

## Editorial

# What Is the Best Treatment for Stage IV Colorectal Cancer?

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For decades, clinicians have seen patients who present with extensive stage IV colorectal cancer, frequently with hepatomegaly, weight loss, and poor performance status. Such patients receive supportive care or, if performance status allows, a trial of systemic chemotherapy. With the increased use of preoperative imaging, clinicians are now seeing many patients who present with asymptomatic or minimally symptomatic stage IV colorectal cancer. Management of such patients lacks a significant evidence base. Cook et al.<sup>1</sup> have used the Surveillance, Epidemiology, and End Results (SEER) database from 1988 to 2000 to analyze the patterns of care of such patients. The authors have thoughtfully analyzed these population-based data and have carefully couched their conclusions with appropriate caveats. The data are quite clear in demonstrating that most patients undergo surgical resection of their primary tumors despite the presence of unresectable distant disease—hence, palliative surgery. The SEER data are incomplete in pivotal areas, and this invalidates comparisons of up-front operation versus systemic chemotherapy followed by surgical resection only for subsequent obstruction, perforation, or hemorrhage. The median survival for initial-resection patients was 11 months, compared with 2 months for those who did not undergo resection. These differences suggest that the groups were vastly different with regard to the extent of disease and comorbidities; these elements are not captured in the SEER database. In addition, many patients who present with stage IV

disease have the diagnosis made at the time of primary tumor resection, at which time the decision for resection has already been made.

The authors<sup>1</sup> clearly define the key arguments: elective operations have a much lower morbidity and mortality than emergency operations, so we should remove the primary tumor and then proceed with chemotherapy with hopes for a good response. However, additional issues relevant to this paradigm are that (1) initial operative intervention (with or without laparoscopic-assisted resection) delays systemic chemotherapy; (2) with recent advances in systemic therapies, median survival with metastatic disease approaches 2 years; (3) it is likely that response at metastatic sites will also be associated with tumor regression at the primary tumor site; and (4) obstruction is uncommon with proximal cancers. We do not know the natural history of unresected primary tumors in patients receiving state-of-the-art chemotherapy who survive 2 to 3 years with initial stage IV cancer.

In the absence of prospective clinical data (either randomized or a broad cohort of well-defined clinical and tumor data), stage IV colorectal cancer patients may be treated on the basis of the extent of metastatic disease, comorbidities, location of the primary tumor, symptoms related to the primary tumor, age, and the desire for and likelihood of tolerating systemic chemotherapy. My personal management algorithm is summarized in Table 1.

Rectosigmoid and rectal cancer patients are more problematic than those with colon cancer. Abdominoperineal resection is not an attractive palliative operation. Six weeks of radiotherapy may stop or prevent bleeding, but it is time-consuming and uncomfortable. The main clinical challenge is the large cohort of patients with stage IV disease and asymptomatic or minimally symptomatic distant

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**TABLE 1.** *Management algorithm*

Primary tumor location	Primary symptoms	Extent of metastatic disease	Initial primary operation
Colon	None	Minimal	Yes
Colon	None	Extensive	No
Colon	Yes	Any	Yes
Rectosigmoid	Any	Minimal	Yes
Rectosigmoid	None	Extensive	No
Rectum	None	Minimal	No
Rectum	Yes	Minimal	Yes: APR or XRT
Rectum	Yes	Extensive	Yes: colostomy

APR, abdominoperineal resection; XRT, radiotherapy.

disease. Symptoms may be related to partial obstruction or gross or occult bleeding with anemia. The presence of iron-deficiency anemia alone should not be an indication for operative resection without a trial of appropriate anemia treatment.

Only a randomized trial will clarify the most appropriate management strategy: primary tumor resection with postoperative chemotherapy versus systemic chemotherapy with operation only for obstruction, hemorrhage, or perforation (at a time that the patient is not moribund from metastatic cancer). End points would be overall survival and quality-of-

life indicators. Cook et al.<sup>1</sup> have provided the benchmark data to justify such a trial. The National Surgical Adjuvant Breast and Bowel Project (NSABP) has begun a Phase II trial of upfront chemotherapy.

#### REFERENCE

1. Cook AD, Single R, McCahill LE. Utilization of surgical resection of primary tumors in patients presenting with stage IV colorectal cancer: an analysis of SEER data, 1988–2000. *Ann Surg Oncol* (in press).

