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Cytoreductive Surgery with or Without Hyperthermic Intraperitoneal Chemotherapy in Patients with Peritoneal Hepatocellular Carcinoma

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Background and Objectives: The benefit of Sorafenib is not well described in patients with peritoneal hepatocellular carcinoma (HCC). Although cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) have shown favorable outcomes in certain malignancies, their role in peritoneal HCC remains unknown. We present a series of patients with peritoneal HCC treated with CRS+/−HIPEC and evaluate their clinicopathologic characteristics and outcomes.

Methods: Between 07/07-08/12, 14 patients with limited disease to the peritoneum underwent CRS. Seven of these patients received additional HIPEC treatment. Primary endpoint was overall survival.

Results: Operative treatment was directed for metachronous peritoneal disease in the majority (92.8%) of patients. Mean intraoperative PCI was 9.9 (± 8.3) and complete mascroscopic cytoreduction (CCR 0-1) was achieved in all but one case. Overall major morbidity rate (Clavien-Dindo III-IV) at 30 days was 7.1%. One postoperative death occurred in a patient with extensive tumor burden (PCI = 33, CCR2). Median follow-up after initial surgery was 43.8 months and the median time to metachronous peritoneal recurrence was 23 months. Three-year recurrence rate after peritoneal resection was 100%. Median survival of the cohort CCR0-1 was 35.6 months.

Conclusion: Treatment of peritoneal HCC remains challenging and survival is poor. In well-selected candidates, however, CRS +/− HIPEC may prolong survival compared to systemic therapy alone in patients with peritoneal HCC.

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KEY WORDS: **hepatocellular carcinoma; peritoneal carcinomatosis; cytoreductive surgery; hyperthermic intraperitoneal chemotherapy**

INTRODUCTION

Liver cancer is the fifth most common cancer worldwide and the second most frequent cause of cancer-related death [1]. Hepatocellular carcinoma (HCC) represents the major subtype accounting for up to 85% of primary liver cancers [1]. Despite improved outcome with curative treatments achieving five-year survival rates up to 75%, recurrence remains high [2,3,4,5]. Extrahepatic metastasis is associated with poor prognosis due to limited effective treatment options [6–9]. A subgroup of patients with HCC present with peritoneal metastasis (Figure 1); the incidence of this is approximately 18% based on autopsy findings [9,10]. The benefit of sorafenib, the only proven systemic therapy for metastatic HCC, is not well described in patients with peritoneal dissemination of HCC [11,12]. However, several studies have demonstrated that surgical resection may benefit a select group of patients with isolated extrahepatic disease [9,10,13–20].

Although cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) have shown favorable outcomes in certain malignancies [21–23], their role in peritoneal HCC remains unknown. We present a series of patients with peritoneal HCC treated with CRS with and without HIPEC and evaluate their clinicopathologic characteristics and outcomes.

METHODS

Institutional review board (IRB) approval was obtained for this study.

All patients receiving CRS with and without HIPEC for peritoneal carcinomatosis (PC) of HCC origin between July 2007 and August 2012 were included. Peritoneal metastasis was defined as either metachronous after hepatic resection (HR) for primary HCC or synchronous metastasis. Data for this retrospective analysis was retrieved from a prospectively maintained database. The primary endpoint measured was overall survival.

After initial evaluation at our institution, a contrast-enhanced cross-sectional imaging study (CT scan or MRI) of the chest, abdomen, and pelvis was done as a means of quantifying peritoneal disease burden and ruling out extra-abdominal spread. Nonresectable visceral hepatic metastases or distant metastases were contraindications to CRS and HIPEC. All patients referred to our institution are first evaluated by a multidisciplinary team where we consider tumor burden on imaging studies, liver function, overall health including nutritional status, ECOG performance score, and number of comorbidities. We only proceed with surgery in patients with good liver function in whom a complete cytoreduction is considered feasible. Inclusion criteria for resection required patients to have Child's A liver disease or better with no clinical evidence of significant portal hypertension (platelet count $<100{,}000/\mu l$ and/or presence of splenomegaly, varices, or ascites on imaging).

