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Does Primary Tumor Side Matter in Patients with Metastatic Colon Cancer Treated with Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy?

Kaitlyn J. Kelly, MD[1], Masumah Alsayadnasser, MD[1], Florin Vaida, PhD[2], Jula Veerapong, MD[1], Joel M. Baumgartner, MD, MAS[1], Sameer Patel, MD[3], Syed Ahmad, MD[3], Robert Barone, MD[4], and Andrew M. Lowy, MD[1]

[1]Department of Surgery, Division of Surgical Oncology, Moores Cancer Center, University of California, San Diego, La Jolla, CA; [2]Department of Family Medicine and Public Health, Division of Biostatistics and Bioinformatics, University of California, San Diego, San Diego, CA; [3]Department of Surgery, Division of Surgical Oncology, University of Cincinnati, Cincinnati, OH; [4]Department of Surgery, Sharp Memorial Hospital, San Diego, CA

ABSTRACT

Background. Primary tumor location has been shown to be prognostic of overall survival (OS) in patients with both locally advanced and metastatic colorectal cancer. The impact of sidedness on prognosis has not been evaluated in the setting of peritoneal-only metastases treated with cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC).

Methods. A retrospective review of prospectively maintained databases of patients with peritoneal surface malignancy undergoing CRS/HIPEC from three high-volume centers was performed.

Results. A total of 115 patients with metastatic colon cancer to the peritoneum who underwent CRS/HIPEC with mitomycin C were identified. Fifty-one patients (45%) had left-sided primary tumors, and 64 (55%) had right-sided primary tumors. Patients with right-sided tumors were more likely to be older (median age 56 vs. 49 years, $p = 0.007$) and to have signet ring cell histology (17% vs. 4%, $p = 0.026$). Patients with right-sided tumors had median disease-free survival (DFS) and OS of 14 months (95% confidence interval [CI] 10.5–17.5) and 36 months (95% CI 27.4–44.6), respectively, versus 16 months (95% CI 11.0–21.0) and 69 months (95% CI 24.3–113.7) for those patients with left-sided tumors. On multivariate analysis, primary tumor side was an independent predictor of both DFS and OS.

Conclusions. In this study, there was a dramatic, clinically significant difference in OS between patients with right- and left-sided tumors, and primary tumor side was an independent predictor of DFS and OS. Primary tumor side should be considered in patient selection for CRS with or without HIPEC.

Colon cancer remains the fourth leading cancer by incidence and the second leading cause of cancer-related death in the US, with over 95,000 new cases diagnosed annually. In recent years, multiple advances have been made in the understanding of colon cancer biology, and it has become clear that there are clinical and biological differences in tumors that arise in the right side of the colon (mid-gut origin) versus those that arise on the left side (hind-gut origin). In addition to embryologic origin, the bacterial flora of the right and left colon are distinct. Right-sided colon tumors are more often found in female patients, have a tendency toward more advanced stage at diagnosis, and more often have mucinous histology. In terms of biology, primary tumor sidedness is associated with differences in the rates of microsatellite instability, chromosomal instability, mutations in RAS, BRAF, APC, SMAD4, TP53, and PIK3CA genes, epidermal growth factor receptor (EGFR) pathway alterations, and, perhaps most importantly, prognosis.[1–5]

Patients with tumors arising from the right side of the colon have been shown to have a significantly worse prognosis than those with tumors of the left side in all but

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K. J. Kelly, MD
e-mail: k6kelly@ucsd.edu

early-stage (I/II) disease.[6] This difference in prognosis has been most widely studied in the setting of patients with metastatic disease undergoing treatment with systemic therapy.[5,7–10] More recently, primary tumor sidedness has also been shown to be prognostic in patients with localized disease undergoing surgery and adjuvant therapy,[6,11,12] as well as in patients with regional metastatic disease undergoing curative-intent therapy with resection of liver metastases.[13,14]

