Initial Presentation With Stage IV Colorectal Cancer

How Aggressive Should We Be?

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Hypothesis: The appropriate surgical treatment of patients with colorectal cancer who are found on initial presentation to have stage IV disease is controversial. With presumed limited life expectancy, the role of primary colon or rectal resection has been questioned, as has the utility of synchronous hepatic resection.

Design: A retrospective chart review.

Setting: The University of Chicago Hospitals, Chicago, Ill, a tertiary-care referral center.

Patients: One hundred twenty patients were identified through The University of Chicago Hospitals Tumor Registry whose initial presentation showed stage IV colorectal cancer and who underwent laparotomy.

Main Outcome Measures: The primary end points of the study were perioperative morbidity and mortality and overall survival.

Results: Median survival and 5-year survival were 14.4 months and 10%, respectively. Survival was greater for patients younger than 65 years than for those who were aged 65 years or older (18.3 vs 9.8 months; \( P = .007 \)). Carcinomatosis was associated with significantly decreased survival when compared with less extensive stage IV disease (6.7 vs 18.1 months; \( P < .001 \)). Patients who underwent any form of resection of hepatic metastases achieved a survival advantage over those with unresectable liver lesions (median survival, 29.6 vs 10.2 months; \( P < .001 \)). Overall, 27 patients (22.5%) developed postoperative complications. Seven patients (5.8%) died during the postoperative period.

Conclusions: Age of 65 years or older, carcinomatosis, and extensive (bilobar) liver involvement are associated with decreased survival and increased postoperative morbidity and mortality and may negate any potential benefit patients derive from resection of the primary lesion. A substantial number of patients with synchronous hepatic metastases have protracted survival that justifies resection of the primary colorectal tumor at initial presentation. Despite the presence of stage IV disease, resection of the primary tumor and, when feasible, liver metastases is indicated.

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PATIENTS AND METHODS

The University of Chicago Hospitals (Chicago, Ill) Tumor Registry was examined to identify patients who were initially seen with stage IV colorectal cancer and who underwent laparotomy from January 1, 1984, to December 31, 1998. All patients underwent exploration with either noncurative management of the primary tumor or attempted curative resection of the primary and metastatic disease. Noncurative resection was defined as surgical removal of the primary tumor with residual metastatic disease at the time of surgery.

Clinic charts were retrospectively reviewed for patient demographics, symptoms, location of primary and metastatic disease, perioperative data, morbidity, mortality, and survival. Long-term follow-up was obtained through hospital records, clinic charts, and telephone conversations with either primary physicians or patients’ families. All statistical evaluations were based on the date of the patient’s death or the date of last follow-up.

All survival data are expressed as medians unless otherwise indicated. The major end points of this study were perioperative morbidity and mortality and overall survival. All statistical evaluations were performed with log-rank analysis, and actuarial survival was calculated by the Kaplan-Meier method. Differences were considered statistically significant at P<.05.

RESULTS

From January 1, 1984, to December 31, 1998, 120 patients with stage IV colorectal cancer underwent laparotomy. There were 46 women (38.3%) and 74 men (61.7%); age ranged from 28 to 88 years (mean, 62.0 years) (Table 1). Symptoms on initial examination were documented in 116 patients (96.7%). The most common symptoms or findings were abdominal pain in 37 patients (31.9%), anemia and/or guaiac-positive stool in 32 (27.6%), change in bowel habits in 30 (25.9%), anorexia and/or weight loss in 29 (25.0%), and hematochezia in 27 (23.3%) (Table 2). One hundred eleven admissions (92.5%) were elective, 5 were considered urgent (4.2%), and 4 (3.3%) were not classified.

One hundred two patients (85%) had died by last follow-up; median survival was 14.4 months, and 5-year survival was 10%. The impact of age on survival was evaluated by stratifying patients into subgroups (<55 years, 55-64 years, 65-74 years, and >74 years). Length of survival progressively increased with increasing age (Table 3). When patients younger than 65 years were compared with patients 65 years of age or older, a significant survival advantage was apparent in the younger group (median survival, 18.3 vs 9.8 months; P = .007).