# Surgical Resection of Primary Tumors in Patients Who Present With Stage IV Colorectal Cancer: An Analysis of Surveillance, Epidemiology, and End Results Data, 1988 to 2000

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**Background:** Surgical resection of the primary tumor for patients who present with incurable stage IV colorectal cancer is controversial. National practice patterns have not been described. We evaluated the use of primary tumor resection in patients presenting with stage IV colorectal cancer.

**Methods:** Patients with stage IV colorectal cancer diagnosed between 1988 and 2000 were selected from the Surveillance, Epidemiology, and End Results database. Patients undergoing primary tumor resection were analyzed on the basis of sex, race, year of diagnosis, and the anatomical site of the primary tumor. We compared the survival of resected and nonresected patients.

**Results:** A total of 17,658 (66%) of the 26,754 patients presenting with stage IV colorectal cancer underwent primary tumor resection. Patients with resected disease were more likely to be young (mean age of 67.1 vs. 70.3 years) and to have right-sided tumors (75.3%, 73.0%, and 45.6%, respectively, for right, left, and rectal;  $P < .001$ ). In all age groups, patients undergoing resection had higher median and 1-year survival rates (colon: 11 vs. 2 months, 45% vs. 12%,  $P < .001$ ; rectum: 16 vs. 6 months, 59% vs. 25%,  $P < .001$ ) when compared with patients who did not undergo resection.

**Conclusions:** Most patients who present with stage IV colorectal cancer undergo resection of the primary tumor. The proportion of patients undergoing resection depends on patient age and race and the anatomical location of the primary tumor. The degree to which case selection explains the treatment and survival differences observed is not known. Further investigation of the role of surgery in the management of incurable stage IV colorectal cancer is warranted.

**Key Words:** SEER Program—Palliative surgery—Colonic neoplasm—Rectal neoplasm.

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Colorectal cancer is the second leading cause of cancer death in the United States, with 57,100 deaths and an estimated 147,500 new colorectal malignancies diagnosed in 2003.<sup>1</sup> An alarming 20% of patients

with newly diagnosed colorectal cancer will present with stage IV disease at the time of diagnosis, with reported 5-year survival rates of just 8%.<sup>1</sup> Unlike the role of surgical resection in earlier stages of this disease, resection of the primary colorectal tumor is not considered curative for patients who present with stage IV disease unless it is performed with simultaneous resection of all metastatic disease. An estimated 75% to 90% of patients who present with distant metastases do not have metastatic disease that

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can be surgically resected.<sup>2</sup> Resection of the primary tumor in noncurative surgery is indicated for palliation of symptoms of obstruction, perforation, or intractable bleeding.

The approach to the asymptomatic patient who presents with surgically incurable stage IV disease and an intact primary tumor is more controversial. Some surgeons have advocated nonoperative management in minimally symptomatic patients,<sup>3</sup> whereas others have advocated for resection of the primary tumor.<sup>4,5</sup> Arguments for initial resection of the primary colorectal tumor in patients with distant metastases have included a lower reported 3% to 6% operative mortality for elective colorectal cancer resection in patients with stage IV disease, compared with the more ominous 20% to 40% operative mortality rates for emergent resection in patients with bowel obstruction and advanced disease.<sup>6-8</sup> Advocates for resection of asymptomatic primary tumors have emphasized the importance of resection before patients develop disabling symptoms such as weight loss and nutritional depletion secondary to near obstruction, anemia from a bleeding primary tumor, or physiologic and immune compromise related to chemotherapy. In contrast, other cancer physicians have advocated a nonoperative approach, reserving surgery for patients who become symptomatic. Reported incidences<sup>3,9,10</sup> of symptom development and adverse events directly related to unresected primary lesions in patients managed nonoperatively are as low as 10% to 25%.

The literature on this topic is limited to several retrospective single-institution reviews.<sup>4,5,9,10</sup> The current national practice pattern in the United States has not been reported. The purpose of this study was to evaluate the current incidence of surgical resection in the United States for patients who present with stage IV colorectal cancer and to evaluate potential factors that may lead to selection of surgery. Furthermore, we wanted to describe any emerging trends in practice patterns for this clinical scenario.