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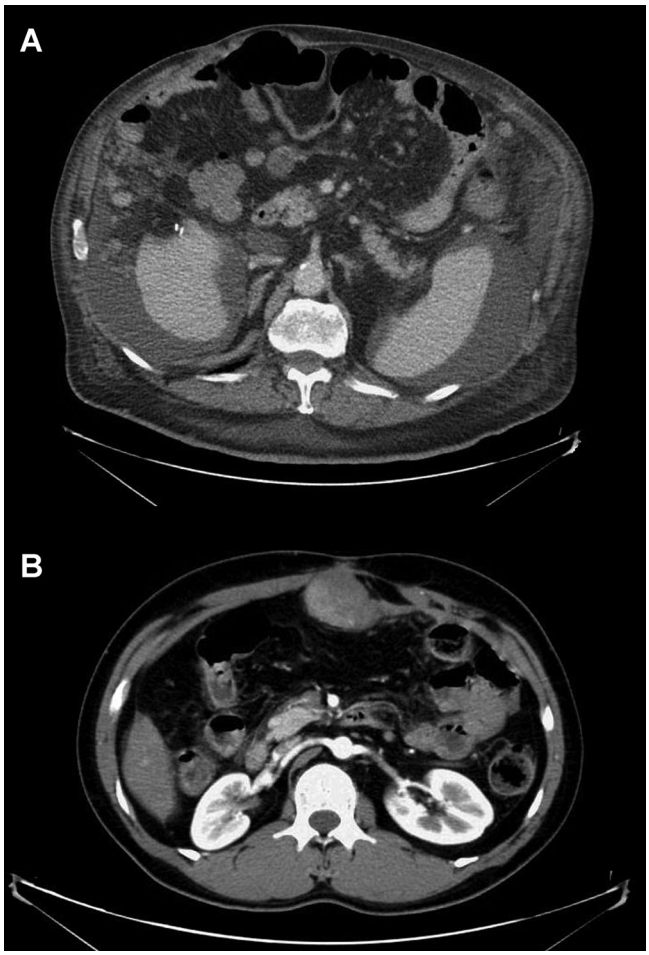

Fig. 1. a) Peritoneal HCC post hepatectomy with high PCI score (33), b) Peritoneal HCC post hepatectomy with low PCI score (3).

Surgery commenced selectively with a diagnostic laparoscopy to assess the feasibility of thorough cytoreduction. If the disease burden was acceptable, a midline laparotomy was made and the patient was explored. The peritoneal cancer index was recorded. This index described by Jacquet and Sugarbaker is a widely used system of staging PC [24,25]. It quantitatively determines the distribution and implant size of the cancer throughout 13 abdominopelvic regions. The size of the largest implant is scored for each abdominopelvic region. The sum of each region's numerical score results in the total PCI score, which varies from 1 to 39. If not previously performed, the primary tumor was resected. Additional tumor debulking was then performed as dictated by the distribution of disease. This included resection of intra-abdominal organ(s) densely involved by tumor, omentectomy, and stripping of all peritoneal surfaces affected, including those of the subdiaphragmatic spaces, the paracolic recesses, and the anterior abdominal wall. The completeness of cytoreduction was then recorded using the Jacquet/Sugarbaker Classification System: CCR-0, no residual macroscopic disease; CCR-1, residual peritoneal deposits < 2.5 mm; CCR-2, residual deposits between 2.5 mm and 2.5 cm; CCR-3, residual deposits >2.5 cm or confluent tumors. The aim was an "complete macroscopic cytoreduction," defined as an eradication of all peritoneal nodules ≥ 2.5 mm in diameter (CCR 0-1) [24,25].

Following cytoreduction, HIPEC was performed as previously described in a select group of patients based on surgeon's preference. The closed abdomen technique was used in all cases. Mitomycin C was the agent used in our series because of its heat-stability, well-established pharmacokinetics in HIPEC, and survival benefit in the treatment of appendiceal and colorectal PC [21,22]. Mitomycin C was administered over two doses for a 90 min perfusion period with a target intraperitoneal temperature of 41–43°C. A 40 mg dose was split between 30 mg for the first 60 min and 10 mg for the last 30 min. Following surgery, patients were typically extubated and transferred to a telemetry unit for 24–48 hr of initial monitoring.

Major postoperative complications were defined according to the Clavien-Dindo Classification System (III-V) and included any complication requiring endoscopic, radiologic or surgical intervention, or any life-threatening postoperative condition requiring intensive care unit management [26]. In addition, the complications were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 (http://ctep.cancer.gov/forms/CTCAEv3.pdf). Perioperative mortality was defined as any death within 30 days of surgery or during the same hospitalization.

