Original Article

Variation in Hospital Treatment Patterns for Metastatic Colorectal Cancer

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BACKGROUND: There are many treatment options for metastatic colorectal cancer (CRC). However, to the authors' knowledge, national treatment patterns for metastatic CRC, and the stability of hospital treatment patterns over time, have not been well described. **METHODS:** Data from the 2006 through 2011 National Cancer Data Base were used to study adults with newly diagnosed metastatic CRC (84,161 patients from 1051 hospitals). Using hierarchical models, the authors characterized hospital volume in the use of different treatment modalities (primary site resection, metastatic site resection, chemotherapy, and palliative care). The authors then assessed variation in the receipt of treatment according to the hospitals' relative volume of services used. Finally, the extent to which hospital treatment patterns changed over the past decade was examined. **RESULTS:** Overall use of volume of services varied widely (5.0% in the hospitals with low volumes of service to 22.3% in the hospitals with high volumes of service). As hospitals' volumes of services increased, adjusted rates of metastatic site surgery (6.6% to 30.8%; $P<.001$) and multiagent chemotherapy (37.8% to 57.4%; $P<.001$) use increased, but primary site resection demonstrated little variation (56.8% vs 59.5%; $P=.024$). It is interesting to note that use of palliative care also increased (8.1% to 11.3%; $P=.002$). Hospital treatment patterns did not change over time, with hospitals with high volumes of service consistently using more metastatic site resection and multiagent chemotherapy than hospitals with low volumes of service. **CONCLUSIONS:** There is wide variation in hospital treatment patterns for patients with metastatic CRC, and these patterns have been stable over time. It appears that much of the approach for metastatic CRC treatment depends on the hospital in which the patient presents. ***Cancer*** **2015;121:1755-61.** © *2015 American Cancer Society.*

KEYWORDS: metastasis, colorectal cancer, metastatic, hospital variation, patterns of care.

INTRODUCTION

Nearly 20% of patients with colorectal cancer (CRC) present with metastasis at the time of diagnosis.[1-3] Historically, liver metastasis portended a dismal prognosis because of limited therapeutic options.[2,4] However, over the last 20 years, there have been expansions in both systemic treatment options and liver-directed interventions, including improved results with liver surgery because of better techniques and more specialty-trained surgeons.[5-12] With contemporary treatment modalities, recent reports cite a nearly 30-month survival among patients with metastatic CRC, compared with historic survival rates of 8 months without treatment.[13-15]

Nevertheless, to the best of our knowledge, there is little consensus regarding optimal treatments for this patient population,[16,17] and increasing concerns that patients are not being appropriately referred for chemotherapy and surgical resection.[18,19] To date, national patterns of care for patients with metastatic CRC have not been well described. Although decisions for any given patient with metastatic CRC depend on clinicopathologic characteristics and individual preferences, it is possible that treatments are influenced by where a patient presents for care. In addition, the question of how quickly clinical advances for metastatic CRC diffuse across the country has not been fully examined previously.

In the current study, we used national clinical registry data to assess treatment patterns for patients with metastatic CRC. Our goal was to determine the degree to which different treatment modalities such as metastatic site surgery or multiagent chemotherapy can characterize a hospital's overall "aggressiveness" in treatment. We also assessed what hospital attributes were associated with treatment, and to what extent treatment patterns have changed over the past decade.

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The data used in the study were derived from a deidentified National Cancer Data Base file. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology used, or the conclusions drawn from these data by the investigators.

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MATERIALS AND METHODS

Data Source and Study Population

We used data from the National Cancer Data Base (NCDB) Participant User File (PUF). The NCDB is a joint project of the American College of Surgeons Commission on Cancer (CoC) and the American Cancer Society. Data from >1500 CoC-accredited hospitals represent nearly 70% of all newly diagnosed patients with cancer in the United States and are collected using standardized coding schemata. Details of data abstraction have been previously described, and it is important to note that CoC programs are required to identify treatment that their patients received from all sources, even if the treatment occurred at facilities other than theirs.[20,21] To allow for attribution of 1 patient to 1 hospital, patients were assigned to a CoC-accredited hospital for analysis if they received their first treatment course at the reporting facility.

