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Metastatic Colorectal Cancer: Survival Comparison of Hepatic Resection Versus Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy

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Abstract

Background—Liver resection has long been considered the standard of care for resectable colorectal hepatic metastases (HM). Patients with colorectal peritoneal surface disease (PSD) are now also being treated with aggressive therapy in the form of cytoreductive surgery (CS) and hyperthermic intraperitoneal chemotherapy (HIPEC).

Methods—A retrospective comparison of optimally-treated colorectal cancer patients with HM or PSD obtained from prospectively maintained databases (1991–2010).

Results—Liver resection was performed on 179 patients with HM, while 93 PSD patients received a complete cy-toreduction followed by HIPEC. Patients differed in terms of age, performance status, site of primary cancer, T stage, and the use of perioperative chemotherapy. Five-year overall survival for HM patients was 36 %, with a median survival of 46 months, compared with 26 % and 34 months in patients with PSD ($p = 0.024$). When stratified by resection status, R0 HM ($n = 170$) and R0 PSD ($n = 48$) patients had similar median survival (49 vs. 41 months; $p = 0.39$). Median survival following R1 resection was also similar among HM ($n = 9$) and PSD ($n = 45$) patients (28 vs. 23 months; $p = 0.68$). Multivariate analysis identified distinctly different independent prognostic factors between HM and PSD patients. Major morbidity was 21 and 23 % ($p = 0.88$), while mortality was 3.9 versus 5.4 % ($p = 0.55$) in the HM and PSD patients, respectively.

Conclusion—Colorectal HM and PSD are distinct biologic diseases with different presentations and unique prognostic factors. However, long-term survival following CS/HIPEC is comparable to

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liver resection when stratified by completeness of resection. Furthermore, perioperative morbidity and mortality are similar.

The liver is the most common metastatic site of colorectal cancer.^{1,2} Hepatic metastases (HM) is present in 25 % of patients at the time of diagnosis,^{3–6} and 35–55 % of patients will develop HM after primary colorectal resection^{6–8} and over half of colorectal cancer patients will develop HM during their lifetime.⁹ In patients with resectable HM, median survival (OS) between 30 and 74 months can be achieved following hepatic resection^{10–24} and up to 24 % will be disease-free at 10 years.^{10,15, 19} Given these outcomes, hepatic resection for colorectal HM has become the standard of care. Similar outcomes occur following lung resection for resectable colorectal lung metastases.^{25,26}

Colorectal metastasis to the peritoneum occurs in 20–30 % of colorectal cancer patients.^{2,27} Colorectal peritoneal surface disease (PSD) is found in 10–15 % of patients at the time of initial diagnosis^{2,28,29} and occurs in up to half of patients with recurrent disease after curative resection.^{29,30} Cytoreductive surgery (CS) plus hyperthermic intraperitoneal chemotherapy (HIPEC) in patients with colorectal PSD has resulted in 5-year OS rates up to 45 %, with median OS between 24 and 63 months after complete CS and HIPEC.^{31–40} While encouraging, these results are associated with significant morbidity and mortality; thus, CS/HIPEC continues to be a controversial therapy.

Some clinicians have suggested that colorectal HM and colorectal PSD can be treated with equal success.^{41,42} In an earlier report,⁴¹ we analyzed outcomes in optimally-treated HM and PSD patients. While the difference was not significant, there was a trend toward better survival in HM patients (41 vs. 34 months, respectively; $p = 0.32$), raising the possibility that the analysis was underpowered. Herein, we re-evaluate our series of metastatic colorectal cancer patients, adding over 4 years of experience, and compare survival rates, prognostic factors, and operative outcomes in HM and PSD patients.

METHODS

This study was approved by the Institutional Review Board of Wake Forest School of Medicine. A review of patients with metastatic colorectal cancer was performed from prospectively maintained databases of patients who underwent hepatic resection or CS/HIPEC. Demographic and perioperative data were collected prospectively.

