

Long-term progression-free survival of hepatocellular carcinoma with synchronous diffuse peritoneal metastasis treated by CRS+HIPEC

A case report and literature review

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Abstract

Rationale: Hepatocellular carcinoma (HCC) with peritoneal metastasis (PM) is rare. There has been no standard treatment for this severe disease, and the conventional palliative therapy could only reach an overall survival of 6 to 14 months

Patient concerns: A 38-year-old male with a chief complain of “abdominal distension and diagnosis of HCCPM for 3 months”, was suffering from severe diarrhea and moderate anemia.

Diagnosis: Diagnostic laparoscopic exploration with biopsy and the following pathology confirmed the diagnosis of HCC with PM.

Interventions: The patient was treated with cytoreductive surgery (CRS) plus hyperthermic intraperitoneal chemotherapy (HIPEC) followed by 6 cycles of intraperitoneal chemotherapy and 6 cycles of intravenous chemotherapy.

Outcomes: Till January 15, 2019, the patient has progression-free survival for over 22 months.

Lessons: CRS plus HIPEC combined adjuvant intraperitoneal and intravenous chemotherapy may improve progression-free survival for some HCC with PM patients and should be considered as an option for such patients.

Abbreviations: AFP = alpha fetoprotein, CC = completeness of cytoreduction, CRS = cytoreductive surgery, CT = computed tomography, HCC = hepatocellular carcinoma, HIPEC = hyperthermic intraperitoneal chemotherapy, OS = overall survival, PCI = peritoneal cancer index, PFS = progression free survival, PM = peritoneal metastasis, PSOGI = peritoneal surface oncology group international.

Keywords: bidirectional chemotherapy, cytoreductive surgery, hepatocellular carcinoma, hyperthermic intraperitoneal chemotherapy, peritoneal metastasis

1. Introduction

Hepatocellular carcinoma (HCC) is one of the most common cancers in China, with an incidence of 466.1/100,000, and a mortality of 422.1/100,000.^[1] It metastasizes to lungs, bones, lymph nodes, and adrenal gland. However, HCC peritoneal

metastasis (HCCPM) without distant spread is rare, with an incidence of 2% to 18% at the time of surgery or following autopsy.^[2] Synchronous PM of HCC is caused by tumor rupture, with an associated mortality of up to 50%.^[2]

There has been no standard treatment for HCCPM, and the conventional palliative therapy could only reach an overall survival (OS) of 6 to 14 months.^[3] There is an urgent need for innovative treatment of HCCPM.

Cytoreductive surgery (CRS) plus hyperthermic intraperitoneal chemotherapy (HIPEC) has been recommended by Peritoneal Surface Oncology Group International (PSOGI) as the standard treatment for selected patients with pseudomyxoma peritonei, malignant peritoneal mesothelioma, and resectable PM of colorectal cancer. Some small sample cohort studies have reported that CRS+HIPEC could improve the median OS of HCCPM.^[3,4] However, the role of CRS+HIPEC in treating HCCPM needs to be verified.

This work reports a case of synchronous HCCPM successfully treated with CRS+HIPEC followed by adjuvant bidirectional chemotherapy.

2. Case report

A 38-year-old male came to our clinic on March 6, 2017, with a chief, complain of “abdominal distension and diagnosis of HCCPM for 3 months”. He was suffering from severe diarrhea and moderate anemia.

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Patient has provided informed consent for publication of the case.

The authors declare no conflicts of interests in this article.

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Three months before he became to our clinic, the patient developed abdominal distension accompanied by intermittent abdominal cramps and diarrhea. He was treated with *Bacillus licheniformis* capsules, bifidobacterium triad, and trimebutine maleate tablets. However, the symptoms were not released, and he was hospitalized in other hospital. A computed tomography (CT) scan showed that a tumor mass in left lobe of liver about 5 centimeters in diameter, multiple nodules in peritoneum, and ascites. Tumor marker test showed alpha-fetoprotein (AFP) of over 10,000 ng/mL (normal <25 ng/mL).

On January 4, 2017, he had a laparoscopic exploration which found that masses in left lobe of liver about 4 centimeters in diameter, numerous tumor implants in greater and lesser omentum, mesentery, and subphrenic peritoneum, and bloody ascites. A biopsy was performed. The following pathology diagnosed as HCCPM. He was treated with Sorafenib for 400 mg/d after surgery. However, there was no improvement in his general condition and CT scan showed progression of disease. Then the patient was referred to our hospital.

