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Primary Tumor Sidedness is Predictive of Survival in Colon Cancer Patients Treated with Cytoreductive Surgery With or Without Hyperthermic Intraperitoneal Chemotherapy: A US HIPEC Collaborative Study

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ABSTRACT

Introduction. The clinical relevance of primary tumor sidedness is not fully understood in colon cancer patients with peritoneal metastasis treated with cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC).

Methods. This was a retrospective cohort study of a multi-institutional database of patients with peritoneal surface malignancy at 12 participating high-volume academic centers from the US HIPEC Collaborative.

Results. Overall, 336 patients with colon primary tumors who underwent curative-intent CRS with or without HIPEC were identified; 179 (53.3%) patients had right-sided primary tumors and 157 (46.7%) had left-sided primary tumors. Patients with right-sided tumors were more likely to be older, male, have higher Peritoneal Cancer Index (PCI), and have a perforated primary tumor, but were less likely to have extraperitoneal disease. Patients with complete cytoreduction (CC-0/1) had a median disease-free survival (DFS) of 11.5 months (95% confidence interval [CI] 7.6–15.3) versus 13.1 months (95% CI 9.5–16.8) [$p = 0.158$] and median overall survival (OS) of 30 months (95% CI 23.5–36.6) versus 45.4 months (95% CI 35.9–54.8) [$p = 0.028$] for right- and left-sided tumors; respectively. Multivariate analysis revealed that right-sided primary tumor was an independent predictor of worse DFS (hazard ratio [HR] 1.75, 95% CI 1.19–2.56; $p = 0.004$) and OS (HR 1.72, 95% CI 1.09–2.73; $p = 0.020$).

Conclusion. Right-sided primary tumor was an independent predictor of worse DFS and OS. Relevant clinicopathologic criteria, such as tumor sidedness and PCI, should be considered in patient selection for CRS with or without HIPEC, and guide stratification for clinical trials.

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Colon cancer is the second leading cause of cancer death in men and women in the US. Primary tumor sidedness is prognostic of survival in patients with metastatic colon cancer, with right-sidedness being associated with poorer survival.[1–5] This has been shown for patients with widespread metastatic disease treated with systemic therapy, and for those with regional metastasis to the liver treated with liver-directed therapies.[6,7] Approximately 2–5% of patients with colon cancer present with metastatic disease confined to the peritoneal cavity, and this subset of patients has a particularly poor prognosis.[8] This observation is demonstrated in the American Joint Committee on Cancer (AJCC) staging system for colon cancer where metastasis to the peritoneum is distinguished from metastases to other sites and labeled 'M1c'. Even with modern chemotherapy agents and combination regimens, patients with isolated peritoneal metastasis have a dismal median overall survival (OS) of approximately 16 months with systemic therapy.[8]

The treatment associated with the best survival outcomes for patients with peritoneal metastatic colon cancer is cytoreductive surgery (CRS) with or without hyperthermic intraperitoneal chemotherapy (HIPEC). High-quality, large, retrospective series have shown median survival rates of over 30 months for patients treated with CRS and HIPEC.[9,10] More recently, the PRODIGE 7 trial randomized patients to CRS with or without HIPEC with oxaliplatin.[11] This study showed excellent OS rates of 41.7 versus 41.2 months with and without HIPEC, respectively, but no difference in OS between the groups. However, there was a trend toward improved disease-free survival (DFS) in the HIPEC arm in the first 18 months after surgery, and there was an OS benefit in the subset of patients with a Peritoneal Cancer Index (PCI) in the range of 11–15.

While PRODIGE 7 has called into question the role of HIPEC in the treatment of peritoneal metastatic colorectal cancer, it is clear that patients who can undergo complete gross resection of peritoneal metastatic disease can enjoy prolonged survival. These operations are often extensive and can carry significant morbidity, and thus patient selection is paramount to achieving optimal outcomes. The impact of primary tumor sidedness on survival in patients with peritoneal metastatic colorectal cancer is not known. Because sidedness is associated with survival in metastatic disease to other sites, this study aimed to investigate the role of primary tumor sidedness in patients with peritoneal metastatic colon cancer treated with CRS with or without HIPEC. The hypothesis was that sidedness is prognostic of survival in this patient population and should be considered as a stratification factor for future clinical trials in this patient population.