Peritoneal metastasis is another form of regional metastasis from colorectal cancer. While much less common than liver metastasis, peritoneal metastasis is associated with a uniquely poor prognosis compared with other sites of metastasis, and, as such, has garnered its own designation as 'M1c' disease in the 8th edition of the American Joint Commission on Cancer (AJCC) staging system.[15,16] Cytoreductive surgery (CRS) with or without hyperthermic intraperitoneal chemotherapy (HIPEC) offers the greatest chance of long-term survival for patients with peritoneal metastatic disease, yet these operations are associated with considerable morbidity. Thus, optimizing patient selection for those most likely to benefit from this aggressive treatment strategy is highly desirable.[17–20,22] The impact of primary tumor location on prognosis for patients with peritoneal metastatic colon cancer treated with CRS/HIPEC is not known.

METHODS

Study Design and Patients

This was a multi-institutional study that included three high-volume centers for CRS/HIPEC: the University of California, San Diego; the University of Cincinnati; and Sharp Memorial Hospital, San Diego. The participating institutions maintain Institutional Review Board-approved prospective databases of patients with peritoneal surface malignancy. A waiver of the Health Insurance Portability and Accountability Act (HIPAA) was obtained and these databases were queried for patients who underwent CRS/HIPEC for colon adenocarcinoma between 1992 and 2016. Right-sided primary tumors were defined as those of the cecum or ascending colon, whereas left-sided primary tumors were defined as those of the descending or sigmoid colon. Patients with appendiceal or rectal primary tumors were excluded. Furthermore, patients with primary tumors of the transverse colon were also excluded, as in other studies,[13] because it was not possible to determine whether these tumors originated from the proximal, middle, or distal transverse colon.

Data

Demographic variables collected included age, sex, and body mass index (BMI), while clinical variables included primary tumor side, differentiation, prior chemotherapy, mucinous histology, signet ring cells, adjuvant chemotherapy, Peritoneal Carcinomatosis Index (PCI), extraperitoneal disease, completeness of cytoreduction (CC) score, total number of lymph nodes examined, and number of positive lymph nodes. Extraperitoneal disease was defined as biopsy-proven or radiographic metastasis to the liver parenchyma or to sites outside of the peritoneal cavity. PCI was determined as described by Jacquet and Sugarbaker, with a possible score of 0–39.[21] CC score was defined as 0 if a complete gross cytoreduction was achieved, 1 if tumor was debulked to deposits < 2.5 mm in thickness, or 2 if residual gross lesions were 2.5 mm–2.5 cm in thickness. Survival analyses were performed for patients who underwent complete cytoreduction (CC-0). Overall survival (OS) was defined as the time from surgery to the time of death by any cause or last follow-up, whereas disease-free survival (DFS) was defined as the time from surgery to the time of documented recurrence or last follow-up.

Statistics

Continuous variables were reported as median and range, and categorical variables were reported as total number and percentage of the total group. Continuous variables were analyzed for association with primary tumor sidedness by non-parametric tests (Wilcoxon rank-sum), and categorical variables were analyzed using the Chi-square or Fisher's exact tests. Significant associations were defined as those with a p value < 0.05. PFS and OS for patients with right- versus left-sided primary tumors were compared using the log-rank test. Univariate Cox proportional hazards regression was utilized to evaluate associations between individual factors and DFS and OS. Variables found to be associated with a p value < 0.20 on univariate analysis, as well as variables of clinical interest, were included in multivariate models to identify independent predictors of DFS and OS. All analyses were reviewed by a biostatistician (FV) using SPSS software version 24 (IBM Corporation, Armonk, NY, USA).