## MATERIALS AND METHODS

Patient demographics, the incidence of surgery performed, and survival data were extracted from the Surveillance, Epidemiology, and End Results (SEER) database, a national prospective database that gathers demographic, pathologic, clinical, and survival data.<sup>11</sup> The SEER program currently collects and publishes cancer incidence and survival data from 11 population-based cancer registries and 3 supplemental reg-

istries that cover approximately 14% of the US population. Because SEER is a population-based registry, cases are obtained from all hospitals or other facilities in a given geographical area that provide screening, diagnostic, or therapeutic services to patients with cancer. This includes both inpatient and outpatient cases in which only pathologic specimens were reviewed at the reporting facility.<sup>12</sup> Geographical areas were selected primarily for their ability to operate and maintain a population-based cancer-reporting system and for their epidemiologically significant population subgroups.<sup>13</sup> The mortality data reported by SEER are provided by the National Center for Health Statistics.<sup>14</sup> Mortality is defined as death due to any cause, including surgery. The SEER registries routinely collect data on patient demographics, primary tumor site, morphology, disease stage at initial diagnosis, first course of treatment, and follow-up for vital status. SEER specifically defines the stage of disease as the initial stage at which the patient presented. Metastases that develop after the initial diagnosis do not change the initial stage assigned to patients in the SEER registry.<sup>15</sup> The SEER data are considered highly valid. Each of the SEER registries holds the highest level of certification of data quality as provided by the North American Association of Central Cancer Registries. Annually, the SEER registries are subjected to evaluations of the quality and completeness of their data and are held to the SEER program's standard of 98% for the completeness of case ascertainment. To check the accuracy of the data elements collected, the SEER registries reabstract medical records from a sample of cases.<sup>11</sup>

Patients were selected for colorectal malignancies that presented as stage IV disease between 1988 and 2000. Stage IV colon or rectal cancer is defined as a carcinoma arising in the colon or rectum (cecum to rectal ampulla) with evidence of metastatic disease.<sup>16</sup> Patients were excluded from this study if the colorectal cancer was not the first or only malignancy diagnosed, if the diagnosis was made at autopsy, or if the histology suggested a noncolonic primary tumor (e.g., linitis plastica) or appendiceal cancer. To better define the incidence of primary tumor resection in a noncurative setting, we excluded 2478 patients whose surgical treatment potentially included resection of metastatic disease by excluding procedures that involved the partial or total removal of other organs. Applying the above-mentioned selection criteria led to 26,754 patients for whom the following variables were extracted:

1. Age
2. Sex

TABLE 1. Patient characteristics

Characteristic	n	Surgery		No surgery	
		n	%	n	%
Total	26,754	17,657	66	9,097	34
Age (y) <sup>a</sup>					
≤39	712	505	70.9	207	29.1
40–49	1,816	1,296	71.4	520	28.6
50–59	3,853	2,764	72.5	1,089	28.5
60–69	6,913	4,852	70.2	2,061	29.8
70–79	8,010	5,262	65.7	2,748	34.3
≥80	5,450	2,978	54.6	2,472	45.4
Sex					
Male	14,396	9,600	66.7	4,796	33.3
Female	12,358	8,057	65.2	4,301	34.8
Race					
White	21,589	14,331	66.4	7,258	33.6
Black	3,132	1,953	62.4	1,179	37.6
Other	2,033	1,373	67.5	660	32.5
Site of primary tumor <sup>b</sup>					
Right colon	10,361	7,806	75.3	2,555	24.7
Left colon	10,504	7,671	73.0	2,833	27.0
Rectum	4,163	1,898	45.6	2,265	54.4
Not specified	1,726	282	16.3	1,444	83.7

<sup>a</sup>The mean age for the surgical group was 67.1 years; for the nonsurgical group, it was 70.3 years.

<sup>b</sup>The site of the primary tumor was classified as follows: *right colon* includes the cecum, appendix, ascending colon, hepatic flexure, and transverse colon; *left colon* includes the splenic flexure and descending, sigmoid, and rectosigmoid colon; and *rectum* refers to the rectal ampulla.

3. Race
4. Age at diagnosis
5. Year of diagnosis
6. Site of primary tumor
7. Surgical procedure
8. Survival in months from diagnosis

Surgical resection of the primary colorectal tumor was defined as any type of colon resection, including partial colectomy, total colectomy, proctocolectomy, or proctectomy. We defined right-sided lesions as those located in the cecum, ascending colon, hepatic flexure, or transverse colon. Left-sided lesions included those found in the splenic flexure or the descending, sigmoid, or rectosigmoid colon. Rectal cancer referred to lesions arising in the rectal ampulla. There were 1726 patients for whom the anatomical location of the primary tumor was unidentified, and these were excluded from the analysis of practice variation based on the tumor anatomical location.