At our department, a contrast-enhanced CT showed that masses in left lobe of liver, nodules on gall bladder wall, multiple nodules or masses in peritoneum, and omentum cake, and ascites

(Fig. 1A–C). Laboratory test showed that AFP of over 20,000 ng/mL, cancer antigen (CA)-125 of 269.3 U/mL, hemoglobin of 74 g/L, total protein of 39.7 g/L, albumin of 21.2 g/L, alanine aminotransferase of 78 U/L, aspartate transaminase of 66 U/L, prothrombin time of 8.5 seconds, partial thromboplastin time of 23.0 seconds. D-Dimer of 2020 ng/mL.

On March 16, 2017, the patient underwent a 13-hour CRS+HIPEC. The intraoperative peritoneal cancer index (PCI) was 30 (Fig. 1D–F). We drained about 2000 mL hemorrhagic ascites and then performed total anterior parietal peritonectomy, left extrahepatic lobectomy, great omentectomy, lesser omentectomy, subphrenic peritonectomy, pelvic peritonectomy, and resection of nodules in the mesentery. After CRS, a few of tumor nodules on the surface of the bowel were left. Accordingly, the completeness of cytoreduction (CC) score was 2 (Fig. 1G). An open-technique HIPEC was performed following CRS, using cisplatin of 120 mg, and docetaxel of 120 mg each for 30 minutes, at 43°C, respectively. Pathology confirmed moderate differentiated HCCPM (Fig. 1H, I).

From March 25, 2017, the patient had 6-cycles of adjuvant normothermic intraperitoneal chemotherapy through a port which was inserted during CRS+HIPEC procedure. The regimens