After 2008, following the results of the SHARP trial, patients in our series with peritoneal disease were treated with sorafenib. Two patients were treated prior to 2008 and therefore, did not receive the agent. Sorafenib (400 mg daily) was used with adjuvant intent 6 weeks post CRS-HIPEC.

Surveillance consisted of a physical examination, complete blood count, alpha fetoprotein measurement, and contrast-enhanced CT scan (or MRI) of the chest, abdomen, and pelvis every 3 months for the first year, every 4 months for the second year, and biannually thereafter.

Statistical Analysis

Continuous variables were presented as mean $\pm$ standard deviation and compared using the Student's *t*-test. Categorical variables were expressed as valid percentages and compared using the chi-square test or Fisher's exact test as appropriate. Recurrence and survival outcomes were calculated using the Kaplan-Meier method and compared with the log-rank test. Incomplete cytoreduction (CCR 2-3) was considered an immediate recurrence and excluded from the outcome analysis. Statistical analysis was carried out using SPSS 20.0 (Chicago, IL).

RESULTS

During the study period, 352 and 246 patients underwent curative hepatic resection (HR) and orthotopic liver transplantation (OLT), respectively for the treatment of HCC. None of the patients had a history of pre-existing ruptured HCC or local ablation therapy and only one patient had a previous percutaneous tumor biopsy prior to the initial surgery. Fourteen patients developed limited peritoneal disease and underwent CRS (n = 12 post HR, n = 2 post OLT). Seven (50%) of these patients received HIPEC treatment, 12/14 patients were treated with sorafenib as systemic therapy.

Operative treatment (CRS + / − HIPEC) was directed for metachronous peritoneal disease in the majority (92.8%) of patients. In one case, the resection of the primary liver tumor was carried out at the same time as the debulking. The clinical and pathologic data are summarized in Table I. Overall, the average age at diagnosis of peritoneal metastasis was 54.5 ($\pm$ 13.0) years and 85.7% were male. The omentum was the most common site of spread (85.7%). All patients (100%) had a well-preserved liver function (Child A liver disease or better) and adequate performance status (ECOG $\leq$1). The perioperative outcomes are outlined in Table II. The mean intraoperative PCI was 9.9 ($\pm$ 8.3) and complete cytoreduction (CCR 0-1) was achieved in all but one case. Multivisceral resection ($\geq$ 3 organs) was required in 50% of patients. Coexisting recurrent intrahepatic HCC lesions were identified and resected in six patients (42.8%).

The overall morbidity rate (Clavien-Dindo I-IV) at 30 days was 28.5% (n = 4) secondary to cardiac arrhythmia (CTCEA Grade 2),

TABLE I. Clinical, Pathologic and Primary Liver Tumor Data of Patients with Peritoneal HCC Undergoing CRS (#8–14) or CRS-HIPEC (#1–7)

	CRS-HIPEC							CRS								
Variables	#1	#2	#3	#4	#5	#6	#7	#8	#9	#10	#11	#12	#13	#14	Median (SE), n % CRS-HIPEC	Median (SE), n % CRS
Clinical and pathologic data																
Age	49	59	62	58	67	54	28	74	51	72	51	44	35	60	58(4.8)	51(5.4)
Gender	M	M	M	M	M	M	M	M	F	M	M	F	M	M		
Ethnicity	Asian	Asian	Asian	White	White	Hispanic	Asian	White	Asian	White	White	Asian	Asian	Asian		
Underlying Liver disease	HepB	none	HepB	NASH	ALD	HepC	HepB	none	HepB	HepB	HepC	HepB	HepB	HepB		
ECOG status	0	0	0	0	1	1	0	0	0	0	1	0	0	0		
Cirrhosis/Child Pugh Score	Y/A	N	N	N	Y/A	N	N	N	N	Y/A	N	N	Y/A	N	28.6%	28.6%
Synchronous/Metachronous	Rec	Rec	Rec	Rec	Rec	Rec	Sync	Rec	Rec	Rec	Rec	Rec	Rec	Rec		
Primary liver tumor																
Largest tumor size	2.5	7.5	18	6	3.5	3.5	4.3	7.2	12	6.5	3.2	4.1	1.5	1.8	4.3(2.0)	4.1(1.4)
Number of lesions	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1 (0)	1 (0)
Tumor differentiation	poor	poor	mod	mod	well	well	poor	well	poor	well	poor	mod	poor	mod		
Satellites	N	Y	N	N	N	Y	N	N	N	N	N	N	Y	N	28.6%	85.7%
Vascular Invasion	micro	macro	macro	micro	micro	none	none	none	micro	none	none	none	micro	micro		
Type of Treatment of primary tumor	HR	HR	HR	HR	HR	OLT	HR	HR	HR	HR	OLT	HR	HR	HR		