METHODS

Patients and Procedures

This was a retrospective cohort study of the US HIPEC Collaborative Database comprising of data from 12 high-volume academic centers: University of California San Diego, The Ohio State University, Mayo Clinic, MD Anderson Cancer Center, University of Cincinnati, H. Lee Moffitt Cancer Center, Medical College of Wisconsin, Emory University, University of Massachusetts, Johns Hopkins University, City of Hope, and the University of Wisconsin. The Collaborative Database is comprised of 2372 patients with peritoneal surface malignancy treated at these institutions between 2000 and 2017. Data on each of these patients up until 31 December 2017 were collected and submitted to the database. This database has Institutional Review Board approval at all participating centers.

Of 2372 total patients, 428 with colorectal primary cancers treated with CRS were identified. Patients with rectal primary tumors ($n = 25$) were excluded. Tumors originating from the cecum or ascending colon were classified as right-sided and those originating from the descending or sigmoid colon were classified as left-sided. Due to the lack of granularity in describing the exact location (proximal vs. distal) of transverse colon tumors in the database, patients with tumors originating from the transverse colon ($n = 28$) were excluded. Additionally, patients who underwent surgery with palliative-intent ($n = 39$) were excluded.

Cytoreduction and HIPEC was performed by institutional protocols at participating centers. Mitomycin C (median dose 40 mg, range 24–69 mg) was the HIPEC agent utilized in 304 (97%) cases and oxaliplatin (median dose 460 mg, range 380–460 mg) was utilized in 10 (3%) cases. The target temperature for hyperthermia ranged from 39 to 43 °C, but was in the range of 40–43 °C in 80% of cases. The median duration of perfusion was 90 min (range 30–100). HIPEC was performed with a closed technique in 280 (89%) cases and an open technique in 34 (21%) cases.

Statistical Analysis

The database contained approximately 550 variables organized into demographic, preoperative, operative, and postoperative categories. Relevant demographic and clinical variables to our cohort and questions of interest were identified and analyzed. Significant associations were defined as those with a p value < 0.05. Continuous variables were analyzed using the Wilcoxon rank-sum test and then reported as median and range. Categorical variables were analyzed using the Chi square test. The extent of peritoneal tumor burden, as quantified by the PCI, was

determined at the time of CRS/HIPEC and is scaled from 0 to 39, as described by Sugarbaker. The completeness of cytoreduction (CC) was scored by the operating surgeon as CC-0 for no gross disease remaining, CC-1 for residual nodules < 0.25 cm, CC-2 for nodules 0.25–2.5 cm, and CC-3 for nodules > 2.5 cm.

DFS was defined as the time from surgery to the time of recurrence, or the time of last follow-up if no recurrence, while OS was defined as the time from surgery to the time of death, or the time of last follow-up if no death. Only patients who underwent complete cytoreduction (CC-0 or CC-1) were included in survival analyses. Survival analyses were conducted using the log-rank test and expressed with Kaplan–Meier curves. Cox proportional hazards regression was utilized to evaluate the associations between clinical variables and DFS and OS. Any variables that were found to be statically significantly different between the groups at baseline, and/or to have a p value < 0.20 on univariate analysis, were included in multivariate analysis. All analyses were performed using SPSS software (Version 25, IBM Corporation, Armonk, NY, USA).

RESULTS

Patients and Baseline Clinical Variables

A total of 336 patients with primary colon cancer who underwent CRS with or without HIPEC for curative intent were identified. Of this cohort, 179 (53.3%) patients had right-sided primary tumors and 157 (46.7%) had left-sided tumors (Table 1). Patients with right-sided tumors were more likely to be older (median age 57 years vs. 51 years; $p < 0.001$) and male (52% vs. 38%; $p = 0.012$). BMI was noted to be similar between the groups (26 vs. 27 for the right vs. left groups, respectively). Approximately 60% had synchronous peritoneal metastasis at diagnosis, whereas 40% had metachronous disease, although these proportions were not significantly different among patients with right- versus left-sided primary tumors. Nearly 70% of patients in each group had received some form of systemic therapy prior to treatment with CRS.