We identified all patients aged >17 years who presented with metastatic cancer of the colon, rectosigmoid, or rectum from 2006 through 2011 using *International Classification of Diseases for Oncology, 3rd Edition* topographical and histology codes. Patients with unknown treatment status or who were missing information regarding metastatic disease assessment were excluded from analysis. We also excluded patients who were treated at hospitals with <20% chemotherapy administration for AJCC stage III CRC because this likely reflects incomplete documentation,[22,23] and patients at hospitals with a very low annual volume of patients with stage IV disease (<5 patients with stage IV metastatic CRC per year) to reduce random variation caused by small sample sizes.

To stratify hospitals for analysis, we defined use of a high volume of services based on the percentage of patients in each hospital receiving all 3 of the following modalities for their disease: primary site resection, metastatic site resection, and chemotherapy (single-agent or multiagent). Metastatic site resection was defined as resection of disease from distant organ sites and/or distant (nonregional) lymph node basins. Surgical treatment denoted in the PUF as palliative care treatment was not considered metastatic site resection. Other outcomes included receipt of single-agent or multiagent chemotherapy, primary site resection (excluding destruction, fulguration, and transanal excisions when used as a solitary treatment), and palliative care.

Statistical Analysis

Variation in hospital volumes of service

We first assessed variation in treatment strategies among hospitals. To do this, we used random intercept hierarchical logistic regression models specifying the hospital as the higher level, and adjusted all outcomes for patient age, sex, and race, as well as their interactions, patient primary insurer, median ZIP code income and education levels, Charlson/Deyo score,[24] and primary tumor location as covariates. Hierarchical models account for within-hospital and between-hospital outcome variation and minimize the influence of random variation from small sample sizes on model-based estimates.[25-27] Hospitals were grouped into equal quintiles of use ("volumes of service") based on the adjusted percentages of patients undergoing primary and metastatic site resections as well as chemotherapy.

Patient demographics and tumor characteristics as well as hospital attributes (CoC accreditation status and US census region) were compared across hospital quintiles, ranging from hospitals with low volumes of service (HLVS) to hospitals with high volumes of service (HHVS). In addition, we examined adjusted rates of chemotherapy use (single-agent and multiagent), primary site resection, metastatic site resection, and use of palliative care services to determine the relative use of treatments across hospital quintiles.

Hospital treatment patterns over time

We assessed temporal changes in hospital treatment patterns. To achieve this, we used additional data from the NCDB PUF for the years 2003 and 2004 to characterize hospitals' volumes of service between 2003 and 2004 and grouped them into quintiles using the same methods described above. We then used hospitals' volumes of service from 2003 through 2004 as a benchmark to compare their treatment rates over 3 subsequent time periods: 2005 through 2006, 2007 through 2008, and 2009 through 2011. The earlier data points were not used for the primary analysis. Specifically, we assessed adjusted rates of overall volumes of service, as well as use of primary site resection, metastatic site resection, multiagent chemotherapy, and palliative care for each time period.

Finally, to assess the robustness of our findings, we performed several sensitivity analyses. In one, we restricted the study cohort to patients with definitive T classification of their primary tumor because these patients were more likely to have undergone resection of their primary site of disease. In another, we restricted the cohort to "average-risk" patients, defined a priori as those aged <80 years, who did not refuse any treatment modality, and who were not deemed to be high risk by their treating physician. In another, we excluded treatment with single-agent chemotherapy, thereby only defining aggressive treatment as

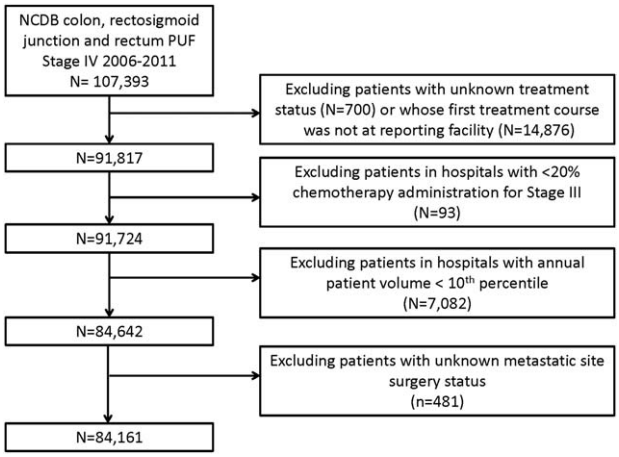

Figure 1. Study cohort derivation is shown. NCDB indicates National Cancer Data Base; PUF, Participant User File.

multiagent chemotherapy in addition to primary site and metastatic site resections.