Practice variations of tumor resection based on patient age, sex, and race; year of diagnosis; and anatomical site of the primary tumor were evaluated for possible association with surgical resection. We categorized age into the following six groups: ≤39, 40 to 49, 50 to 59, 60 to 69, 70 to 79, and ≥80 years. The statistical significance of trends in the year of diagnosis was assessed with the Cochran-Armitage trend test.<sup>17</sup> Logistical regression analysis was used to cal-

culate simple and adjusted odds ratios (ORs) along with 95% confidence intervals (CIs) for the likelihood of surgery associated with several predictor variables. Two-sided P values were used throughout, and values < .05 were considered statistically significant.

## RESULTS

The characteristics for the entire cohort of 26,754 patients are listed in Table 1. Overall, the SEER data show that two-thirds of patients who presented with stage IV colorectal cancer underwent a resection of the primary colorectal tumor. More men than women presented with stage IV colorectal cancer (14,396 men and 12,358 women; Table 1). Younger patients (< 50 years) comprised 9.4% of our patient cohort. The percentage of patients undergoing surgical resection was higher during the first 4 years included in this study and trended toward less use of resection in the most recent time period (68.0%, 65.9%, and 64.1% for 1988–1991, 1992–1996, and 1997–2000, respectively; Fig. 1). The decreasing trend over time for the percentage of patients who underwent operation was significant when all ages were combined, according to a Cochran-Armitage trend test ( $P < .001$ ).<sup>17</sup> The trend remained significant after controlling for age by using logistic regression. We found several differences between patients treated with surgical resection of the

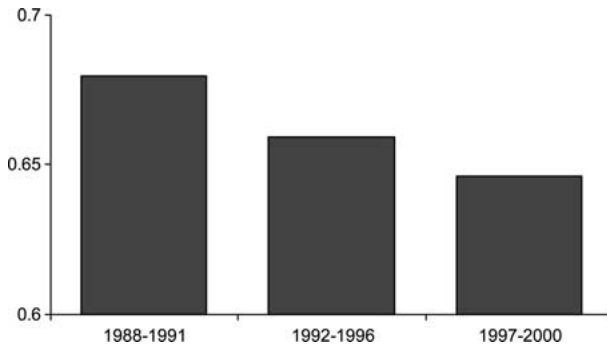


FIG. 1. Percentage of patients undergoing resection of primary stage IV colorectal tumors from 1988 to 2000.

primary tumor and those treated nonsurgically. These included patient age, sex, and race and the anatomical site of the primary tumor. Patients with stage IV colorectal cancer who underwent operation at the time of initial diagnosis were significantly younger than those treated nonoperatively. The mean age of patients who underwent resection was 67.1 years, compared with 70.3 years for those who did not undergo resection. The rate of resection was just more than 70% in the first four age groups ( $\leq 39$ , 40–49, 50–59, and 60–69 years) and decreased to 66% and 55% in the last two age groups (Table 1). The rates of surgical resection among men and women were generally balanced, but there was a slightly higher use of surgical resection for women in the 50- to 59-year-old age category (OR, 1.19; 95% CI, 1.03–1.38), and a similar trend was seen for the 40- to 49-year-old age group (OR, 1.21; 95% CI, .98–1.48), as shown in Table 2. However, among the oldest patients ( $> 80$  years), simple and adjusted ORs showed that women were less likely to undergo operation (simple OR, .81; 95% CI, .73–.90; adjusted OR, .78; 95% CI, .69–.88).

Race was also shown to be associated with the likelihood of undergoing a surgical resection of the primary tumor (Table 2). Most of each racial group was treated surgically. Simple ORs showed a decreased likelihood of surgical treatment for black patients, and this was statistically significant for all age groups  $\geq 60$  years of age. No differences were seen for the likelihood of operation when nonwhite/non-black (“other” in Table 2) patients were compared with white patients.

The rate of resection of the primary colorectal tumor varied according to the anatomical location of the tumor (Table 2). Among the 26,754 patients identified in the SEER database who presented with stage IV colorectal cancer, tumor location data were

available for 25,028 patients (93.5%). Patients with rectal cancers were the least likely to undergo resection of the primary tumor (45.6% for rectum vs. 74% for colon). Among patients of all age groups, patients with rectal cancer had a significantly decreased likelihood of undergoing resection compared with patients with a right-sided colon cancer, with ORs ranging from .18 to .28. Patients with left-sided colon cancers were also less likely to undergo operation compared with patients with right-sided colon cancers, with ORs ranging from .78 to .93, and this was statistically significant in three of the age groups evaluated.