Of tumor-related variables analyzed, the only statistically significant association with sidedness was perforation (28% for right-sided vs. 15% for left-sided; $p = 0.036$). Tumor differentiation, obstruction, lymphovascular invasion (LVI), perineural invasion (PNI), and others were not significantly different between the groups. Patients with right-sided primary tumors had a higher PCI (median 11 vs. 9; $p = 0.045$) and were less likely to have extraperitoneal disease (16% vs. 27%, $p = 0.021$) than those with left-sided primaries. A total of 314 patients (93.5%) underwent CRS with HIPEC, while 22 (6.5%) underwent curative-intent CRS without HIPEC. The use of HIPEC was more common among patients with right-sided tumors compared with left-sided tumors (96% vs. 90%; $p = 0.037$). Approximately 88% of patients achieved a CC (CC-0 or CC-1) with no significant differences based on tumor sidedness. Other operative variables, such as operative time and estimated blood loss, did not have a significant association with tumor sidedness. The only postoperative variable found to be significantly different was the administration of adjuvant chemotherapy (right 29% vs. left 42%; $p = 0.034$).

Survival

The 297 patients with colon cancer who underwent CC (CC0 or CC1) at CRS were included in the survival analyses (Table 2). In this cohort, only age, sex, and PCI differed significantly at baseline between patients with right- and left-sided primary tumors (data not shown). Median DFS was 12.2 months (95% confidence interval [CI] 13.8–24.0) and was significantly lower in the right-sided group compared with the left-sided group (11.5 months [95% CI 7.6–15.3] vs. 13.1 months [95% CI 9.5–16.8]; $p = 0.158$) (Fig. 1). Univariate analysis demonstrated right-sided tumor (hazard ratio [HR] 1.24, 95% CI 0.92–1.66; $p = 0.161$), PCI (HR 1.04, 95% CI 1.02–1.06; $p < 0.001$), and CC score 1 (HR 1.62, 95% CI 1.09–2.39; $p = 0.016$) were associated with reduced DFS. HIPEC administration was associated with improved DFS (HR 0.24, 95% CI 0.12–0.50; $p < 0.001$). On multivariate analysis, female sex (HR 1.58, 95% CI 1.09–2.30; $p = 0.016$), right-sided primary (HR 1.75, 95% CI 1.19–2.56; $p = 0.004$), HIPEC administration (HR 0.04, 95% CI 0.01–0.33; $p = 0.003$), and PCI (HR 1.04, 95% CI 1.01–1.07; $p = 0.002$) were independent predictors of DFS. Median DFS for patients who underwent complete CRS without HIPEC was 2.90 months (95% CI 0.9–4.9).

Median OS for all patients was 35.0 months (95% CI 26.8–43.2), but was significantly shorter for patients with right-sided primary tumors (30.0 months [95% CI 23.5–36.6] vs. 45.4 months [95% CI 35.9–54.8]; $p = 0.028$) (Table 3, Fig. 2). Univariate analysis demonstrated right-sided primary (HR 1.52, 95% CI 1.04–2.21; $p = 0.030$), PCI (HR 1.08, 95% CI 1.05–1.11; $p < 0.001$), poor differentiation (HR 1.42, 95% CI 0.91–2.18; $p = 0.111$), CC score 1 (HR 3.02, 95% CI 1.95–4.68; $p < 0.001$), and node positivity (HR 1.72, 95% CI 1.14–2.58; $p = 0.010$) were associated with reduced OS. On multivariate analysis, right-sided primary tumor (HR 1.72, 95% CI 1.09–2.73; $p = 0.020$), PCI (HR 1.09, 95% CI 1.05–1.12; $p < 0.001$), and node positivity (HR 2.05, 95% CI 1.30–3.24; $p = 0.002$) were found to be

TABLE 1 Associations between primary tumor sidedness and clinical and operative variables in 336 patients with colon cancer who underwent CRS with or without HIPEC