Site of the primary cancer was clearly identified in 116 patients (96.7%): right colon in 37 (31.9%), left colon in 48 (41.4%), transverse colon in 7 (6.0%), and rectum in 24 (20.7%). Median survival for patients with a rectal primary tumor was longer than for patients with a colon primary tumor (23.2 vs 12.9 months; P = .05). The most commonly performed procedures were right colectomy (39 patients), sigmoid colectomy (25 patients), and low anterior resection (15 patients) (Table 4). Hepatic resections were performed in 34 patients in addition to the above procedures.

Site of metastatic disease was documented during either exploration or perioperative staging, with the following findings: solitary liver metastases in 49 patients (40.8%), multiple unilobar liver metastases in 9 (7.5%),
bilobar liver metastases in 38 (31.7%), lung metastases in 11 (9.2%), and carcinomatosis in 42 (35.0%). Median survival was significantly shorter for patients with carcinomatosis (6.7 vs 18.1 months; P < .001). In patients with unilobar liver metastases, median survival was 20.3 months, which was significantly longer than that for patients with more extensive liver disease or metastases to other regions (P = .007). For patients with bilobar hepatic metastases, median survival was 12.8 months (Table 5).

Comparisons were made in 90 patients for whom pathological findings for the primary tumor were available. There were 7 well-differentiated tumors, 63 moderately differentiated tumors, and 20 poorly differentiated tumors. Patients with well- to moderately differentiated primary tumors survived significantly longer than patients with poorly differentiated cancers (14.4 vs 6.7 months; P = .03). Positive lymph nodes were detected in 65 specimens (72.2%) but did not influence survival (12.9 months for patients with positive nodes vs 18.7 months for those with negative nodes; P = .89). All colonic margins in this series were negative on final pathological review.

Seventy-one (59.2%) of our patients received some form of additional therapy. Of these patients, 55 (77.5%) received postoperative chemotherapy, with the majority receiving fluorouracil and leucovorin calcium. Other patients received systemic chemotherapy in the form of a variety of phase I and II agents. Few patients received preoperative therapy: chemotherapy in 2 (2.8%) and chemotherapy and radiation in 4 (5.6%). Postoperative radiation therapy was administered to 10 patients (14.1%): 2 (2.8%) received radiation therapy alone and 8 (11.3%) received combined radiation and chemotherapy. Patients treated with systemic chemotherapy and/or radiation therapy trended toward a survival advantage when compared with patients who did not receive additional treatment (median survival, 17.1 vs 7.6 months; P = .04).

One third of our patient population had either concurrent or staged resection of liver and/or lung metastases. Twenty-four patients (20.0%) underwent resection for solitary liver metastases, 4 patients (3.3%) for multiple unilobar liver metastases, 6 patients (5.0%) for bilobar liver metastases, and 6 (5.0%) for lung metastases, 1 (0.8%) of which required bilateral thoracotomies. Patients who underwent liver resection, including those with multiple and bilobar metastases, had a significant survival advantage compared with patients with liver metastases who did not undergo resection (median survival, 29.6 vs 10.2 months; P < .001).

Postoperative complications occurred in 27 patients (22.5%), with wound infection being the most common (Table 6). In this cohort, 20 patients had primary colon cancer and 7 had primary rectal lesions. Two of the patients were operated on for urgent symptoms. Twenty-one patients (77.7%) had widespread metastases: 14 with carcinomatosis, 6 with extensive hepatic metastases, and 1 with malignant ascites.

There were 7 postoperative deaths (5.8%). Five of the 7 deaths were in patients who were older than 65 years. Of note, 2 of the 7 deaths were in patients who came for examination in extremis with abdominal pain and were diagnosed as having complete bowel obstruction. All 7 patients had either carcinomatosis (5 patients) or extensive hepatic metastases (2 patients). Three of the 7 deaths were due to pulmonary embolism.