M, male; F, female; Y, yes; N, no; Rec, recurrence/metachronous; Syn, synchronous; HR, hepatic resection; OLT, liver transplantation; Mod, moderate; HepB, hepatitis B; HepC, Hepatitis C; ALD, alcoholic liver disease.

neutropenia (CTCEA Grade 2), and respiratory failure (CTCEA Grade 4). None required an operative re-exploration. One postoperative death (7.1%) (CTCEA Grade 5) occurred in a patient with extensive tumor burden (PCI = 33, CCR 2) undergoing CRS-HIPEC with recurrent peritoneal disease. His course was complicated by an acute cardiac event.

The median follow-up after initial surgery (HR or OLT) was 43.8 months and the median time to metachronous peritoneal recurrence was 23 months. Median time from peritoneal resection (CCR 0-1) to progression of disease in patients with complete macroscopic cytoreduction was 5.1 months. The three-year recurrence rate after peritoneal resection was 100% (Fig. 2a). The median survival of the entire cohort CCR 0-1 was 35.6 months (Fig. 2b). The median survival for the CRS-HIPEC (CCR 0-1) was 42.1 months.

DISCUSSION

Treatment of peritoneal HCC remains challenging following HR. Surgical metastasectomy may be of benefit in patients with limited extrahepatic HCC recurrence, and these series have included patients with PC [7–10,13–20]. Over the past decade, aggressive cytoreduction with HIPEC has altered the treatment of PC from diverse visceral malignancies [21–23]. To our knowledge, we report the first published series examining the characterics and outcome of this technique in the treatment of peritoneal HCC. Similar to other published series on this topic, the main limitation of our study is its retrospective nature, relatively small sample size, and patient selection bias.

Despite the reported incidence of 2%–18% at autopsy, the occurrence of PC from HCC at initial resection is rare compared to cholangiocarcinoma [7,9,10]. Overall, extrahepatic metastasis occurs in 13%–42% of HCC patients with lung (55%) being the most frequent and PC (11%) the least frequent distribution sites [7,9]. The risk factors and mechanism associated with peritoneal HCC have not been well established. Previously reported risk factors for peritoneal tumor dissemination include spontaneous tumor rupture, percutaneous tumor biopsy, and percutaneous ablation therapy [9,10,13–20]. In our series, none of the patients had a history of pre-existing ruptured HCC or local ablation therapy and only one patient had a previous percutaneous tumor biopsy prior to the initial surgery. This is consistent with previously reported series, establishing the need to further investigate the true mechanism of peritoneal HCC. Poorly-differentiated HCC, is another reported factor associated with PC [9,10], was present in 42.8% of patients in our series.

Diagnosis of peritoneal HCC can be difficult and is based on clinical suspicion and imaging studies. A correlation has been reported between the AFP level and the presence of PC [9,10]; in our series, 46.1% of patients had normal AFP levels (<10 ng/ml). This may be explained by the limited disease and mean PCI score of 9.9 (± 8.3) in our series. In addition, we did not notice a correlation between AFP levels and PCI scores. In our series, CT was the modality of choice on which diagnosis was based. CT manifestations of HCC-PC are similar to those of other visceral malignancies and include ascites, thickening and enhancement of parietal peritoneum, omental caking or nodular changes, and masses in the visceral peritoneum. Typical findings in our series were localized hypervascular masses or omental nodules (Fig. 1).

Peritoneal carcinomatosis has been traditionally regarded as a lethal endpoint of a variety of intraabdominal tumors [22,23]• Patients with peritoneal HCC are classified as having advanced disease stage according to the Barcelona-Clinic Liver Cancer (BCLC) staging system for whom systemic treatment with sorafenib is indicated [27]. Encouraged by the success of sorafenib, a number of other studies have been undertaken using other targeted agents in combination with sorafenib, head-to-head against sorafenib (erlotinib [SEARCH trial], brivanib, [BRISK-FL trial], or Linifanib vs. Sorafenib) or as second-line after progression on or inability to tolerate sorafenib (Everolimus vs. Placebo [EVOLVE-1 trial], Brivanib vs. Placebo [BRISK trial]). All completed studies have been negative to date [28–32].