Baseline variable	Right [*n* = 179]	Left [*n* = 157]	*p* value
Age, years	57 (20–78)	51 (23–95)	< 0.001
Female sex	86 (48)	97 (62)	0.012
BMI	26 (17–44)	27 (18–79)	0.397
Synchronous peritoneal disease	92 (61)	81 (60)	0.934
Differentiation			0.449
Well to moderate	89 (64)	87 (68)	
Poor	51 (36)	41 (32)	
Neoadjuvant chemotherapy	124 (70)	108 (69)	0.932
Adjuvant chemotherapy	43 (24)	50 (32)	0.034
PCI	11 (0–31)	9 (0–32)	0.045
Operative time, min	470 (0–983)	480 (120–1246)	0.901
Estimated blood loss, mL	300 (10–6000)	300 (0–2000)	0.709
HIPEC administration	172 (96)	142 (90)	0.037
CC score			0.671
0	135 (76)	116 (73)	
1	24 (13)	22 (14)	
2	4 (2)	5 (3)	
3	4 (2)	7 (5)	
Unreported	12 (7)	7 (5)	
Extraperitoneal disease	26 (16)	38 (27)	0.021
Total lymph nodes examined	16 (0–80)	14 (0–105)	0.079
Number of positive nodes	1 (0–42)	1 (0–25)	0.192
Any positive nodes	82 (53)	80 (59)	0.283
Primary T stage			0.497
0	1 (1)	1 (1)	
1	0 (0)	0 (0)	
2	3 (2)	6 (4)	
3	50 (32)	53 (39)	
4	98 (64)	75 (55)	
X	2 (1)	1 (1)	
Node-positive	82 (53)	80 (59)	0.283
Perforation	29 (28)	14 (15)	0.036
Obstruction	15 (14)	18 (18)	0.397
LVI	31 (36)	39 (48)	0.130
PNI	17 (21)	21 (28)	0.267

Data are expressed as *n* (%) or median (range)

CRS cytoreductive surgery, *HIPEC* hyperthermic intraperitoneal chemotherapy, *BMI* body mass index, *PCI* Peritoneal Cancer Index, *LVI* lymphovascular invasion, *PNI* perineural invasion, *CC* complete cytoreduction

independent predictors of OS. Median OS for patients who underwent complete CRS without HIPEC was 35.0 months (95% CI 26.3–43.7).

DISCUSSION

It is known that right- and left-sided colon tumors are clinically and biologically different.[2,7,12–14] Right-sided tumors, derived from the embryologic midgut, more often occur in women and more frequently harbor BRAF mutations, microsatellite instability, hypermutation, and mucinous histology. Left-sided tumors, derived from the hindgut, more often exhibit chromosomal instability and pathways that are sensitive to epidermal growth factor receptor (EGFR) inhibitors. Right-sided tumors have repeatedly been shown to be associated with poorer prognosis in the setting of metastatic disease. A recent retrospective analysis of the CRYSTAL and FIRE-3 trials

TABLE 2 Univariate and multivariate Cox regression analyses of factors associated with disease-free survival in 297 patients with colon cancer who underwent CRS/HIPEC with complete cytoreduction (CCR0 or CCR1)

Factor	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Right-sided primary tumor	1.24	0.92–1.66	0.161	1.75	1.19–2.56	0.004
HIPEC administration	0.24	0.12–0.50	< 0.001	0.04	0.01–0.33	0.003
Age	1.01	0.99–1.02	0.320	–	–	–
Female sex	1.02	0.76–1.37	0.913	1.58	1.09–2.30	0.016
BMI	1.00	0.98–1.03	0.829			
PCI	1.04	1.02–1.06	< 0.001	1.04	1.01–1.07	0.002
Extraperitoneal disease	1.17	0.80–1.71	0.414	–	–	–
Poor differentiation	1.38	0.99–1.92	0.057	–	–	–
Adjuvant chemotherapy	0.80	0.58–1.11	0.178			
Node-positive	1.24	0.92–1.69	0.163	–	–	–
Perforation	0.85	0.54–1.33	0.475			
CC score 1	1.62	1.09–2.39	0.016	–	–	–