RESULTS

Baseline Clinical and Operative Variables

A total of 115 patients who underwent CRS/HIPEC for colon cancer were identified. Of these, 64 (55%) had right-sided primary tumors and 51 (44%) had left-sided primary

tumors (Fig. 1). Median age was 56 years (range 20–79) for patients with right-sided tumors, and 49 years (range 25–77) for patients with left-sided tumors ($p < 0.05$). Patients with left-sided tumors were more likely to be female (71% vs. 53%), but this difference was not statistically significant. The median BMI was 26 (range 17–43) and was not different between the two groups. A total of 27 patients (42%) with right-sided primary tumors had synchronous peritoneal metastasis, versus 20 patients (39%) with left-sided primary tumors ($p = 0.849$). The majority (> 88%) of patients received systemic chemotherapy prior to CRS/HIPEC. Forty-four percent of patients had poorly differentiated tumors, while 56% had well- to moderately differentiated tumors, and this did not differ between the two groups. More patients with right-sided primary tumors had signet ring cell histology (17% vs. 4%; $p < 0.05$). Approximately 40% of patients in both groups received some form of adjuvant systemic therapy following CRS/HIPEC.

The median PCI found at the time of surgery was 9 (range 0–32). The median operative time was 423 min (range 138–960) and estimated blood loss was 250 mL (range 15–4000). A complete cytoreduction (CC-0) was achieved in 83% of patients, and a CC-1 cytoreduction was achieved in 13% of patients. Five patients (4%) had residual gross disease > 2.5 mm, all of whom had right-sided primary tumors. Ten patients (9%) had extraperitoneal disease. The median number of lymph nodes examined at the time of CRS/HIPEC was 2 (range 0–43), and the median number of lymph nodes involved with disease was 0 (range 0–20). There were no differences in any other operative variables between patients with right- or left-sided primary tumors. Baseline clinical and operative variables are shown in Table 1.

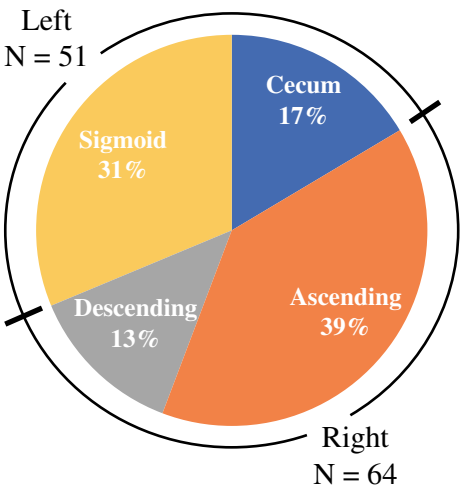

FIG. 1 Distribution of primary tumor site among 115 patients with peritoneal metastatic colon cancer who underwent cytoreductive surgery/hyperthermic intraperitoneal chemotherapy

Disease-Free Survival

A total of 95 patients (83%) underwent complete (CC-0) CRS and were the subject of survival analyses. Median follow-up was 22.0 months. The median DFS for this group was 15.0 months (95% confidence interval [CI] 12.6–17.4), and 14.0 months (95% CI 10.5–17.5) for patients with right-sided primaries compared with 16.0 months (95% CI 11.0–21.0) for those with left-sided primaries ($p = 0.696$) [Fig. 2]. On univariate analysis, the only factors found to be associated with reduced DFS were increasing BMI (hazard ratio [HR] 1.06, 95% CI 1.01–1.12, $p = 0.020$) and poorly differentiated histology (HR 1.82, 95% CI 1.10–3.02, $p = 0.020$). On multivariate analysis, the only independent predictor of reduced DFS was right-sided primary tumor (HR 2.27, 95% CI 1.09–4.76; $p = 0.029$). The results of the univariate and multivariate analyses for DFS are shown in Table 2.

Overall Survival

The median OS for patients undergoing complete cytoreduction was 40.0 months (95% CI 22.8–57.2), and the median OS for those with right-sided primary tumors was 36.0 months (95% CI 27.4–44.6) compared with 69.0 months (95% CI 24.3–113.7) for those with left-sided primary tumors ($p = 0.137$) [Fig. 2]. On univariate analysis, factors found to be associated with reduced OS were increasing PCI (HR 1.05, 95% CI 1.01–1.09, $p = 0.034$) and poorly differentiated histology (HR 2.55, 95% CI 1.18–5.48, $p = 0.017$). On multivariate analysis, independent predictors of reduced OS were right-sided primary tumor (HR 2.57, 95% CI 1.13–5.84, $p = 0.021$), increasing PCI (HR 1.05, 95% CI 1.01–1.10, $p = 0.033$), and poor differentiation (HR 3.64, 95% CI 1.55–8.55, $p = 0.003$). The results of the univariate and multivariate analyses for OS are shown in Table 3.