We performed all statistical analyses using Stata Release 12 statistical software (StataCorp LP, College Station, TX). All reported *P* values were 2-sided with alpha set at $P = .05$. Model discrimination was evaluated using the c-statistic and calibration was assessed with the Hosmer-Lemeshow goodness-of-fit test.[28,29] The study protocol was reviewed and deemed "not regulated" by the University of Michigan Institutional Review Board.

RESULTS

We initially identified 107,393 patients with metastatic CRC in the NCDB PUF for 2006 through 2011. After applying exclusion criteria, the cohort included 84,161 patients treated in 1051 hospitals, as shown in Figure 1. Over the study period, 48,525 patients (57.7%) underwent nonpalliative primary site resection, 47,026 patients (55.9%) received chemotherapy (40,203 [47.8%] of whom received multiagent and 6823 [8.1%] of whom received single-agent treatments), and 15,847 patients (18.8%) underwent nonpalliative resection of metastatic disease. All 3 therapies were used in 8688 patients (10.3%).

Patient and hospital characteristics, stratified by quintiles, ranging from HLVS to HHVS, are shown in Table 1. Receipt of treatments varied from 5.0% in the HLVS hospitals to 22.3% in the HHVS (*P* for trend $<.001$). Compared with the HLVS quintile, patients in the HHVS were, on average, slightly younger, more frequently black, more likely to have private insurance, and more likely to have multiple comorbid conditions as measured by a Charlson/Deyo score of at least 2. Hospitals in the HHVS quintile were more likely to have an academic/research classification (28.6% vs 16.6%) and were more likely located in the Great Lakes/Midwest regions (35.7% vs 19.9%) compared with those in the HLVS quintile. There was a relative decrease in the representation of comprehensive community cancer centers in the HHVS quintile (52.9% vs 61.1%). Patient volumes were higher in the HHVS quintile hospitals (18.9 vs 14.0 patients/year).

Variation in treatment modalities as well as palliative care use across hospitals is shown in Figure 2. What constituted the services rendered for cancer treatment varied across hospitals. For example, rates of metastatic site surgery varied the most across hospitals (6.6% in the HLVS to 30.8% in the HHVS; *P* for trend $<.001$), whereas primary site resections varied the least (56.8% vs 59.5%, respectively; *P* for trend $= .024$). Use of multiagent chemotherapy increased as hospital overall aggressiveness increased (37.8% to 57.4%; *P* for trend $<.001$), whereas use of single-agent chemotherapy was found to be similar across hospitals (8.1% to 8.3%; *P* for trend $= .249$). Adjusted rates of palliative care were lowest in the HLVS, and tended to increase as volumes of service increased (8.1% to 11.3%; *P* for trend, .002). The study cohort for 2003 through 2011 that was used to assess temporal changes in treatment included 114,068 patients. In general, the past treatment patterns of hospitals were strong predictors of their future treatment patterns, and differences between hospitals with regard to their rates of therapy use did not appreciably change over time, as shown in Table 2. HHVS (based on past treatment rates) had consistently higher rates of metastatic site resection, multiagent chemotherapy, and palliative care use compared with HLVS over time. Table 2 displays the adjusted odds of receiving various treatments for patients treated in HHVS versus HLVS based on past treatment patterns, after accounting for patient age, sex, race, insurance type, ZIP code-level income and education levels, comorbidities, and primary tumor location. For example, between 2005 and 2006, patients treated in HHVS versus HLVS had 2.85 the odds (95% confidence interval, 2.38-3.40) of undergoing metastatic site surgery. Between 2009 and 2011, the same patients had 2.08 the odds (95% confidence interval, 1.75-2.47) of undergoing metastatic site surgery. In contrast, primary site resection rates were similar across quintiles over time, and converged by the most recent time period evaluated.