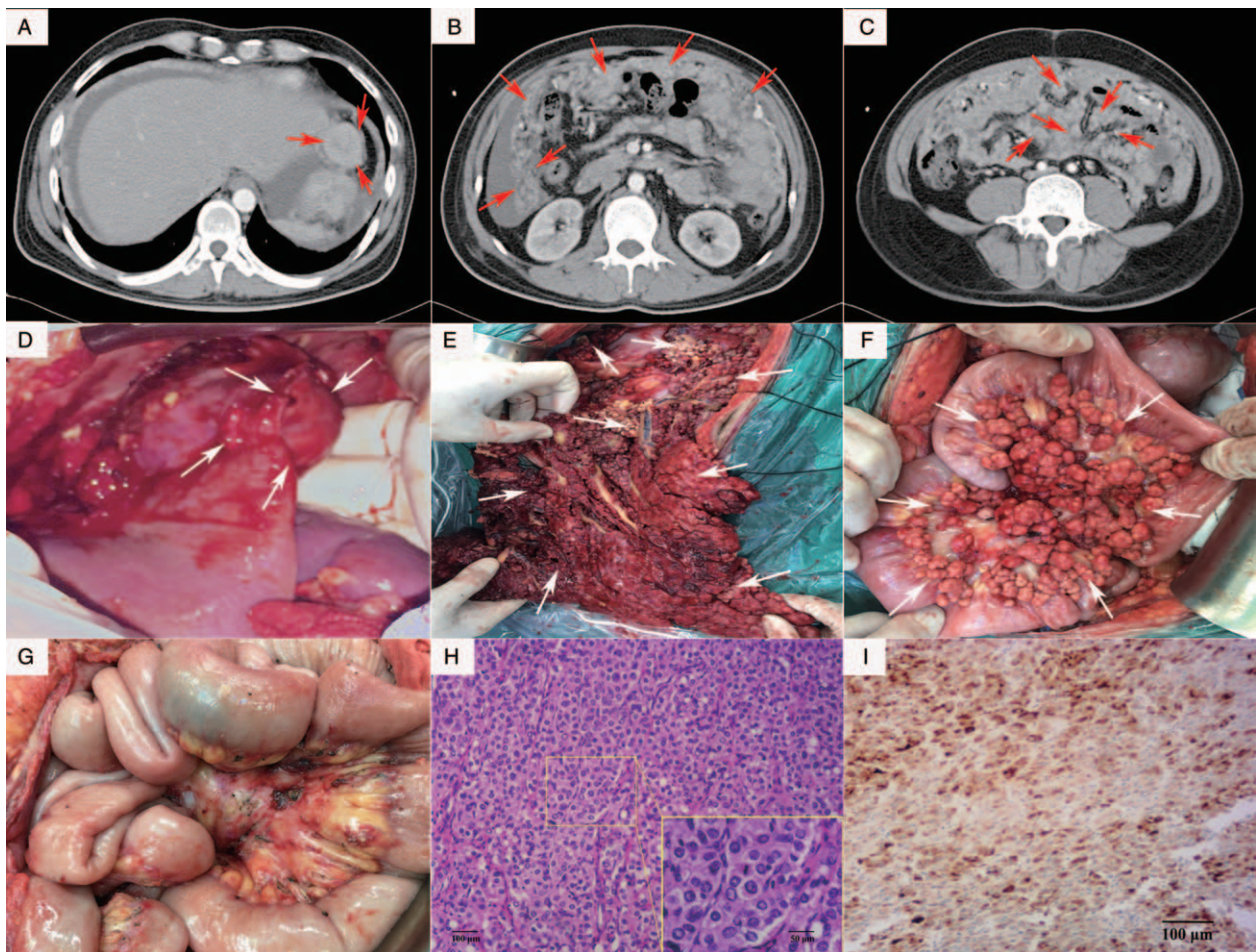


Figure 1. Pre-operative CT scan, laparotomic exploration, and pathology. (A) Contrast-enhanced CT showed that ascites, masses in left lobe of liver; (B, C) numerous nodules or masses in peritoneum, and omentum cake; (D) Laparotomic exploration showed masses in left lobe of liver; (E) omentum cake full of grape-size tumor implants and markedly enlarged blood vessels; (F) diffuse tumor nodules on the surface of the small bowel mesentery; (G) the tumor implants on the mesentery were all removed after CRS; (H) Pathology examination comforted the diagnosis of hepatocellular carcinoma, intermediately differentiated (hematoxylin and eosin stain, 100× for the main microphotograph, and 200× for the insertion); (I) the tumor cells are positive for alpha-fetoprotein (AFP) stain, confirming the hepatocellular origin. Arrows point to the lesions. CRS=cytoreductive surgery, CT=computed tomography.