Major hepatic resections were categorized as resections of ≥ 4 segments. Minor hepatic resections included resections of <4 segments. Radiofrequency ablation and/or portal vein embolization were used as indicated. Hepatic resections were designated as margin-negative (R0) or margin-positive (R1) based on histologic examination.

Our technique of CS/HIPEC has been previously described.³⁷ The objective of CS in PSD patients is to remove all macroscopic tumor, after which residual microscopic disease is treated with HIPEC. After aggressive cytoreduction, a resection status is assigned according to the following scale: R0—complete removal of all visible tumor and negative cytology or microscopic margins; R1—removal of all gross disease but with microscopic residual disease; R2—residual macroscopic, unresectable disease. Both R0 and R1 resections were

considered to be optimally treated based on the rationale that HIPEC sufficiently treats microscopic tumor cells left behind. R2 resections were excluded from the analysis since they were never considered to be disease-free. Both HM and PSD patients were given perioperative chemotherapy at their medical oncologist's discretion.

Operative complications were categorized according to the Clavien-Dindo Classification of Surgical Complications:⁴³ Grade I—minor deviations from normal postoperative recovery; Grade II—require pharmacological therapy; Grade III—require surgical, endoscopic, or radiologic intervention without general anesthesia (IIIa) or with general anesthesia(IIIb); Grade IV—life-threatening complications requiring intensive care management for single organ dysfunction (IVa) or multi-organ failure (IVb); Grade V—patient mortality.

Descriptive statistics for continuous data and frequencies/proportions for categorical data were generated. To compare study groups, independent *t*-tests were used for continuous data, and Chi-square tests were utilized for categorical data. The Kaplan–Meier method was used to estimate OS; χ^2 approximation of the log-rank test was used to assess the univariate effect of independent measures on survival times. To assess best-fit models, stepwise regression was used separately for the two groups. Independent variables were removed singularly, with the model refit; this was done iteratively until all non-significant variables were removed.

RESULTS

Between December 1991 and September 2010, 179 HM patients underwent hepatic resection for colorectal HM. Among 185 patients with colorectal PSD who received CS/HIPEC, 93 received a complete cytoreduction (R0/1). As summarized in Table 1, significant differences exist between R0/1 HM and R0/1 PSD patients. PSD patients were younger, but generally had a poorer performance status. PSD patients had more invasive (T3/4) tumors but nodal stage was similar. Also, relatively few PSD patients had primary rectal cancer. Interestingly, more PSD patients were treated with preoperative chemotherapy, while postoperative chemotherapy was more common following hepatic resection. This pattern likely reflects treatment biases resulting in early surgical referral for HM patients, whereas PSD patients are often referred after progression on chemotherapy.

Minor liver resections were performed in 100 HM patients (56 %). Seventy-nine patients underwent major resections: 62 patients (35 %) received a hemihepatectomy, while 17 patients (9 %) underwent an extended hepatectomy or a hemihepatectomy plus an additional wedge/segment resection. The mean number of liver lesions was 1.9 (range 1–7) and the mean size of the largest lesion was 4.2 cm (range 0.2–16). Bilobar disease was present in 40 patients (22 %). Sixteen patients (8.9 %) underwent simultaneous colorectal resection for their primary tumor, and radiofrequency ablation was performed in 11 patients (6.1 %). Margins were negative (R0) in 170 HM patients (95 %), while nine had positive margins (R1).

PSD patients underwent peritonectomy and various organ resections, as indicated, depending on the location and extent of disease. Forty-eight patients received an R0

resection while 45 received an R1 resection. The frequency of specific organs resected is found in Supplemental Table A [see electronic supplementary material (ESM)]. Median follow-up was 58 and 89 months for HM and PSD patients, respectively. Median OS was significantly longer in HM patients compared with PSD patients (45.7 vs. 33.6 months; $p = 0.031$); however, when stratified by resection status, there was no difference in survival (Table 2). Kaplan–Meier survival curves comparing these groups are shown in Fig. 1.