The sensitivity analyses confirmed the trends we observed. Variation in hospital relative volumes of service and its components persisted when assessing "average-

TABLE 1. Hospital and Patient Characteristics Across Quintiles of Hospital Volumes of Service[a]

Quintile of hospital volumes of service	Q1 HLVS	Q2	Q3 Average	Q4	Q5 HHVS
No. of hospitals	211	210	210	210	210
Adjusted receipt of high volumes of service, % of patients	5.0	7.8	10.6	14.7	22.3
Hospital Characteristics			No. of Hospitals (%)		
Mean no. of patients with AJCC stage IV disease/y (SD)[b]	13.8 (8.4)	13.3 (9.6)	16.1 (11.7)	16.0 (10.8)	18.9 (15.6)
Facility type[b]					
Community cancer center	45 (21.3)	59 (28.1)	43 (20.5)	44 (21.0)	39 (18.6)
Comprehensive community cancer center	129 (61.1)	130 (61.9)	122 (58.1)	112 (53.3)	111 (52.9)
Academic/research cancer center	35 (16.6)	21 (10.0)	44 (21.0)	54 (25.7)	60 (28.6)
Facility census region[b]					
Atlantic	27 (12.8)	32 (15.2)	37 (17.6)	34 (16.2)	27 (12.9)
Northeast	8 (3.8)	18 (8.6)	14 (6.7)	20 (9.5)	11 (5.2)
Great Lakes/Midwest	43 (20.4)	43 (20.5)	51 (24.3)	70 (33.3)	77 (36.7)
Mountain/West/Pacific	71 (33.7)	63 (30.0)	54 (25.7)	40 (19.1)	30 (14.3)
South/Southeast	62 (29.4)	54 (25.7)	53 (25.2)	46 (21.9)	65 (31.0)
Patient Characteristics			No. of Patients (%)		
Mean age (SD), y[b]	65.9 (13.9)	66.6 (14.1)	66.3 (13.9)	65.7 (14.2)	64.5 (14.2)
Female sex	7312 (47.9)	6788 (47.9)	8259 (47.9)	8313 (48.4)	9651 (47.6)
Race[b]					
White	10,339 (67.7)	9662 (68.1)	12,054 (69.9)	11,897 (69.3)	14,259 (70.3)
Black	2357 (15.4)	1816 (12.8)	2270 (13.2)	2370 (13.8)	3070 (15.1)
Hispanic	970 (6.4)	1176 (8.3)	1094 (6.3)	688 (4.0)	612 (3.0)
Asian/Pacific Islander	494 (3.2)	470 (3.3)	398 (2.3)	406 (2.4)	460 (2.3)
Other	1107 (7.3)	1056 (7.4)	1437 (8.3)	1805 (10.5)	1894 (9.3)
High school degree by ZIP code (%)[b]					
>80%	7107 (46.6)	6673 (47.1)	6910 (40.1)	6529 (38.0)	8350 (41.1)
≤80%	7412 (48.5)	6691 (47.2)	9200 (53.3)	9725 (56.7)	10,811 (53.3)
Unknown	748 (4.9)	816 (5.8)	1143 (6.6)	912 (5.3)	1134 (5.6)
ZIP code-level median income[b]					
<$34,999	5858 (38.4)	4578 (32.3)	5706 (33.1)	5385 (31.4)	6712 (33.1)
>$35,000	8663 (56.7)	8787 (62.0)	10,404 (60.3)	10,869 (63.3)	12,449 (61.3)
Unknown	746 (4.9)	815 (5.7)	1143 (6.6)	912 (5.3)	1134 (5.6)
Primary insurer[b]					
Private	4950 (32.4)	4830 (34.1)	5913 (34.3)	6171 (35.9)	7769 (38.3)
Medicare	7486 (49.0)	7215 (50.9)	8749 (50.7)	8377 (48.8)	9749 (48.0)
Other	1789 (11.7)	1402 (9.9)	1649 (9.6)	1755 (10.2)	1884 (9.3)
Not insured	1042 (6.8)	733 (5.2)	942 (5.5)	863 (5.0)	893 (4.4)
Charlson/Deyo score ≥2[b]	1058 (6.9)	985 (6.9)	1282 (7.4)	1350 (7.9)	1563 (7.7)
Primary tumor location[b]					
Colon	11,436 (74.9)	10,650 (75.1)	12,793 (74.1)	12,732 (74.2)	14,983 (73.8)
Rectosigmoid junction	1306 (8.6)	1187 (8.4)	1500 (8.7)	1412 (8.2)	1691 (8.3)
Rectum	2525 (16.5)	2343 (16.5)	2960 (17.2)	3022 (17.6)	3621 (17.8)

Abbreviations: HHVS, hospitals with high volumes of service; HLVS, hospitals with low volumes of service; Q, quintile; SD, standard deviation.
[a] Models used to derive hospital-adjusted service volumes accounted for patient age, sex, race, insurance type, ZIP code-level income and education levels, comorbidities, and primary tumor location.
[b] Univariate *P* value was <.05 (derived from analysis of variance/Pearson chi-square test).

risk" patients or those with liver-only metastases. When excluding patients aged >80 years and without a high comorbidity burden, hospital treatment rates were generally higher, but the stability of treatment patterns persisted in the same fashion as above. When assessing patients with definitive T classifications, rates of receipt of multiagent chemotherapy and metastatic site surgery were increased overall, but with persistent variation noted across hospitals and the same overall temporal trends as in the primary analysis. Differences in hospital characteristics across the quintiles demonstrated the same trends as in the primary analysis.