DISCUSSION

It has been well-established that primary tumor location is an important prognostic factor in metastatic colorectal cancer, such that primary tumor sidedness is now considered a stratification factor for prospective clinical trials of systemic therapies. Several recent studies have shown primary tumor side is also prognostic in patients with regional metastatic disease undergoing curative-intent resection of liver metastasis. Creasy and colleagues reported on a series of 907 patients with long-term follow-

TABLE 1 Baseline clinical and operative data in 115 patients with peritoneal metastatic colon cancer who underwent CRS/HIPEC

	Right [$n = 64$]	Left [$n = 51$]	p value
Baseline variables			
Age, years [median (range)]	56 (20–79)	49 (25–77)	0.007
Female sex	34 (53)	36 (71)	0.057
BMI [median (range)]	26 (17–42)	26 (18–43)	0.759
Synchronous peritoneal disease	27 (42)	20 (39)	0.849
Prior chemotherapy	56 (88)	46 (90)	0.772
Differentiation			0.947
Well to moderate	36 (56)	29 (57)	
Poor	28 (44)	22 (43)	
Mucinous histology	26 (41)	23 (45)	0.630
Signet ring cells	11 (17)	2 (4)	0.026
Adjuvant chemotherapy	27 (42)	20 (39)	0.926
Operative variables			
PCI [median (range)]	9 (0–28)	9 (0–32)	0.791
Operative time, min [median (range)]	412 (138–870)	451 (220–960)	0.387
Estimated blood loss, mL (range)	200 (20–4000)	350 (15–2000)	0.230
CC score			0.105
0	52 (81)	43 (84)	
1	7 (11)	8 (16)	
2	5 (8)	0	
Extraperitoneal disease	4 (6)	6 (12)	0.297
Lymph nodes examined [median (range)]	5 (0–37)	1 (0–43)	0.138
Number of positive nodes (range)	0 (0–20)	0 (0–10)	0.448
Any positive nodes	22 (34)	13 (26)	0.335

Data are expressed as n (%) unless otherwise specified

CRS cytoreductive surgery, *HIPEC* hyperthermic intraperitoneal chemotherapy, *BMI* body mass index, *PCI* Peritoneal Carcinomatosis Index, *CC* completeness of cytoreduction

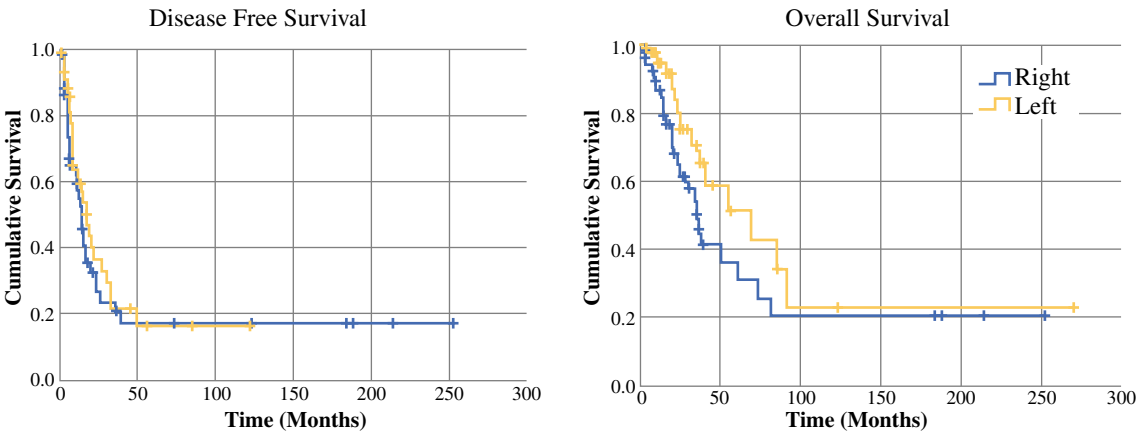

FIG. 2 Kaplan–Meier curves illustrating recurrence-free survival and overall survival in 95 patients who underwent complete cytoreductive surgery/hyperthermic intraperitoneal chemotherapy stratified by primary tumor side

