

## Hepatocellular Carcinoma Peritoneal Metastases: Report of Three Cases and Collective Review of the Literature

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### Abstract

**Introduction:** Patients with peritoneal metastases (PM) from hepatocellular carcinoma (HCC) often experience a rapid demise even after a complete removal of intrahepatic tumour. Localised PM may now be adequately controlled and managed with cytoreductive surgery (CRS). **Treatment:** Three patients underwent CRS for HCC PM. **Outcome:** The first patient survived 21 months from the time of CRS and is alive with the disease. The second patient died 4 months after CRS. The third patient survived 10 months since CRS and is also alive with the disease. Collectively, the survival of 24 patients with HCC PM extracted through a collective literature review who were treated with cytoreductive surgery had 1- and 2-year survival percentages of 83% and 71%, respectively. **Conclusion:** Careful selection of patients with localised disease to the peritoneal cavity for CRS, taking into consideration the performance status, liver function and tumour biology may lead to a successful outcome in patients with HCC PM.

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**Key words:** Cytoreductive surgery, Peritoneal dissemination

### Introduction

Peritoneal dissemination of hepatocellular carcinoma (HCC) is a rare presentation, with an incidence of 2% to 6% detected during autopsy or laparoscopy.<sup>1</sup> Although uncommon, the morbid and fatal complications associated with peritoneal metastases, especially in patients with liver cirrhosis and coagulation deficiencies, deserve renewed attention given recent advances in the multi-modality management of peritoneal metastases.<sup>2</sup> This phenomenon where HCC being the tumour origin, as suggested by Kaido et al,<sup>3</sup> is most frequently observed following a ruptured HCC where direct spillage and spread of cancer cells into the peritoneal cavity occurs. The overall incidence of spontaneous rupture ranges from 5% to 15% and carries a high mortality rate of up to 50%.

### Case Reports

#### Case 1

A 63-year-old man was incidentally diagnosed with a large HCC following abnormal liver function test during a routine annual medical examination. Hepatobiliary ultrasound

demonstrated 2 solid mass lesions in the right lobe of the liver. The abdomen and pelvic computed tomography (CT) scan showed an exophytic enhancing solid mass, with central necrosis that partially compressed the Inferior Vena Cava (IVC) leading to the dilatation of left intrahepatic bile ducts. A preoperative fine needle aspiration biopsy (FNA) of the liver mass was performed and cytology was indicative of dysplastic cells consistent with HCC. Intraoperatively, the tumour appeared to have ruptured without any macroscopic evidence of extrahepatic disease. The liver was not cirrhotic. An extended right hepatectomy with resection of part of the IVC was performed and the abdominal cavity was lavaged. Histopathology showed a large but well demarcated and partly encapsulated, moderate to poorly differentiated tumour with clear margins. Postoperatively he received adjuvant Iodinated Lipiodol-131 to reduce the risk of intrahepatic recurrence. The patient remained free of disease for 17 months.

Recurrence was detected by rising alpha fetoprotein (AFP) levels and his CT imaging revealed 2 ill-defined soft tissue masses anterior to the proximal abdominal aorta and the neck of pancreas, respectively. As he had a good performance

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status and the tumour appeared as discrete masses, the patient underwent further surgery. Intraoperatively, peritoneal spread of HCC was confirmed with soft tumour plaques present in the lesser sac, omentum on the lesser curvature of the stomach, and on the diaphragm. The masses were completely excised using limited peritonectomy procedures. Following complete cytoreduction of the peritoneal tumours, he remained tumour free for 12 months before detection of further recurrence involving segment 5 of the liver and several other ill-defined masses that appeared within the small bowel mesentery on imaging scans. The patient proceeded for repeat hepatic resection and peritonectomy and the patient was commenced on Sorafenib postoperatively.

Following his third surgery, the patient remained tumour free for a period of 6 months, before recurrence in segment 6 of the liver and peritoneal deposits present in the pelvis. The patient was subjected to his fourth cytoreductive surgery which was completed uneventfully. In total, 4 cytoreductive surgeries have been performed and the patient has survived 41 months since initial diagnosis and 21 months since peritoneal dissemination of HCC.