DISCUSSION

Using national clinical registry data, the results of the current study demonstrated broad variation in hospital treatment patterns for metastatic CRC. There were wide differences noted in the volumes of service rendered, driven in large part by differential rates of metastatic site resection and chemotherapy use across hospitals, rather than differential rates of primary site resection. It is interesting to note that hospitals' volume of cancer-directed treatments paralleled their use of palliative care services. Higher volumes of service were notably observed in hospitals with higher levels of cancer center accreditation.

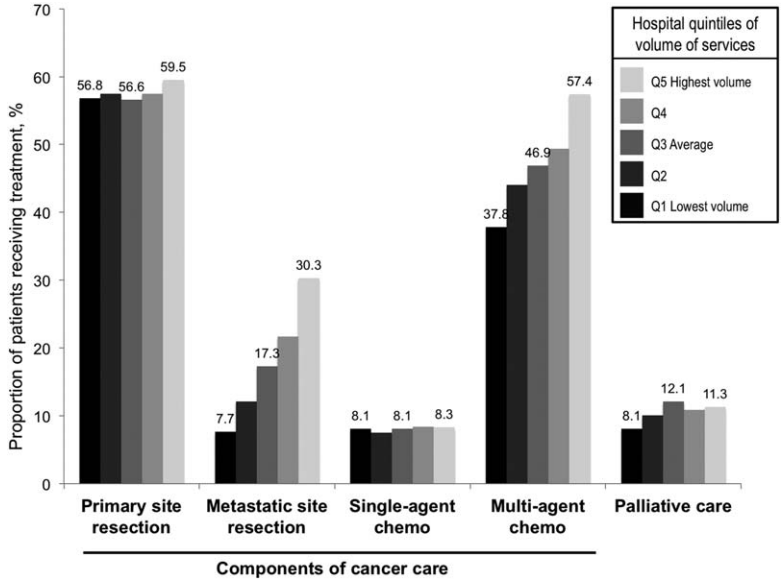

Figure 2. Treatment modality variation is shown across levels of hospital volume of services. chemo indicates chemotherapy; Q, quintile.

Moreover, hospitals' treatment patterns were stable over the past decade. These findings suggest that, to a large degree, the treatment of patients with metastatic CRC is dictated not by the disease itself, but by the cancer program in which the patient is treated.

Patterns in metastatic CRC treatment have been difficult to define. In the current study, we found structural and regional differences across volumes of service, suggesting that both area-level and hospital-level attributes contribute to differences in treatment. Regional differences in resource use and intensity of care are well described, both from a cost and payment perspective.[30-32] Similar variation in volumes of service at a hospital level are noted in this large database. These findings suggest that although clinicopathologic factors certainly influence treatment, much of the approach toward metastatic CRC depends on the hospital at which the patient is treated. It is interesting to note that those hospitals with the highest volumes of service for the treatment of metastatic CRC also generally had a higher use of palliative care. This finding may reflect nuanced differences in the philosophy of those hospitals toward overall cancer care in general, rather than simply offering "aggressive" care to every patient. Variation within any given hospital could certainly reflect patient preferences, but also could reflect how physicians within a certain hospital approach treatments differently and whether that is more highly influenced by patient or provider characteristics is unknown.

In addition to displaying broad variability, hospital treatment patterns were found to be largely unchanged over the past decade. For other cancers with poor prognoses (eg, esophagus, pancreas), there has been a trend toward offering more surgical treatments to older and sicker patients.[33] To the best of our knowledge, whether patients with metastatic CRC are treated similarly has not been as extensively investigated on a national basis. The complement of efficacious therapies for metastatic disease, including chemotherapy, biological agents, surgical resection, and nonsurgical liver-directed interventions, continues to expand.[6,7,13,16,34] At the same time, there are more specialty-trained liver surgeons and overall decreases in morbidity and mortality associated with liver surgery.[12,35] Despite this, it appears that these advances have not been promulgated across the country and may be limited only to a subset of hospitals that may have already demonstrated an approach toward overall cancer care that is demonstrated by not only generally higher volumes of service but a higher use of palliative care.