up data available.[13] While primary tumor sidedness was not associated with DFS in this study, the median OS following resection of liver metastases was 3.6 years for patients with right-sided primary tumors versus 5.2 years for those with left-sided primaries ($p = 0.004$). When accounting for other known prognostic clinicopathologic factors, primary tumor side remained an independent predictor of OS.

TABLE 2 Univariate and multivariate analyses of factors associated with disease-free survival

Factor	Univariate analysis			Multivariate analysis[a]		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Right-sided primary tumor	1.19	0.72–1.95	0.498	2.29	1.10–4.77	0.023
Age at surgery	1.01	0.99–1.03	0.124	–	–	NS
Female sex	0.66	0.40–1.11	0.116	–	–	NS
BMI	1.06	1.01–1.12	0.020	1.07	0.99–1.13	0.062
Synchronous peritoneal disease	0.90	0.54–1.49	0.679			
Prior chemotherapy	0.47	0.17–1.30	0.247			
PCI	1.02	0.99–1.06	0.212			
Extraperitoneal disease	1.70	0.77–3.74	0.187	2.20	0.69–6.98	0.203
Poor differentiation	1.82	1.10–3.02	0.020	1.67	0.84–3.36	0.183
Mucinous histology	0.81	0.51–1.27	0.355			
Signet ring cells	1.26	0.60–2.63	0.541			
Nodal metastasis	1.19	0.74–1.91	0.467			
Adjuvant chemotherapy	0.77	0.48–1.26	0.304			

HR hazard ratio, *CI* confidence interval, *NS* non-significant, *BMI* body mass index, *PCI* Peritoneal Carcinomatosis Index

[a]Multivariate model included age at surgery, sex, BMI, right-sided primary tumor, extraperitoneal disease, and differentiation. Backward model selection was performed

TABLE 3 Univariate and multivariate analyses of factors associated with overall survival

Factor	Univariate analysis			Multivariate analysis[a]		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Right-sided primary tumor	1.64	0.85–3.17	0.144	2.53	1.11–5.757	0.021
Age at surgery	1.02	0.99–1.05	0.105	–	–	NS
Female sex	0.55	0.27–1.12	0.109	0.58	0.24–1.44	0.241
BMI	1.00	0.92–1.09	0.970			
Synchronous peritoneal disease	0.69	0.36–1.35	0.277	–	–	–
Prior chemotherapy	1.06	0.32–3.48	0.930			
PCI	1.05	1.01–1.09	0.034	1.06	1.01–1.11	0.026
Extraperitoneal disease	0.78	0.19–3.28	0.738			
Poor differentiation	2.55	1.18–5.48	0.017	3.11	1.27–7.58	0.013
Mucinous histology	1.04	0.76–1.44	0.803			
Signet ring cells	2.47	0.58–10.45	0.219	–	–	NS
Nodal metastasis	1.45	0.75–2.78	0.269			
Adjuvant chemotherapy	0.95	0.46–1.93	0.878			

HR hazard ratio, *CI* confidence interval, *NS* non-significant, *BMI* body mass index, *PCI* Peritoneal Carcinomatosis Index

[a]Multivariate model included age at surgery, sex, signet ring cell histology, right-sided primary tumor, PCI, and differentiation. Backward model selection was performed

Patients with peritoneal metastatic colorectal cancer have a distinctly poor prognosis, with a median OS of 12–16 months with best-available systemic therapy.[15] Along with systemic therapy, CRS with or without HIPEC has been adopted as the standard-of-care for selected patients with isolated peritoneal metastasis because a median survival of up to 40 months can be achieved with complete (CC-0) cytoreduction.[18,19] Factors known to be associated with recurrence and death following CRS/HIPEC in colorectal cancer include high PCI, incomplete cytoreduction, lymph node metastasis, and poorly differentiated disease. To our knowledge, the impact of primary tumor sidedness on prognosis in patients with peritoneal metastatic disease treated with CRS/HIPEC has not been previously reported.