#### Case 2

A 55-year-old man with colicky abdominal pain on a background of chronic hepatitis from hepatitis B virus (HBV) and diagnosed HCC underwent surgical resection of a ruptured segment 6 HCC. Intraoperatively, standardised transection of the liver was performed and the ruptured contents were lavaged. Histopathology examination revealed a well to moderately differentiated HCC with clear margins. Adjuvant Iodinated Lipiodol-131 was administered 3 months post surgery. However, at 9 months post surgery, abdominal CT revealed a small liver lesion and a right sided lower abdominal mass that was suggestive of peritoneal

tumour. The patient was explored and apart from the right iliac fossa mass, there was evidence of extensive tumour nodules present involving the omentum and small bowel mesentery. Complete cytoreduction of peritoneal metastases was performed. After surgery, his condition continued to decline with intermittent episodes of nausea and vomiting that were suggestive of a malignant obstruction.

Three months after the second surgery, a recurrence occurred with rising AFP levels and imaging evidence of large multifocal intrahepatic HCC with evidence of macroscopic vascular invasion. Owing to the poor performance status and rapidly deteriorating liver function, a decision was made for best supportive care. The patient deteriorated rapidly and was palliated. The survival time after cytoreduction of peritoneal metastases was 4 months.

#### Case 3

A 19-year-old lady who experienced a 3 day history of vomiting and jaundice on a background of weight loss and anorexia that occurred over a period of 7 months was diagnosed with a large HCC following imaging scans. The tumour occupied >50% of the total liver volume and involved the right hepatic vein. It also demonstrated extrahepatic organ invasion with involvement of the upper pole of the right kidney, the stomach anteriorly with extensive upper abdominal lymphadenopathy. The patient was treated with Sorafenib over a period of 10 months with a partial response.

After neoadjuvant chemotherapy, the patient underwent an operation, for which, peritoneal metastases was diagnosed at laparotomy. Extensive hepatic resection, complete cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) using cisplatin (50 mg/m<sup>2</sup>) at 41.5°C for 90 minutes was performed to remove macroscopic and microscopic tumour deposits that involved the pelvic peritoneum, serosal surface of the small bowel and lymph nodes. Microscopic decontamination of peritoneal tumour cells was performed using the HIPEC procedure. After surgery, she remained disease-free for 3 months before developing mediastinal lymphadenopathy. Owing to her youth and fitness, she underwent further thoracic surgery. The patient remained disease-free for a period of 5 months before imaging evidence noted further peritoneal lesions. The patient is presently alive with the disease and is undergoing Sorafenib therapy. The patient has survived 10 months after CRS for peritoneal dissemination of HCC.

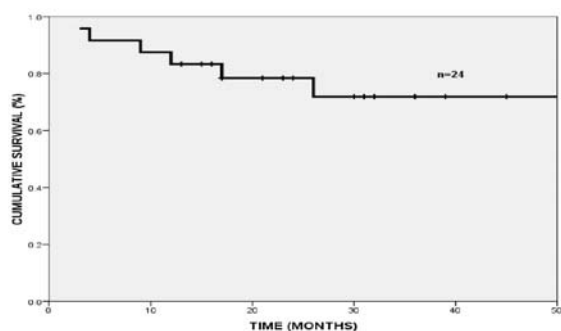


Fig. 1. Combined survival analysis of 24 patients from the current study and collective review of the literature with hepatocellular carcinoma peritoneal metastases after cytoreductive surgery.

#### Collective Review of Current Literature for Radical Surgery of Hepatocellular Carcinoma Peritoneal Metastases

From 1999 to 2009, 19 studies (inclusive of case reports) reported the survival outcomes of patients with hepatocellular carcinoma peritoneal metastases (Table 1). The majority of studies have reported patients undergoing

Table 1. Outcomes of Patients from 19 Studies with Hepatocellular Carcinoma Peritoneal Metastases after Radical Surgical Treatment