It is also possible that differential knowledge and understanding of the treatment options for metastatic CRC breeds variation in care patterns. It has been demonstrated that rates of adherence to recommended treatment measures for cancer are highly correlated with the level of evidence supporting them.[36,37] In contrast with other stages of CRC, to the best of our knowledge there are fewer standardized treatments for metastatic disease that

TABLE 2. Effect of Hospitals' Past Use of High Volumes of Service on Adjusted Odds of Receiving Different Treatments[a]

	Adjusted OR of Receiving Treatment if Diagnosed in HHVS Versus HLVS Based on 2003 Through 2004 Treatment Patterns (95% CI)		
Treatment	2005 to 2006	2007 to 2008	2009 to 2011
Primary site surgery	1.13 (1.01-1.27)	1.02 (0.91-1.14)	1.00 (0.89-1.13)
Metastatic site surgery	2.85 (2.38-3.40)	2.31 (1.94-2.76)	2.08 (1.75-2.47)
Multiagent chemotherapy	2.05 (1.75-2.41)	1.87 (1.59-2.19)	1.73 (1.49-2.01)
Palliative care	1.89 (1.38-2.57)	1.52 (1.14-2.04)	1.32 (0.99-1.74)

Abbreviations: 95% CI, 95% confidence interval; HHVS, hospitals with high volumes of service; HLVS, hospitals with low volumes of service; OR, odds ratio.

[a] Models used to derive hospital-adjusted service volumes accounted for patient age, sex, race, insurance type, ZIP code-level income and education levels, comorbidities, and primary tumor location. Patterns persisted in sensitivity analyses (excluding patients without definitive T classification or excluding elderly patients, those who refused treatment, or those who were deemed too high risk for any treatment).

carry strong guideline endorsement and there are few guidelines for the use of palliative services.[17,31,36,37] Furthermore, the indications and timing for resection, both for the primary tumor and metastases, continue to evolve.[9,13,16,38,39] Finally, emerging evidence suggests substantial heterogeneity in physicians' understanding of what constitutes "resectable" disease.[18,40,41]

There are important limitations to the current study. First, we were unable to assess the extent to which treatment represented appropriate care. However, our intent was to provide an assessment of variations in national treatment patterns independent of inferences regarding appropriate care at the individual patient level. Similarly, due to limitations of the PUF data, we could not assess factors relevant to patient selection, surgical decision-making (eg, size and location of metastases), and type and sequencing of multimodality treatments (eg, choice of agents and use of agents preoperatively or postoperatively). However, the observed variation in resection rates was not substantially altered when focusing on "average-risk" patients or patients with liver-only metastases, and therefore is unlikely to be fully explained by differences in patients' resectability. Second, we were unable to assess patients with metachronous metastatic disease due to the lack of these types of data in the NCDB PUF. As such, the results of the current study should be interpreted within the context of patients with metastatic disease at the time of presentation. Third, we could not assess use of certain liver-directed interventions (such as radiofrequency ablation or transarterial chemoembolization) if they were not included as a part of a surgical procedure. Finally, these data represent a group of hospitals meeting stringent structural, process, and patient volume accreditation requirements by the CoC, which tend to be generally larger, more frequently urban, and have more cancer-related services available to patients than other hospitals.[42] These results may not be generalizable to all hospitals, but these data are representative of the vast majority of hospitals in the United States most likely to treat this patient population, although referral patterns are not able to be defined.

There is broad variation in how hospitals approach the treatment of patients with metastatic CRC, including the use of palliative care services. Moreover, the stability of hospitals' treatment patterns suggests that a particular hospital's generalized approach to cancer care may have as strong an influence on a patient's treatment as their disease status. Why such differences in treatment patterns persist are unclear because improved outcomes after certain treatment strategies are widely reported in the literature. Improvement of care may involve improved knowledge dissemination, increased multidisciplinary collaboration between medical and surgical oncologists in treatment decisions, and, when appropriate, increased referral to specialty centers for patients with metastatic CRC.

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CONFLICT OF INTEREST DISCLOSURES

Dr. Krell received payment from Blue Cross/Blue Shield of Michigan for data entry for work performed outside of the current study.

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