We compared survival among patients who underwent surgical resection of the primary colon or rectal tumor and among those treated without surgical resection. Differences in patients selected for operation compared with those managed nonoperatively according to comorbid conditions, performance status, or burden of metastatic disease could not be examined because of limitations of the SEER data. Although each of these factors probably contributes to the selection of individual patients for surgical resection, the differences in survival time between the two groups merit attention and may warrant further study. Patients who underwent surgical resection of the primary colon or rectal tumor had longer survival times than those who did not undergo resection (Table 3). The median survival for stage IV colon cancer patients undergoing resection was 11 months, compared with 2 months for such patients not undergoing surgical resection; 1-year survival rates were 45% and 12%, respectively. Similarly, patients with rectal cancer who underwent surgical resection also had better median (16 vs. 6 months) and 1-year (59% vs. 25%) survival rates than those who did not undergo resection. Similar results were seen for patients in each of the six age groups examined, with significantly better survival in the surgery versus no-surgery groups. Overall, survival rates were noted to be lower in the older age groups, beginning at age 60 years, for both surgically treated and non-surgically treated patients.

## DISCUSSION

Stage IV colorectal cancer is not uncommon. Colorectal cancer is the second most common cause of cancer death in the Western world, and overall, 20% of patients will have metastatic disease at the time of disease presentation.<sup>12</sup> In the United States, approximately 29,600 patients presented with stage

TABLE 2. Simple and adjusted odds ratios for likelihood of surgery

Age group (y)	Variable <sup>a</sup>	Simple odds ratio	95% CI	Adjusted odds ratio <sup>b</sup>	95% CI
≤39	Female sex	1.07	.77–1.48	.99	.68–1.43
	Race				
	Black	.96	.61–1.51	.74	.45–1.23
	Other	1.00	.61–1.63	1.02	.60–1.74
	Site				
	Left colon	.86	.55–1.34	.84	.54–1.31
40–49	Rectum	.18	.11–.29 <sup>c</sup>	.18	.11–.28 <sup>c</sup>
	Year of diagnosis	.99	.94–1.03	.99	.94–1.04
	Female sex	1.21	.98–1.48	1.03	.82–1.29
	Race				
	Black	.79	.60–1.03	.69	.51–.92 <sup>c</sup>
	Other	.74	.54–1.03	.79	.56–1.12
50–59	Site				
	Left colon	.78	.60–1.03	.78	.59–1.02
	Rectum	.25	.19–.33 <sup>c</sup>	.24	.18–.33 <sup>c</sup>
	Year of diagnosis	.97	.95–1.00	.98	.95–1.01
	Female sex	1.19	1.03–1.38 <sup>c</sup>	1.09	.93–1.28
	Race				
60–69	Black	.86	.70–1.04	.81	.65–1.00
	Other	1.11	.85–1.44	1.12	.85–1.48
	Site				
	Left colon	.82	.68–.97 <sup>c</sup>	.80	.67–.96 <sup>c</sup>
	Rectum	.27	.22–.33 <sup>c</sup>	.27	.22–.33 <sup>c</sup>
	Year of diagnosis	.98	.96–.99 <sup>c</sup>	.98	.96–1.00
70–79	Female sex	1.07	.96–1.18	1.05	.93–1.18
	Race				
	Black	.78	.67–.91 <sup>c</sup>	.71	.60–.84 <sup>c</sup>
	Other	1.04	.86–1.26	1.04	.85–1.28
	Site				
	Left colon	.93	.82–1.06	.92	.81–1.05
≥80	Rectum	.28	.24–.32 <sup>c</sup>	.27	.23–.32 <sup>c</sup>
	Year of diagnosis	.99	.98–1.01	.99	.98–1.01
	Female sex	1.02	.93–1.12	.98	.89–1.09
	Race				
	Black	.73	.63–.84 <sup>c</sup>	.68	.58–.79 <sup>c</sup>
	Other	.99	.82–1.19	.99	.81–1.21
≥80	Site				
	Left colon	.82	.73–.92 <sup>c</sup>	.81	.72–.90 <sup>c</sup>
	Rectum	.25	.22–.29 <sup>c</sup>	.24	.21–.28 <sup>c</sup>
	Year of diagnosis	.98	.97–.99 <sup>c</sup>	.98	.97–.99 <sup>c</sup>
	Female sex	.81	.73–.90 <sup>c</sup>	.78	.69–.88 <sup>c</sup>
	Race				
Black	.79	.66–.96 <sup>c</sup>	.70	.57–.87 <sup>c</sup>	
Other	.95	.75–1.21	.93	.71–1.20	
≥80	Site				
	Left colon	.79	.70–.90 <sup>c</sup>	.77	.68–.88 <sup>c</sup>
	Rectum	.22	.18–.27 <sup>c</sup>	.21	.18–.26 <sup>c</sup>
Year of diagnosis	.98	.97–.99 <sup>c</sup>	.99	.97–1.00	