Among HM patients, improved survival was associated with lesions, largest lesion ≤ 6.5 cm, need for ≤ 1 blood transfusion, disease-free interval >1 year, the use of adjuvant chemotherapy, and the lack of extrahepatic disease. Improved survival among PSD patients was associated with lower lymph node ratio, disease-free interval >1 year, and the lack of liver metastases. Complete univariate analysis results are shown in Supplementary Tables B and C (see ESM). Using a stepwise Cox regression model, multivariate analysis demonstrated different independent prognostic factors among HM and PSD patients, as highlighted in Table 3.

The incidence of major complications (Grades III–V) following CS/HIPEC in PSD patients was similar following hepatic resection in HM patients (23 vs. 21 %; $p = 0.88$). Likewise, operative mortality was similar between the HM and PSD patients (3.9 vs. 5.4 %; $p = 0.55$). The causes of the seven postoperative deaths in the HM group were pneumonia (2), hepatic failure, cere-brovascular accident, bowel perforation, intraoperative blood loss, and pulmonary embolism. The five postoperative deaths in the PSD group were due to bowel perforation (2), severe neutropenia, pneumonia, and pulmonary embolism.

DISCUSSION

Over the past several decades, aggressive surgical resection for colorectal HM has become the standard of care worldwide. In contrast, CS/HIPEC remains controversial despite single and multi-institutional experiences publishing favorable and consistent results, including one randomized trial⁴⁰ and several comparison studies^{44,45} showing survival benefit using CS/HIPEC in conjunction with systematic chemotherapy for colorectal PSD over chemotherapy alone.

Based on the oncologic principle that both HM and PSD represent oligometastatic disease states where curative resection is possible, an important question becomes whether CS/HIPEC for colorectal PSD can achieve similar results compared with hepatic resection for colorectal HM. Indeed, outcomes from recent publications on hepatic resection for colorectal HM and on CS/HIPEC for colorectal PSD are remarkably similar (Table 4). In addition, Cao et al.⁴² compared outcomes in 237 HM patients following margin-negative liver resection with 46 PSD patients treated with complete CS/HIPEC, and reported equivalent OS (37 months; $p = 0.79$).

The current study is the largest available directly comparing optimally-treated colorectal HM and PSD patients. Overall, PSD patients exhibited poorer prognosis compared with HM patients; however, the difference was driven by resection status. Only 5 % of HM patients were margin-positive, while 48 % of PSD patients underwent an R1 resection. When

compared based on resection status, survival was remarkably similar. This observation supports the paradigm that the peritoneum is a distinct organ system and eradication of PSD can yield favorable long-term outcomes, similar to HM.

PSD patients who undergo an R1 cytoreduction followed by HIPEC have been considered disease-free under the rationale that HIPEC adequately treats residual tumor cells. Both R0 and R1 resections have therefore been considered optimal cytoreductions and grouped together in most analyses. However, our results suggest that this assumption may not be accurate. The survival difference between R0 and R1 cytoreductions in PSD patients approaches statistical significance, and with more patients would likely have a significant *p* value. This underscores the importance of complete cytoreduction for PDS.

The distinction between an R0 and R1 cytoreduction is difficult to define. The assessment of resection status is made by the surgeon at the end of the operation based on the extent of disease and how it was cytoreduced. PSD that is stripped from the peritoneum, enucleated or treated with a Cavitronic Ultrasonic Surgical Aspirator, is assumed to have microscopic residual disease and assigned an R1 status. In reviewing the operative reports from the current study, R0 resections were generally assigned when the peritoneal disease was low volume and amendable to wide margin excisions. Our data suggest that *any* residual PSD may increase the patient's risk for worse survival. Furthermore, the completeness of cytoreduction may be a marker for less aggressive disease. Tumor biology likely contributes greatly to the extent of disease at the time of diagnosis, and since surgical resectability is determined by the volume of disease and tumor location at the time of surgery, patients with favorable biology may be more likely to achieve a more complete cytoreduction.