Multivariate model included right-sided primary tumor, HIPEC administration, age, sex, PCI, tumor differentiation, adjuvant chemotherapy, nodal status, and CC score of 1. Backward model selection was performed

CRS cytoreductive surgery, *HIPEC* hyperthermic intraperitoneal chemotherapy, *HR* hazard ratio, *CI* confidence interval, *BMI* body mass index, *PCI* Peritoneal Cancer Index, *CC* complete cytoreduction

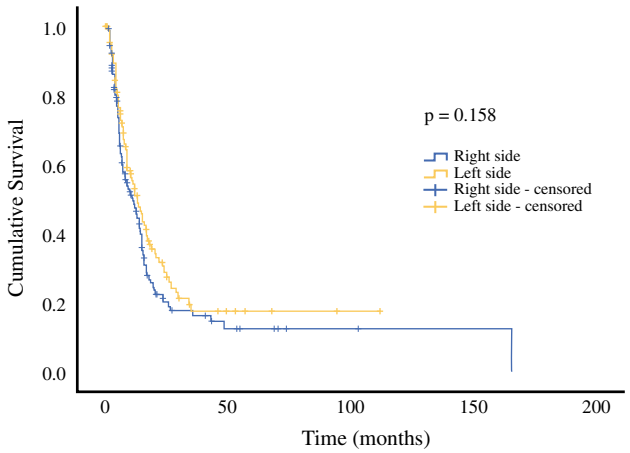

FIG. 1 Kaplan–Meier curve of overall survival in 297 patients with colon cancer who underwent CRS/HIPEC with complete cytoreduction (CCR0 or CCR1) stratified by primary tumor side. *CRS* cytoreductive surgery, *HIPEC* hyperthermic intraperitoneal chemotherapy

showed that primary tumor sidedness was prognostic of OS and predictive of response to cetuximab, even when controlling for RAS mutation status.[15] As a result of this and other reports, it is recommended that tumor sidedness be included as a stratification criterion in systemic therapy trials for patients with stage IV disease.[16]

The aim of the current study was to evaluate the association of primary tumor sidedness with outcome in patients with peritoneal metastatic colon cancer treated with CRS with or without HIPEC. Patients with right-sided primary tumors were slightly older at presentation and were more often male, which is in contrast to previous studies that have shown right sidedness to be associated with female sex. Patients with right-sided primary tumors more often presented with perforation and had a slightly higher PCI, but were less likely to have nodal involvement or extraperitoneal disease than patients with left-sided primaries. They were equally likely to have a CC at CRS and were more likely to receive HIPEC. Despite these differences, having a right-sided primary tumor was an independent predictor of reduced DFS and OS. While prior studies have demonstrated the prognostic importance of tumor-sidedness of patients with metastatic colon cancer receiving systemic chemotherapy or liver-directed therapy, this is the first study to demonstrate that primary tumor sidedness is associated with outcomes after CRS with or without HIPEC.

Additional independent predictors of DFS identified included sex, PCI, and the use of HIPEC. In this study, female sex was an independent predictor of reduced DFS after CRS and HIPEC. This finding has not been reported previously and warrants further investigation. It is established that increasing PCI is prognostic of poor oncologic outcomes in patients with peritoneal metastatic colorectal cancer. The first randomized prospective trial for CRS and HIPEC in this disease demonstrated that patients with a PCI > 25 had extremely poor outcomes, and PCI > 25 was an exclusion criterion for the PRODIGE 7 study. In this study, the use of HIPEC was protective against recurrence. This is an interesting finding considering that there was also a trend toward improved DFS with the use of HIPEC in the PRODIGE 7 trial.[11] Aside from right-sided primary,

TABLE 3 Univariate and multivariate Cox regression analyses of factors associated with overall survival in 297 patients with colon cancer who underwent CRS/HIPEC with complete cytoreduction (CCR0 or CCR1)