CI, confidence interval.

<sup>a</sup>The referent groups for the computation of odds ratios are as follows: sex, male; race, white; and side, right. Year of diagnosis was entered as a numerical variable.

<sup>b</sup>Adjusted odds ratios were computed by using a logistical regression that included each of the variables listed.

<sup>c</sup>Odds ratio significantly different from 1.0 at the .05 level of significance.

IV colorectal cancer in 2002, despite increasing public awareness and wider acceptance of endoscopic screening for colorectal cancer.<sup>12</sup> Although surgical resection of the primary tumor alone, leaving gross residual disease, has demonstrated a survival benefit in the setting of renal cell and ovarian cancer, this has not been demonstrated in patients with colorectal cancer.<sup>18,19</sup> Little evidence exists that removal of the primary colon cancer contributes to improved long-

term patient survival in patients who present with metastatic disease. The major goals of therapy in patients with stage IV colorectal cancer, then, are maintaining quality of life and prolonging survival time.

The role of primary tumor resection in stage IV colorectal cancer has been a matter of some debate. Surgery for palliation has long been advocated for patients with symptoms of obstruction, intractable

**TABLE 3.** Comparison of median and 1-year survival for patients with stage IV colon and rectal cancer

Variable	Median (mo)		1-y Survival rate (%)	
	Surgery	No surgery	Surgery	No surgery
<b>Colon</b>				
All ages (y)	11	2	45	12
≤39	14	5	55	19
40–49	15	5	57	25
50–59	14	4	55	19
60–69	13	3	50	16
70–79	10	2	42	50
≥80	6	2	29	70
<b>Rectum</b>				
All ages (y)	16	6	59	25
≤39	19	10	74	43
40–49	20	7	71	32
50–59	20	8	69	34
60–69	18	6	60	10
70–79	14	4	55	21
≥80	9	3	39	16

bleeding, or symptoms of perforation, even in the presence of unresectable metastatic disease.<sup>20,21</sup> It is interesting to note, however, that the significant associated potential morbidity of major surgery in patients who present with stage IV disease has been recognized.<sup>4,7,22</sup> For patients with surgically incurable stage IV disease and an asymptomatic primary tumor, however, the need to resect the primary tumor is controversial. The importance of aligning goals of palliation with evidence-based outcomes has recently been emphasized.<sup>23,24</sup> Recently, several groups of investigators have compared outcomes for patients who present with stage IV colorectal cancer managed with and without resection of the primary tumor.<sup>3,5,9,10</sup>

Scoggins et al.<sup>10</sup> retrospectively reviewed the records of 89 patients who presented for treatment of stage IV colorectal cancer over a 12-year period at Vanderbilt University. Of this cohort, 23 patients were initially treated nonoperatively, and just 2 (9%) subsequently required an operation to manage symptoms of obstruction from an intact primary tumor. The median survival for their resected group was 14.5 months, compared with 16.6 months for patients who had an intact primary tumor, although this difference was not statistically significant. An operative morbidity rate of 30% and an operative mortality rate of 5% were observed in patients who underwent initial resection, thus prompting this group to question the benefits of initial resection. In a larger series from the Royal Marsden Hospital in London, Tebbutt et al.<sup>9</sup> specifically examined the intestinal complications in patients with metastatic

colorectal cancer who had unresected primary tumors compared with patients who underwent initial resection. Both groups received the best available chemotherapy during that time period and were therefore more likely to be relatively similar with regard to comorbidity and performance status. The main finding of this study was that the incidence of major intestinal complications related to an intact primary tumor among patients who were initially treated with chemotherapy was low. The major complication related to the intact primary tumor was intestinal obstruction, which occurred at a rate of 13.4%. The rate of subsequent obstruction in patients who underwent initial resection, however, was similar (13.2%), thus questioning the merit of initial surgery for preventing symptoms of obstruction.