Recently, Franko et al.⁴⁶ combined data from two phase III trials (N9741 and N9841) using modern systemic chemotherapy regimens, and compared outcomes in 364 patients with colorectal PSD to 1,731 patients with metastatic colorectal cancer from other sites. They found that PSD was associated with a 30 % reduction in median OS compared with patients with non-PSD metastases (12.7 vs. 17.6 months; *p* < 0.001). They concluded that colorectal PSD is more aggressive and more chemotherapy resistant compared with other sites. Based on this observation, one would expect survival in patients with HM to be better than patients with PSD when stratified by resection status, which we did not observe. Given that the only difference in treatment between our two groups was the application of HIPEC, could the difference in outcomes between PSD and non-PSD colorectal cancer due to resistance to systemic chemotherapy be overcome by HIPEC?

If this is true, then there are significant advantages of HIPEC. Delivery of intraperitoneal chemotherapy allows much higher concentrations to be administered without systemic toxicity due to the peritoneal/plasma barrier,^{47–49} and hyperthermia has been shown to intensify the cytotoxic effects of chemotherapy.^{50–52} Admittedly, the relative contribution of HIPEC to long-term survival compared with CS alone is unknown. Interestingly, while median survival was not different, we observed a sharper decline in survival for R1 patients with HM compared with R1 patients with PSD (see Fig. 1b; Table 2). In fact, among R1 patients, there were no HM survivors at 4 years, while approximately one in five patients with PSD survived beyond 4 years. This observation is certainly limited by the small

number of R1 HM patients ($n = 9$) but, if true, would suggest that HIPEC may provide treatment effect in the setting of residual disease. However, the supposition that HIPEC can equalize or improve the outcomes in the HM and PSD groups in this study cohort is only speculation based on inference and extrapolation. Fortunately, there is currently a randomized, multicenter, prospective trial accruing in France which compares HIPEC versus no HI-PEC following optimal cytoreduction of colorectal PSD (Elias D, personal communication). The results of this study may provide level I evidence regarding the efficacy of HIPEC when coupled with CS.

While long-term outcomes may be similar in well-selected patients, colorectal HM and PSD represent distinct biological diseases, highlighted by differences in clinical presentation and their unique prognostic factors. It is well known that due to its diffuse nature, it is often more difficult to completely resect PSD compared with HM. However, the reported difference in resectability is subject to significant selection bias. In reality, less than 25 % of HM patients are deemed resectable at the time of diagnosis.^{7,10,53} Current imaging for PSD is far inferior to hepatic imaging, allowing unresectable HM to be more easily diagnosed preoperatively, while the extent of PSD is often not determined until surgery. Furthermore, our data clearly show that PSD patients have worse performance status and are far more heavily pretreated with chemotherapy prior to surgical resection compared with HM patients, suggesting that PSD patients are referred for surgical evaluation later in the course of treatment. In our experience, it is not uncommon for patients to be referred for CS/HIPEC only after failing multiple systemic therapies.

Interestingly, published complication rates of CS/HI-PEC are similar to hepatic resection in metastatic colorectal cancer patients (Table 4). Likewise, our experience reports similar major morbidity and mortality between the two procedures. Yet, while most oncologists accept the complication rate for hepatic resection, many claim that the operative morbidity and mortality associated with CS/HIPEC do not justify its use. Early experiences with hepatic resection for colorectal HM reported operative morbidity as high as 46 %, with mortality up to 8 %.^{54–59} Advances in operative technique and critical care management have led to improved outcomes in hepatic surgery as experience has been gained over time.^{10,11,18,60} One would expect similar improvements as experience with CS/ HIPEC is gained and research defines patient selection and optimal treatment strategies. Indeed, a recent article reported improved outcomes in CS/HIPEC over a 10-year time period, showing morbidity drop from 73 to 38 % and mortality drop from 9 to 3 %.⁶¹

