor characteristics, and laboratory test results.

Laboratory indices included prothrombin time, hemoglobin levels, platelet count, total bilirubin, aspartate aminotransferase, alanine aminotransferase, and serum albumin. These parameters were recorded before treatment as well as at several postoperative intervals.

Information regarding treatment procedures, number of HIPEC sessions, postoperative complications, recurrence patterns, follow-up duration, and patient outcomes was also collected.

Patients were followed for one year after surgery. Follow-up information was obtained through outpatient visits or through telephone and written communication for patients unable to attend hospital appointments. Progression-free survival and overall survival were calculated from the time of initial treatment to the date of recurrence, death, or last follow-up.

5. Statistical Analysis

Statistical analysis was performed using SPSS version 25. Continuous variables were expressed as mean values with standard deviations, while categorical variables were expressed as percentages. Repeated-measures analysis of variance was used to evaluate changes in laboratory parameters over time, and survival analyses were conducted to compare clinical outcomes between groups. A significance level of 0.05 was applied, and differences with p values below this threshold were considered statistically significant.

6. Results

Seventy-nine patients met the inclusion criteria and were included

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in the analysis. All patients underwent hepatic resection with negative surgical margins, and histopathological examination confirmed hepatocellular carcinoma in all cases. No perioperative deaths occurred.

The average operative duration was approximately three hours, and the mean postoperative hospital stay was around eleven days.

During HIPEC treatment, patients maintained stable vital signs. Several postoperative complications were observed, including pleural effusion, ascites, pulmonary infections, abdominal infections, bile leakage, postoperative bleeding, and liver failure. Recurrence patterns included both peritoneal implantation metastasis and intrahepatic recurrence.

Laboratory parameters assessing liver and kidney function showed no significant deterioration following intraperitoneal chemotherapy. Additionally, no patients developed intestinal obstruction or severe adhesions related to the perfusion treatment.

Overall complication rates were comparable among the groups, indicating that the addition of HIPEC and increased intra-abdominal pressure did not significantly increase postoperative risk.

Survival analysis demonstrated differences in progression-free survival among the treatment groups. Patients treated with high-pressure HIPEC showed the most favorable outcomes, followed by those receiving low-pressure HIPEC, while patients treated with surgery alone had the lowest progression-free survival rates.

Multivariate analysis identified tumor multiplicity as a significant factor associated with postoperative recurrence. Patients with multiple tumors had a substantially higher risk of recurrence compared with those with solitary lesions. Other clinical variables did not show significant associations with recurrence risk.

7. Discussion

Although treatment outcomes for hepatocellular carcinoma have improved in recent years, the prognosis for patients with ruptured tumors remains poor. Recurrence rates following surgery for ruptured HCC are extremely high, often exceeding 80% within two years after treatment. This is largely attributed to the dissemination of tumor cells into the abdominal cavity following tumor rupture.

Spontaneous rupture of HCC is therefore considered a severe prognostic event. Treatment options include transarterial embolization and surgical resection. Transarterial embolization can rapidly control bleeding and induce tumor ischemia while causing relatively limited physiological stress compared with surgery. However, this method has certain limitations, including incomplete embolization due to collateral circulation and the risk of recurrent bleeding.

Surgical resection remains a widely used treatment approach for ruptured HCC, but it also has drawbacks. In elderly patients or those with significant liver dysfunction, the surgical risk may be considerable. Moreover, manipulation of the tumor during surgery may increase the risk of tumor cell dissemination and peritoneal implantation.

HIPEC has demonstrated promising results in managing peritoneal metastases arising from several abdominal malignancies, including gastric, colorectal, and ovarian cancers. By delivering heated chemotherapy directly into the abdominal cavity, HIPEC can eliminate microscopic tumor cells that remain after surgical removal of visible lesions.

However, research on the use of HIPEC following surgery for ruptured hepatocellular carcinoma remains limited. The present study suggests that combining hepatic resection with intraperitoneal chemotherapy may improve long-term outcomes in patients with ruptured HCC.

Increasing intra-abdominal pressure during HIPEC may further enhance treatment efficacy by promoting deeper penetration of chemotherapeutic agents into tumor tissues. Nevertheless, the optimal pressure range for achieving maximal therapeutic benefit remains unclear and requires further investigation.

Several limitations should be acknowledged. Differences in surgical expertise, patient socioeconomic status, and operating room resources may have influenced treatment outcomes. In addition, although HIPEC showed promising results, it did not significantly reduce the incidence of peritoneal implantation metastasis in this study.

Further large-scale and rigorously designed studies are needed to confirm the safety and effectiveness of increasing intra-abdominal pressure during HIPEC and to determine the optimal parameters for treatment, including drug selection, temperature, duration, and perfusion pressure.

8. Conclusion

The combination of hepatic resection and intraperitoneal hyperthermic chemotherapy appears to be a safe and effective strategy for patients with spontaneously ruptured hepatocellular carcinoma. This approach provides reliable hemorrhage control while targeting residual microscopic disease.

The use of higher intra-abdominal pressure during HIPEC may enhance the therapeutic effectiveness of the treatment and potentially improve long-term patient outcomes. Continued research is necessary to refine this technique and establish standardized treatment protocols.

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