In the only prospective study that we are aware of, Sarela et al.<sup>3</sup> followed up 24 asymptomatic patients with an intact primary tumor and synchronous metastatic disease who were not candidates for curative resection of the primary tumor. During this time period, two-drug chemotherapy consisting of fluorouracil and leucovorin was used for patients who did not undergo surgical resection. Operative intervention was subsequently necessary in six patients (25%), and a median survival of 10.3 months was reported for stage IV patients who were initially treated nonoperatively. The low incidence of problems related to the intact primary tumor in these three studies led each group to question the need for surgical resection of the primary colorectal tumor in the face of surgically unresectable metastatic disease.

The counterargument was made by Ruo et al.<sup>5</sup> at Memorial Sloan-Kettering Cancer Center, who advocated for elective resection of asymptomatic primary colorectal tumors. They retrospectively analyzed the records of 230 patients with stage IV colorectal cancer, of whom 103 were managed nonoperatively. They noted a 20% postoperative complication rate and a 1.6% postoperative mortality rate in patients who underwent initial resection and noted a significantly lower burden of metastatic disease in the group managed operatively. Ruo et al. observed a significant survival advantage for the patients who underwent surgical resection (16 vs. 9 months). Patients in this series who underwent resection, however, were younger, had more right-sided tumors, and had a lower metastatic disease burden (metastases confined to the liver) than those who did not undergo resection. The improved survival in the resected group formed the basis of the recommendation for resection of the asymptomatic primary tumor in the setting of surgically incurable



disease for appropriate surgical candidates, but the authors recognized that the significant differences between their two patient cohorts might have biased survival outcomes.

In this study, we evaluated the current use of surgical resection of colon and rectal tumors for patients presenting with stage IV disease by using a large publicly accessible database. Four important limitations of this study limit the ability to address the true effect of surgical resection on asymptomatic patients with unresectable synchronous metastases. First, this was a secondary analysis of a large public-use database. As a population-based registry organized to reflect significant population subgroups, the SEER database provides a reasonable surrogate of the US population and is currently the largest available database to assess general oncological treatment practices in the United States.<sup>11</sup> It is, however, limited in its assessment of details for various treatments (e.g., radiotherapy and chemotherapy regimens) and is better suited for evaluation of broadly defined utilization and practice patterns. Second, we could not assess the degree to which surgery was indicated for patient symptom management at the time of disease presentation, i.e., palliation of symptoms of obstruction, intractable bleeding, or pain. This is likely to contribute to significant differences in patient populations between the two major treatment groups we examined. Third, data regarding patient comorbidities and performance status are not available in the SEER database. Patients with the most advanced disease or the most serious comorbid conditions may not be offered surgery; the degree to which this explains the better survival of patients who undergo operation is unknown. Additionally, we cannot report when or in what setting the diagnosis of stage IV colorectal cancer was made. The SEER database simply records the initial stage of disease presentation as reflected through individual local registries that examine discharge summaries, operative reports, outpatient treatment records, and tumor board proceedings. Patients with low-volume metastatic disease discovered at the time of operation for a planned curative resection would be segregated to the group undergoing surgical resection, and this alone might significantly contribute to the improved survival we observed in patients who had undergone operation. Finally, the large cohort in this database may allow some results that do not represent meaningful clinical differences to achieve statistical significance. Although the limitations of this study are important to consider, the study does provide sufficient data for an appraisal of the national practice

pattern and raises meaningful questions regarding certain trends within that pattern.

Evaluation of patients entered into the SEER registry from 1988 to 2000 who had stage IV colorectal cancer at the time of presentation demonstrated that two thirds of these patients underwent surgical resection of the primary colorectal tumor—a procedure that was unlikely to be curative. Univariate analyses revealed that there were differences according to age, sex, race, and tumor location in the proportion of patients who underwent surgery. We observed a decreasing rate of tumor resection as patients aged. Much has been written regarding age as a predictor of outcome in surgical patients. This body of literature suggests that increasing age is not a contraindication to elective procedures, although investigators have found that older patients have poorer outcomes with emergent procedures.<sup>25–30</sup> The Colorectal Cancer Collaborative Group conducted a systematic review of the literature and found that elderly patients had an increased frequency of comorbid conditions and were more likely to present with later-stage disease and to undergo emergency operation.<sup>31</sup> The effects of emergent status and comorbid conditions could not be quantified in our study. Yancik et al.<sup>32</sup> found that the prevalence of additional comorbid conditions increased with advancing age in patients with colon carcinoma. These factors may contribute significantly to the decision process in surgical case selection. It is possible that the higher mean age in the nonresected group reflects a higher average comorbidity or disease burden or a poorer performance status.