CONCLUSIONS

Colorectal HM and PSD are distinct disease processes with unique presentations and prognostic factors. However, when aggressive therapy is applied, long-term survival is similar when stratified by completeness of resection. This is the first study to analyze R0 and R1 CS/HIPEC cases separately and demonstrates a possible difference in survival. The exact influence of HIPEC on colorectal PSD is unclear but future trials may help to answer this question. Complication rates after CS/HIPEC have become comparable to rates following hepatic resection for colorectal HM. Finally, similar to accepted recommendations for patients with liver metastases, we recommend that patients with colorectal PSD be

evaluated at a peritoneal surface malignancy center soon after diagnosis. Early referral will allow for a multidisciplinary plan regarding the need for preoperative chemotherapy and the optimal timing for CS/ HIPEC. Such an evaluation, before disease progression, may increase the possibility of complete cytoreduction. Such patients, who achieve complete cytoreductions, can expect long-term outcomes similar to patients who undergo liver resection for colorectal HM.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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FIG. 1.

a Kaplan–Meier survival curves for colorectal cancer patients with HM or PSD. **b** Kaplan–Meier survival curves separated by resection status (R0 and R1). *HM* hepatic metastases, *PSD* peritoneal surface disease

TABLE 1

Demographic and perioperative data of metastatic colorectal patients

Variables	HM	PSD	p-value
Total patients	179 (100)	93 (100)	
Age [median $\pm$ SD (range)]	59 $\pm$ 11 (29–87)	54 $\pm$ 13 (15–80)	0.0001
Gender			0.25
Male	96 (54)	43 (46)	
Female	83 (46)	50 (54)	
Race			0.051
White	152 (85)	83 (89)	
Black	26 (15)	7 (9)	
Other	1 (1)	2 (2)	
Performance status (ECOG)			<0.0001
0	137 (77)	46 (50)	
1	39 (22)	38 (41)	
2	3 (2)	6 (7)	
3 or 4	0	2 (2)	
Primary site			<0.0001
Colon	130 (73)	88 (95)	
Rectum	49 (27)	5 (5)	
T stage of primary lesion			<0.0001
T1	4 (3)	0	
T2	25 (17)	2 (3)	
T3	103 (72)	38 (59)	
T4	12 (8)	24 (38)	
N stage of primary lesion			0.74
N0	62 (38)	26 (37)	
N1	49 (31)	19 (27)	
N2	49 (31)	25 (36)	
Presentation			0.37
Synchronous	81 (45)	48 (52)	
Metachronous	98 (55)	45 (48)	
Disease-free interval ^a			0.75
Median [months (range)]	17.5 (4–161)	17.3 (0–103)	
Preoperative chemotherapy			0.0001
Yes	70 (39)	59 (65)	
No	108 (61)	32 (35)	
CEA level			
Preoperative [median (range)]	6.3 (0.5–613)	4.3 (0.3–87)	0.048
Postoperative [median (range)]	6.0 (0–48)	1.4 (0–18)	<0.0001

Variables	HM	PSD	p-value
Operative time [h; median (range)]	5.0 (1.5–16)	9.0 (4–18)	<0.0001
Estimated blood loss [mL; median (range)] (100–4,000)	600 (30–4,525) 0.15	475	
PRBC transfusion			0.29
Yes	37 (26)	26 (33)	
No	131 (74)	53 (67)	
Length of stay (days; median (range))	6 (0–48)	9 (4–131)	0.0001
Adjuvant chemotherapy			0.003
Yes	102 (62)	34 (41)	
No	63 (38)	48 (59)	

Data are presented as [n (%)] unless otherwise specified

HM hepatic metastases, *PSD* peritoneal surface disease, *ECOG* Eastern Cooperative Oncology Group, *CEA* carcinoma embryonic antigen, *PRBC* packed red blood cells

^aIncludes only patients with metachronous disease, measured from the time of primary resection