In the current study, patients with right-sided primary tumors tended to be older and were more likely to have signet ring cell histology. In this cohort, female sex and mucinous histology were not more frequent in right-sided disease. All patients with gross residual disease > 2.5 mm (CC score > 1) had right-sided primary tumors. In considering the subset of patients who underwent complete (CC-0) cytoreduction, primary tumor sidedness was not associated with DFS on univariate analysis, but when accounting for other variables, it emerged as the only independent predictor of relapse. Possible explanations for this finding include the relatively small sample size and confounding variables, which can mask an association on univariate analysis. Other possibilities include unbalanced group sizes, missing data, and interacting variables, however these factors were not present in this study. Patients with a right-sided primary tumor had a median OS of 35.0 months, essentially half that of patients with left-sided primaries, who had a median OS of 69.0 months. While this difference was not statistically significant on univariate analysis, it was on multivariate analysis, accounting for other clinical factors, including age, sex, poor differentiation, signet ring histology, and PCI. Other independent predictors of OS were PCI and degree of tumor differentiation.

Limitations of this study include its retrospective design, with inability to accurately localize transverse colon lesions, and a lack of data on molecular aberrations. DFS is a difficult endpoint to measure in a retrospective study as surveillance imaging was performed at variable time points. In addition, this is a relatively small cohort of patients who received individualized systemic therapies. Only 2–5% of patients with colorectal cancer have isolated peritoneal metastasis and up to 20% have peritoneal metastasis along with disease at other sites, therefore this is a difficult population to study prospectively.

To date, only two randomized prospective trials of CRS/HIPEC for patients with colorectal cancer have been conducted that were successful in completing planned accrual. The first, performed 15 years ago, showed a survival benefit for CRS/HIPEC, but major limitations were the use of an outdated systemic therapy regimen (5-fluorouracil $\pm$ irinotecan) in both arms and the inclusion of a small cohort of appendiceal cancer patients.[20] The more recent study, entitled PRODIGE 7, has not yet been published, but was presented in abstract form in 2018. This was a multicenter study in which 265 patients who underwent a complete or near-complete cytoreduction (residual tumor nodules < 1 mm) were randomized to receive HIPEC versus CRS alone, with both groups receiving modern systemic therapy. At a median follow-up of 64 months, median survival in the two treatment arms was essentially the same, at 41.2 months in the non-HIPEC arm and 41.7 months in the HIPEC arm. A subgroup analysis found a significant improvement in survival (HR 0.4) favoring the HIPEC arm for patients with a PCI of 11–15, while no difference was observed for patients with either lower or higher disease burdens.[22] While this study did not show an overall survival benefit in the HIPEC arm, it did demonstrate excellent survival with complete CRS.

CONCLUSIONS

The results of the PRODIGE 7 study, as well as those from the current study and others, clearly demonstrate that surgical resection for fit patients with isolated peritoneal metastases from colorectal cancer can result in long-term survival and should be adopted as a standard of care. The value of HIPEC in patients with intermediate disease burdens, and other HIPEC regimens beyond that examined in PRODIGE7, deserve further study. Regardless, it is clear that a key driver of successful outcomes following CRS with or without HIPEC in patients with metastatic colorectal cancer is proper patient selection. The median survival of 69.0 months in patients with left-sided colon primaries in this study is among the longest median OS ever reported for patients with peritoneal metastatic colorectal cancer. These findings suggest that primary tumor sidedness should be considered in patient selection for CRS, with or without HIPEC, for metastatic colorectal cancer. Moreover, as sidedness has been demonstrated to be of prognostic value in systemic therapy trials, it should similarly be utilized as a stratification factor in future prospective surgical studies.

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