Author	Year of publication	Description of disease	Type of treatment	Survival (months)	Patient status (Alive/Dead)
Lin et al <sup>4</sup>	2009	HCC PM	Surgical resection of peritoneal metastases (n = 8)	13.8	NR
			Surgical resections of peritoneal metastases and recurrent hepatic tumour (n = 11)	11.6	NR
Thomas et al <sup>5</sup>	2008	Ruptured HCC PM	Cytoreductive surgery	39	Alive
Yim et al <sup>6</sup>	2008	HCC PM	Cytoreductive surgery	36	Alive
Hung et al <sup>7</sup>	2008	Ruptured HCC PM	Cytoreductive surgery	17	Alive
Ribeiro Jr et al <sup>8</sup>	2007	Ruptured HCC PM	Hepatectomy and nodulectomy	53	Alive
Miyake et al <sup>9</sup>	2006	HCC PM	Combination therapy of interferon-alpha-2b and 5-FU	9	Dead
Otsuka et al <sup>10</sup>	2006	Ruptured HCC PM	Cytoreductive surgery (aborted due to multiple metastases in peritoneal cavity) Oral vitamin E2 and K	15	Alive
Chou et al <sup>11</sup>	2005	HCC PM	Cytoreductive surgery	60	Alive
Ishikawa et al <sup>12</sup>	2005	Ruptured HCC PM with lung metastases	Arterial infusion chemotherapy for multiple HCCs with tumour thrombus of the main portal vein, Systemic chemotherapy for multiple peritoneal and lung metastases	2 days	Dead
Blondon et al <sup>13</sup>	2004	Ruptured HCC PM	Case 1: Cytoreductive surgery Case 2: No surgery, only treatment with Tamoxifen	Case 1 (36) Case 2 (9)	Case 1 & 2 (Alive)
Ryu, et al <sup>14</sup>	2004	Ruptured HCC PM	Cytoreductive surgery	23	Alive
Kaido et al <sup>3</sup>	2004	Ruptured HCC PM	Cytoreductive surgery	45	Alive
Kurachi et al <sup>15</sup>	2002	HCC PM	Cytoreductive surgery	69	Alive
Yoshida et al <sup>16</sup>	2002	HCC PM	Cytoreductive surgery	17	Dead
Takahashi et al <sup>17</sup>	2002	HCC PM	Cytoreductive surgery	60	Alive
Terasaki et al <sup>18</sup>	2000	HCC PM	Cytoreductive surgery	24	Alive
Yunoki et al <sup>19</sup>	1999	Ruptured HCC PM	Cytoreductive surgery	30	Alive
Kosaka et al <sup>20</sup>	1999	Ruptured HCC PM	Cytoreductive surgery	13	Alive
Nakayama et al <sup>21</sup>	1999	HCC PM	Cytoreductive surgery	3	Dead
		HCC PM	Cytoreductive surgery	9	Dead
		Ruptured HCC PM	Cytoreductive surgery	16	Alive
		Ruptured HCC PM	Cytoreductive surgery	12	Dead
		Ruptured HCC PM	Cytoreductive surgery	31	Alive
HCC PM	Cytoreductive surgery	26	Dead		

NR: not reported; HCC: hepatocellular carcinoma; PM: peritoneal metastases

cytoreductive surgery or other forms of surgery which involved the removal of peritoneal tumours. Sixteen studies of 21 patients (Patients 3 to 18) and 3 other patients reported in this series were selected for a combined Kaplan-Meier survival analysis based on follow-up information reported in the publication. In these 24 patients with HCC PM,

patients with documented PM following ruptured HCC (synchronous presentation) or HCC PM as a site of disease recurrence (metachronous presentation) were included, the 1- and 2-year survival percentages were 83% and 71%, respectively (Fig. 1). The median survival percentage was not reached.

In a recent study by Lin et al<sup>4</sup> who reported a study of patients with HCC PM who underwent a variety of treatment strategies, 8 patients who developed metachronous peritoneal recurrence after previous hepatic resection survived a median time of 13.8 months post resection of peritoneal metastases. Eleven patients who underwent resection of recurrence of both intrahepatic and peritoneal recurrence survived 11.6 months. There were no differences in the survival times following the surgical treatment of isolated peritoneal recurrence or combined hepatic and peritoneal recurrence. However, 15 patients with sites of metastases involving other organs apart from the liver and peritoneum (i.e. bone and lung), the median survival time was 2.1 months.

## Conclusion

Surgery appears to be the optimal approach of managing extrahepatic recurrence localised to the peritoneum. The prognosis following an aggressive surgical undertaking to completely remove peritoneal metastases in patients with hepatocellular carcinoma is likely related to the severity of chronic liver disease, the extent of peritoneal tumour involvement and the response to cytoreductive surgery. These factors should form the premise of patient selection for this aggressive treatment approach. At a time when there is a lack of effective systemic treatments, careful selection of patients with limited and localised peritoneal metastases for cytoreductive surgery appears to be a reasonable approach for disease control and prolonging survival.

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