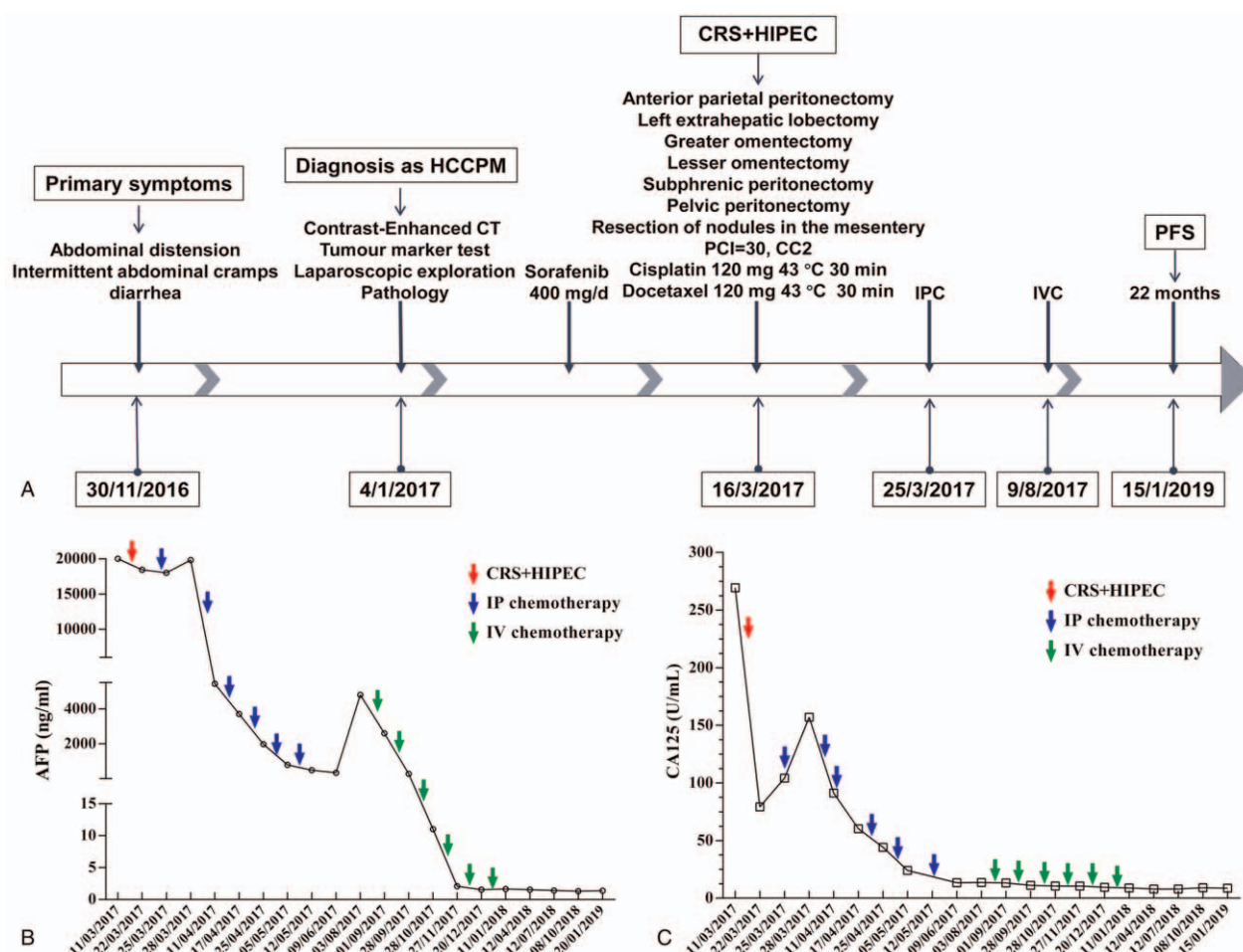


Figure 2. Time line of medical history of a HCCPM patient (A), and changes in AFP (B) and CA125 (C). AFP = alpha fetoprotein, HCC = hepatocellular carcinoma, PM = peritoneal metastasis.

for intraperitoneal chemotherapy were cisplatin 60 mg plus docetaxel 40 mg for the first cycle, and carboplatin 200 mg plus docetaxel 60 mg for the following 5 cycles. The regimen was repeated weekly for 6 cycles.

From August 9, 2017, the patient had 6-cycle of adjuvant intravenous chemotherapy. The regimen was carboplatin 400 mg plus docetaxel 120 mg. The regimen was repeated every 3 weeks for 6 cycles.

The levels of AFP and CA125 were consistently decreased during and after adjuvant chemotherapy. On January 15, 2019, the last follow-up, the patient showed very good clinical condition, the AFP was 1.38 ng/mL, and CT scan showed no evidence of recurrence or progression. The patient is progression-free for over 22 months since CRS+HIPEC (Fig. 2). This case report was approved by the ethics committee of Beijing Shijitan Hospital, Capital Medical University and the informed consents were obtained from the patient.

3. Discussion

This study reported a very rare case of HCC with diffuse synchronous PM. The young patient was treated with CRS + HIPEC and postoperative adjuvant intraperitoneal and intravenous chemotherapy, achieving a progression-free survival of over 19 months till now.

HCCPM has long been considered incurable, and no standard treatment is available for this condition. The prognosis of HCCPM is very poor, with a median survival of 6 to 14 months treated with Sorafenib and/or systemic chemotherapy.^[3] Several groups reported the role of aggressive surgical management for HCCPM^[3,5–10] (Table 1). These works suggest that active cytoreduction if the patient's condition could tolerate major surgery, could bring bigger benefit than other treatment options.

Chua et al summarized 16 case reports published from 1999 to 2009 including 24 patients with PM of HCC. The 1- and 2-year survival rates were 83% and 71% respectively. Moreover, they found that CRS may achieve long-term survival in selected cases.^[4]

Lin et al reported 53 patients of PM of HCC, including 10 synchronous PM and 43 metachronous PM. The median OS for those with surgery was 12.5 months versus 2.1 months for those without surgery ($P = .0013$). The median OS for metachronous PM was 8.6 months, significantly better than 3.8 months for synchronous PM ($P = .0117$).^[5]

Ding et al reported 3 cases of PM of HCC treated with CRS, and obtained OS of 24 months, 4 months, and 10 months, respectively.^[6]

Hashimoto et al resected PM 12 times in 9 patients with HCC, achieving 1-, 3-, and 5-year survival rates of 58%, 52%, and 42%. However, 3 patients with incomplete resection had

Table 1**Literature review on cytoreductive surgery with/without hyperthermic intraperitoneal chemotherapy to treat hepatocellular carcinoma with peritoneal metastasis.**