Some studies however, suggest that in addition to systemic therapy, aggressive surgical treatment may be of benefit in patients with isolated metastasis, in particular peritoneal HCC [7,10,13–20]. The largest study reported by Lin et al. investigates the survival of 53 HCC patients with peritoneal disease [10]. The majority of PC presented as a metachronous peritoneal recurrence (81.1%). Cytoreductive surgery was offered to a select group of patients (65.1%) either with or without combined repeat hepatectomy. The majority of patients had a single site peritoneal metastasis in addition to the intrahepatic recurrence. Median survival of patients undergoing CRS was 12.5 months compared to systemic chemotherapy alone 2.1 months. Fourteen patients underwent CRS +/−

TABLE II. Operative Data and Outcome of Patients With Peritoneal HCC Undergoing CRS (#8–14) or CRS-HIPEC (#1–7)

	CRS-HIPEC							CRS								
Variables	#1	#2	#3	#4	#5	#6	#7	#8	#9	#10	#11	#12	#13	#14	Median (SE), n % CRS-HIPEC	Median (SE), n % CRS
Operative data																
OR time (mins)	305	105	250	388	448	468	308	208	101	164	74	132	75	130	308(47.3)	130(18.3)
EBL (ml)	500	25	100	500	2500	700	500	400	200	300	50	400	150	50	500(315.2)	200(56.5)
Transfusion (Y,N)	N	N	N	N	Y	Y	N	Y	N	N	Y	N	N	N	28.6%	28.6%
Intraop PCI score	12	6	6	10	33	16	20	10	3	3	6	8	3	3	12(3.6)	3.0(1.1)
CC score (0,1,2)	0	0	0	0	2	0	1	0	0	0	0	0	0	0	85.7%	100%
Chemotherapy agent	MMC	MMC	MMC	MMC	MMC	MMC	MMC	none	none	none	none	none	none	none		
Organs resected	L,St, Om	Om, Per	Om, Per	L,Om, Dia,Per	Om,Dia, Per	Om,Dia, Per,L, Sp,Co	Om,L, Dia,Per	Om,L, Dia	Om,St, Co,Pa	Per, Dia	Om,L	Per,Co	Om,Per	Om,Sb		
Intraoperative complications	N	N	N	N	N	N	N	N	N	N	N	N	N	N	0%	0%
Outcome data																
Hospital stay (days)	5	4	6	5	14	69	8	6	5	5	3	7	3	4	6(8.9)	5(0.5)
Morbidity (30 days)	2	0	2	2	5	3	0	0	0	0	0	0	0	0	57.1%	0%
Mortality (90 days) (Y/N)	0	0	0	0	1	0	0	0	0	0	0	0	0	0	14.2%	0%

MMC, mitomycin C; L, Liver; OM, Omentum; Dia, Diaphragm; Sp, Spleen; Per, Peritonectomy; Co, Colon; Sb, Small bowel; St, Stomach; PCI, peritoneal cancer index; CC, cytoreduction; CRS, cytoreduction; HIPEC, heated intraperitoneal chemotherapy; EBL, estimated blood loss; OR, operative; Y, yes; N, no.

Fig. 2. a) Overall recurrence of patients with peritoneal HCC following CRS +/− HIPEC (n = 13), b) Overall survival of patients with peritoneal HCC following CRS +/− HIPEC (n = 13).

HIPEC in our study, with a mean PCI score of 9.9 (± 8.3). Complete cytoreduction was achieved in 93% of cases. Our perioperative results are comparable to that of previously published series [10,22,33,34]. The one postoperative death occurred in a patient with high tumor burden (PCI = 33). We report an overall median survival of 35.6 months which is higher compared to systemic chemotherapy alone in the treatment of PC-HCC. Interestingly, despite having a higher PCI score, patients in the HIPEC group had a median survival of 42.1 months. Since peritoneal disease reflects locoregional spread rather than systemic dissemination, it would be interesting to further investigate the role of HIPEC in the treatment of peritoneal HCC.

CONCLUSION

Treatment of peritoneal HCC remains challenging and survival is poor. In well-selected candidates however, cytoreductive surgery with or without HIPEC may prolong survival compared to systemic therapy alone in patients with HCC and peritoneal carcinomatosis.

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