### Table 4. Surgical Procedures in 120 Patients With Stage IV Colorectal Cancer

<table>
<thead>
<tr>
<th>Site</th>
<th>No. of Patients</th>
<th>Resection type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other</td>
<td>38</td>
<td>Subtotal colectomy 10 (8.3%)</td>
</tr>
<tr>
<td>Secondary tumor</td>
<td></td>
<td>Total colectomy 1 (0.8%)</td>
</tr>
<tr>
<td>Hepatic</td>
<td>34</td>
<td>Right colectomy 39 (32.5%)</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>6</td>
<td>Left colectomy 37 (30.8%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Low anterior resection 15 (12.5%)</td>
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<tr>
<td></td>
<td></td>
<td>Abdominoperineal resection 14 (11.7%)</td>
</tr>
</tbody>
</table>

*P = .007 for unilobar vs all; P < .001 for carcinomatosis vs all.

### Table 5. Influence of Extent of Metastatic Disease on Survival*

<table>
<thead>
<tr>
<th>Site</th>
<th>No. of Patients</th>
<th>Median Survival, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unilobar</td>
<td>58</td>
<td>20.3</td>
</tr>
<tr>
<td>Bilobar</td>
<td>38</td>
<td>12.8</td>
</tr>
<tr>
<td>Carcinomatosis</td>
<td>42</td>
<td>6.7</td>
</tr>
</tbody>
</table>

*P = .007 for unilobar vs all; P < .001 for carcinomatosis vs all.
The treatment of patients who are initially seen with metastatic colorectal cancer is controversial. Patients with widespread stage IV colorectal cancer would achieve no apparent benefit from resection of the primary tumor unless palliation were the primary objective of the intended surgery. Exploration might be considered meddlesome if resection resulted in an unacceptably high incidence of postoperative complications. In addition, since metastatic tumor burden is the life-limiting factor in these patients, protracted postsurgical recovery would delay initiation of therapy targeting disseminated disease and, in some instances, negate potentially effective systemic treatment. Counterbalancing the above argument would be the potential benefit from avoiding downstream complications of obstruction and perforation, especially in a patient in a more compromised condition, if the tumor were left in situ without treatment. Finally, a substantial body of evidence supports hepatic resection in selected patients with limited metastatic disease, although its utility in patients who have synchronous disease is less clear.

Three series have attempted to address some of the issues raised and provide recommendations regarding the treatment of these patients. Liu et al presented a retrospective series of 68 patients with metastatic colorectal carcinoma who underwent palliative resection of the primary tumor, enteric bypass, or exploration alone. Independent variables were analyzed, including patient comorbidities, preoperative serum carcinoembryonic antigen level, results of liver function tests, extent of liver metastases, stage and site of primary tumor, and tumor cell differentiation. Mean survival in their study was 10.6 months in patients in whom the tumor could be resected, compared with 3.4 months in patients who had bypass and 2.0 months in patients who underwent exploration. Operative mortality was 9.5%, principally because of liver failure. The authors described a significant difference in mean (±SD) survival when they compared poorly differentiated with well- or moderately differentiated tumors (8.4 ± 8.2 vs 12.5 ± 9.2 months). Comparison of patients whose liver was less than 50% involved with metastatic disease with those who had greater than 50% involvement revealed a significant survival advantage for the group with less than 50% involvement (mean survival, 14.4 ± 10.6 vs 4.2 ± 4.0 months). They concluded that the poor prognosis of patients with greater than 50% of liver replaced by tumor or poorly differentiated primary cancer suggests that surgery should be proposed only when these patients have complications such as bowel obstruction, perforation, or hemorrhage.

A prospective study performed by Makela et al examined 96 patients with stage IV colorectal carcinoma who underwent exploratory laparotomy with palliative intent. Postoperative morbidity was 24% and mortality was 8%. Median survival in this series was 10 months, with a 5-year survival of 5%. Patients who underwent resection survived a median of 15 months, while those who underwent bypass or simple exploration survived a median of 7 months. These investigators concluded that palliative surgery for colorectal cancer can be successfully performed, with some patients achieving long-term benefits.