TABLE 2

Overall survival for optimally-treated patients with colorectal HM and PSD

	Overall		R0 comparison		R1 comparison	
	HM (%)	PSD (%)	HM (%) ^a	PSD (%) ^b	HM (%) ^a	PSD (%) ^b
<i>n</i>	179	93	170	48	9	45
Overall survival						
1-year	89 ± 2	88 ± 3	88 ± 3	92 ± 4	100	84 ± 5
3-year	62 ± 4	45 ± 5	64 ± 4	58 ± 7	17 ± 15	32 ± 7
5-year	36 ± 4	26 ± 5	38 ± 5	35 ± 8	0	16 ± 6
Median survival (months)	45.7	33.6	49.4	40.7	27.9	23.0
<i>p</i> value	0.024		0.39		0.68	

HM hepatic metastases, *PSD* peritoneal surface disease^a *p* Value of HM R0 versus R1 is 0.006^b *p* Value of PSD R0 versus R1 is 0.076

TABLE 3

Multivariate analysis for overall survival in HM and PSD patients

Variable	Hazard ratio (95% CI)	<i>p</i> value
<i>Hepatic Metastases</i>		
Male gender	0.60 (0.39–0.92)	0.019
Lesion 6.5 cm	0.42 (0.25–0.70)	0.001
Three or less lesions	0.45 (0.25–0.81)	0.008
Extrahepatic disease	2.33 (1.15–4.72)	0.019
<i>Peritoneal Surface Disease</i>		
Age (per 5-year increase)	1.31 (1.13–1.52)	0.0004
R0 resection status (relative to R1)	0.47 (0.25–0.90)	0.023
Rectal primary	5.60 (1.65–19.0)	0.006
Liver metastases	3.15 (1.42–7.00)	0.005
Lymph node ratio (relative to 0–0.2)		0.002
0.2–0.5	1.75 (0.73–4.19)	
0.5	4.12 (1.87–9.09)	

HM hepatic metastases, *PSD* peritoneal surface disease, *CI* confidence interval

Comparison of outcomes in metastatic colorectal cancer patients undergoing hepatic resection or complete cytoreductive surgery plus HIPEC in recent publications

TABLE 4

Study	Year	n	Median survival (months)	5-year survival unless otherwise stated (%)	Major morbidity (%)	Mortality 30-day, unless otherwise stated (%)
Hepatic Resection						
Scheele et al. ¹⁰	1995	434	40	33	16	4.4
Choti et al. ¹¹	2002	226	46	40	19 ^b	0.9 ^c
Wei et al. ¹²	2006	395	53	47	20	1.7
Wang et al. ¹³	2007	923	–	22	–	–
Figueras et al. ¹⁴	2007	501	44	42	35 ^b	4.0
Tomlinson et al. ¹⁵	2007	612	44	17 (10-year)	–	–
Minagawa et al. ¹⁶	2007	369	–	38	–	–
		229	–	44	–	–
Rees et al. ¹⁷	2008	929	43	36	26 ^b	1.5
Nathan et al. ¹⁸	2010	949	52	45	–	0.9 ^c
Present study	2012	170	49	39	22	3.5
Cytoreductive Surgery + HIPEC^a						
Pestieau and Sugarbaker ³¹	2000	44	24	30	–	–
Glehen et al. ³²	2004	23	33	21	23	4
Glehen et al. ²⁹	2004	271	32	31	23	4.0
Verwaal et al. ³³	2005	59	43	43	–	6.0 ^c
Kianmanesh et al. ³⁴	2007	30	63	–	39 ^b	2.3
Verwaal et al. ⁴⁰	2008	22	48	45	–	7.8 ^c
Yan and Morris ³⁵	2008	41	37	62 (3-year)	30	0
Elias et al. ³⁸	2010	341 (colon) 27 (rectum)	32 34	30 38	29 44	4.1 0
Cavalieri et al. ³⁹	2011	124	25	50 (2-year)	27	2.7
Present study	2012	93	34	27	23	2.2

HIPEC hyperthermic intraperitoneal chemotherapy, – indicates not reported

^dNumber of patients, 5-year survival and median survival data only from patients with complete cytoreductive surgery

^bRepresents reported morbidity (major morbidity not specified)

^cReported as all treatment-related deaths