Adjusting for the other covariates, we found a significantly decreased likelihood of primary tumor resection for black patients and for patients with left-sided colon cancers and rectal cancers in most age groups analyzed. The variation in surgical therapy based on race is noteworthy. Differences in treatments and outcomes previously reported have documented that black patients receive fewer colorectal cancer screenings,<sup>33</sup> present at more advanced stages of disease,<sup>34</sup> undergo surgery less often,<sup>35</sup> and have shorter survival times.<sup>35–37</sup> Contributing factors have included socioeconomic status, access to care, and presentation at later stages of disease; each may influence our findings.<sup>33–39</sup> Investigation of factors that may help to explain the difference in selection of surgery on the basis of race is beyond the scope of this article.

The anatomical location of the primary tumor was found to be different in patients who had a surgical resection of the primary tumor versus those who did

not. Left-sided and rectal lesions were less likely to be removed than right-sided cancers. We believe that a potential factor that may account for this finding is the perception among surgeons that right hemicolectomy is associated with lower surgical morbidity than resection of left-sided tumors and rectal cancers. Therefore, surgeons might be more likely to perform this operation electively given equal comorbidity in a patient with advanced cancer compared with an operation that has greater potential morbidity. Rectal lesions were the least often resected in this cohort. Potential factors contributing to these differences could be the perception of greater morbidity and mortality associated with pelvic resection for rectal cancer, the greater potential for permanent colostomy with low rectal cancers in stage IV disease, and the success demonstrated in local control by using combined chemoradiation for locally advanced rectal cancers.<sup>6,40,41</sup> Additionally, options other than proctectomy for less invasive local management are available for patients with stage IV rectal cancer to manage symptoms related to the primary tumor.<sup>42-44</sup>

We found that patients who underwent surgical resection for the primary tumor for stage IV colorectal cancer experienced a longer survival time than those who did not undergo resection. These differences in survival were demonstrated across all age groups. The differences in median survival for both patients with colon cancer (11 vs. 2 months) and patients with rectal cancer (16 vs. 6 months) are dramatic and warrant further investigation. Although the difference in survival for the surgery group remained significant after stratification by race and site (results not shown), the degree to which this difference can be attributed to a treatment effect of surgery, case selection by surgeons, or other factors not captured in the SEER data is not clear. A prospective determination of the patient's comorbid status, the existence or absence of symptoms warranting urgent operation, the patient's performance status, the extent of metastatic disease burden, and the use of chemotherapy would facilitate a more meaningful comparison of the survival of patients treated with and without removal of the primary colorectal tumor. The importance of addressing the utility of surgical resection of a colorectal primary tumor in patients who present with unresectable synchronous metastases is particularly timely. Chemotherapy available to patients in the studies that reported relatively low complication rates related to the intact primary tumor was generally fluorouracil and leucovorin. Newer three-drug chemotherapy regimens now available to patients with metastatic

colorectal cancer are superior, with response rates generally double those of the older fluorouracil/leucovorin regimen.<sup>45-47</sup> The improved response rates with newer regimens may have been partially responsible for the diminished use of surgical resection seen in the later years of this study, although most of these regimens became available outside of clinical trials after the year 2000. Whether more effective chemotherapy decreases complications related to an intact primary tumor remains to be demonstrated.

In summary, this investigation found that most patients who present with stage IV colorectal cancer in the United States undergo resection of the primary tumor. Patients treated with resection of the primary tumor were found to live longer than patients who did not undergo resection of the primary tumor. We have observed that there are several differences in demographics in patients selected for surgical resection, and these factors may have influenced the survival differences demonstrated. Additional study is required to better understand the factors that influence the decision to proceed with surgical resection of the primary colorectal tumor in patients who present with stage IV disease. A prospective evaluation with well-matched patient cohorts is needed to resolve the controversy regarding the palliative benefits of surgical resection of the primary colorectal tumor in patients who present with unresectable distant metastases.

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