Reference	Year	Number of patients	Treatments (No. of patients)	Outcomes (m = months)
Lin et al ^[5]	2009	43 metachronous HCC PM 10 synchronous HCC PM	CRS (28) Chemo/supportive care (15) CRS (3) Chemo/supportive care (7)	Median OS was 8.6 m for all metachronous patients, 12.5 m for CRS group, 2.1 m for Chemo/supportive group Median OS was 3.8 m for all synchronous patients
Ding et al ^[6]	2010	3	CRS (3)	OS was 24 m, 4 m, and 10 m, respectively
Hashimoto et al ^[7]	2013	9	CRS (3)	1-, 3-, 5-year survival rate: was 58%, 52%, and 42%, respectively
Tabrizian et al ^[8]	2014	14	CRS (7) CRS+HIPEC (7)	Median OS was 35.6 m for complete CRS group, and 42.1 m for complete CRS+HIPEC group
Berger et al ^[9]	2016	22	CRS (17) CRS+HIPEC (5)	Median OS was 23.6 m for all patients, 19.5 m for CRS group and 29.7 m for CRS+HIPEC group
Spiliotis et al ^[10]	2017	4	CRS+HIPEC+Sorafenib (4)	Mean OS was 30 m
Mehta et al ^[3]	2018	21	CRS+HIPEC (21)	Median OS was 46.7 m for all patients, 5.9 m for incomplete CRS +HIPEC group. The median OS for complete CRS+HIPEC group was not reached.

CRS = cytoreductive surgery, HCC = hepatocellular carcinoma, HIPEC = hyperthermic intraperitoneal chemotherapy, OS = overall survival, PM = peritoneal metastasis.

survivals of only 4, 9, and 12 months. They concluded that operative resection should be an option for selected patients with PM from HCC when the primary liver neoplasm is under control and have no metastases in other organs.^[7]

Tabrizian et al reported 14 HCC patients with limited PM underwent CRS, including 7 patients received additional HIPEC treatment. The mean PCI was 9.9 ± 8.3 , and complete CRS was achieved in all but 1 case. 3-year recurrence rate after CRS was 100%, median OS for the cohort CC0-1 was 35.6 months. The median survival for the CRS+HIPEC (CC0-1) was 42.1 months. In 1 case, the resection of the primary liver tumor was carried out at the same time as the debulking.^[8]

Berger et al reported 22 patients with PM of HCC treated with CRS, including 5 cases received additional HIPEC. The median OS for all patients was 23.6 months. Moreover, patients with HIPEC have better median OS compared with those who underwent CRS alone (29.7 vs 19.5 months), but this survival difference did not reach statistical significance.^[9]

Spiliotis et al reported 4 patients of HCCPM treated with CRS+HIPEC plus postoperative Sorafenib. The mean PCI was 10.2 and the mean OS was 30 months.^[10]

Mehta et al reported the largest cohort of CRS+HIPEC for PM of HCC. 21 patients underwent CRS+HIPEC for HCCPM from 10 reference centers of PSOGI. The median PCI was 14. Sixteen patients had completed CRS (CC0-1). The median OS was 46.7 months and the median OS for CC2-3 patients was only 5.9 months. The median RFS was 26.3 months. They concluded that CRS+HIPEC is a safe and effective approach in selected patients with PM of HCC.^[3]

Compared to published literature, this patient had 3 special features deserving further discussion. First, according to Lin's study, synchronous PM of HCC had a median OS of 3.8 months, significantly worse than metachronous PM. However, this patient had a progression-free survival (PFS) of over 16 months, which may indicate the important role of CRS+HIPEC in the treatment of HCC with PM, as Mehta et al^[3] reported. Second, a diffuse PM with PCI of 30 underwent incomplete CRS+HIPEC had an incredible PFS compared to an OS of 5.9 months reported in Mehta's study. The improved survival benefit may be explained by postoperative adjuvant intraperitoneal and intra-

venous chemotherapy. The bidirectional chemotherapy could have bigger synergistic tumoricidal and tumor-inhibitory effect than either chemotherapy alone. Third, this patient failed to benefit from Sorafenib, but response well to intraperitoneal and intravenous chemotherapy with cisplatin and docetaxel. This difference indicates that HCCPM had some common features with PM from other origins. Therefore, the experience of PM management, in general, could be helpful in treating HCCPM.

In conclusion, CRS+HIPEC combined adjuvant intraperitoneal and intravenous chemotherapy may improve PFS for selected patients with HCCPM and should be considered as an option for such patients.

Author contributions

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