Factor	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Right-sided primary tumor	1.52	1.04–2.21	0.030	1.72	1.09–2.73	0.020
HIPEC administration	1.02	0.41–2.51	0.971			
Age	1.01	0.99–1.02	0.507	–	–	–
Female sex	0.85	0.59–1.23	0.390	–	–	–
BMI	0.98	0.95–1.01	0.230			
PCI	1.08	1.05–1.11	< 0.001	1.09	1.05–1.12	< 0.001
Extraperitoneal disease	1.29	0.81–2.04	0.282			
Poor differentiation	1.42	0.92–2.18	0.111	–	–	–
Adjuvant chemotherapy	1.04	0.67–1.62	0.846			
Node-positive	1.72	1.14–2.58	0.010	2.05	1.30–3.24	0.002
Perforation	1.05	0.61–1.81	0.852			
CC score 1	3.02	1.95–4.68	< 0.001	–	–	–

Multivariate model included right-sided primary tumor, PCI, tumor differentiation, and CC score. Backward model selection was performed

CRS cytoreductive surgery, *HIPEC* hyperthermic intraperitoneal chemotherapy, *HR* hazard ratio, *CI* confidence interval, *BMI* body mass index, *PCI* Peritoneal Cancer Index, *CC* complete cytoreduction

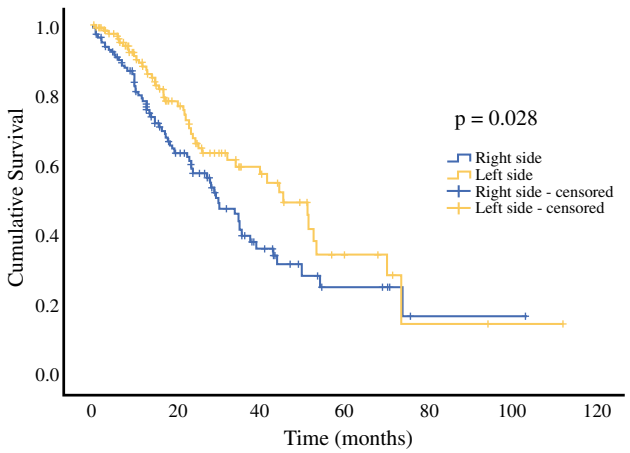

FIG. 2 Kaplan–Meier curve of disease-free survival in 297 patients with colon cancer who underwent CRS/HIPEC with complete cytoreduction (CCR0 or CCR1) stratified by primary tumor side. *CRS* cytoreductive surgery, *HIPEC* hyperthermic intraperitoneal chemotherapy

PCI and nodal metastasis were additional independent predictors of OS. These findings are consistent with other studies that have similarly shown PCI and nodal status to be prognostic after CRS and HIPEC.[9,10,17]

It is important to note that in the current study, DFS and OS were excellent in both right- and left-sided primary disease relative to patients with peritoneal metastatic disease treated with best systemic therapy in previous studies.[8] Patients with right-sided primary tumors had a median OS of 30 months, and those with left-sided primary tumors had a median OS of 45 months. This observation suggests that primary tumor sidedness should not be an exclusion criterion for CRS with or without HIPEC, but it can be used to better inform clinicians and patients about expectations following surgery, and better delineate the risks and benefits of high-risk procedures.

A major limitation of this study is the retrospective design and lack of molecular data on patients in this cohort. Associations between tumor sidedness and specific molecular aberrations, such as microsatellite instability and mutations in RAS, BRAF, SMAD4, APC and PIK3CA, was attempted but these data were not available for the majority of patients (data not shown). Additionally, it is not known why HIPEC was not administered in some patients who underwent curative-intent CRS with CC as these patients were treated prior to the time when PRODIGE 7 was resulted. It could be that HIPEC was not administered due to patient comorbidities, and the observation that HIPEC was associated with improved DFS may be due to selection bias. The strengths of this study include the large sample size, made possible by this multi-institutional collaborative.

CONCLUSIONS

Among patients with metastatic colon cancer with peritoneal dissemination undergoing curative-intent CRS with or without HIPEC, right-sided primary tumor status is independently associated with worse DFS and OS. Along with other important factors such as PCI and nodal metastasis, primary tumor sidedness should be incorporated into patient prognosis and stratification of patients in future clinical trials.

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