In a retrospective series examining 87 patients who underwent palliative resection for either colon or rectal carcinoma, Joffe and Gordon examined age, initial clinical features, location of primary tumor, pathological findings, extent of metastases, and their effects on outcome. A 10% mortality, 50% morbidity, and median survival of 9 months was observed. Three poor prognostic factors were noted to be significant: extensive liver metastases, age greater than 75 years, and history of cardiovascular disease. These authors concluded that patients with these higher risk factors would not benefit from resection unless symptoms of impending obstruction or unremitting bleeding were present.

Based on our experience, we favor an aggressive approach to resection of the primary tumor in all patients in the absence of extensive hepatic metastases or carcinomatosis. Patients with one of these stage IV manifestations have a substantially reduced survival associated with a high postoperative complication rate. In this group of patients, the risks appear to far outweigh any actual or theoretical benefit, since their survival is extremely limited despite any and all current interventions. Patients with such advanced disease pose a most difficult problem, where surgery for symptomatic disease should be performed only if no other alternative is available.

Recently, there have been reports in the literature regarding the use of metallic stents for palliation in patients with obstruction secondary to colonic malignant neoplasms. At least 2 situations seem to merit consideration of this intervention. First, a patient whose disease is considered inoperable may benefit from placement of a stent simply to relieve obstructive symptoms. Second, in the patient who has an acute obstruction, stenting may improve the patient’s clinical condition with bowel decompression, allow complete evaluation of the colon for synchronous lesions, ensure more adequate bowel preparation, and enable the surgeon to perform an elective 1-stage procedure rather than a colostomy and delayed reconstruction.

When treatment is recommended, other variables should be considered on an individual basis, although none is an absolute contraindication. Advanced age correlates with decreased survival, especially for patients in their seventh decade of life or older. Tumor grade suggests biological aggressiveness with poorly differentiated pathological findings, resulting in diminished survival. In addition, quantifying the extent of hepatic involvement is subjective, and therefore management decisions should not be based solely on this or any one single criterion.

There is no curative chemotherapy for patients with widespread metastatic disease, but trials of fluorouracil and leucovorin have demonstrated increased numbers of partial responders and prolongation of time to progression of disease, as well as improved survival and quality of life for patients receiving chemotherapy compared with “best supportive care.” Irinotecan hydrochloride is now considered standard second-line therapy for patients who are nonresponders or have pro-
gressive disease after conventional fluorouracil-based chemotherapy. The modest gains demonstrated with present-day systemic therapy further support our aggressive approach. Patients with unresectable liver lesions, for example, may survive for a year or longer, as noted in our report, and will likely develop symptoms from the primary lesion, some of which may be life threatening. Our series suggests that it might be beneficial to resect the primary lesion on an elective basis when the patient is initially seen with “limited” metastatic disease and acceptable performance status rather than later in the disease process when the patient’s performance status is poor and the manifestation more urgent.

Finally, although this is not the primary objective of this study, our data strongly suggest that synchronous appearance with hepatic metastases is not a contraindication to attempted curative resection of the primary tumor and secondary liver lesions. Patients undergoing either concurrent or staged (approximately 6 weeks after primary resection) hepatic resection have a survival similar to those reported with metachronous appearances of stage IV disease. While others have identified a short disease-free interval as a negative predictor of survival, no treatment other than hepatectomy is associated with a long-term disease-free state and potential cure. Hepatic resection, in addition to being performed for extirpation of the primary tumor, should be offered when appropriate to patients with synchronous liver metastases.

As with any retrospective study, this study suffers from the biases of a chart review. Incomplete records, charting inaccuracies, and variable follow-up are all problems inherent in this type of study. Also, in a study of this size, where 120 cases were collected for 15 years, the numbers of patients in certain categories were inadequate to make statistically relevant comparisons. Selection bias may be present, for example, when comparing patients who received systemic therapy with those who did not. Patients who were more fit were more likely to receive chemotherapy, perhaps contributing to their survival advantage.

When patients are examined with incurable colon cancer, the decision for laparotomy should be based on surgical risk, comorbidity, severity of symptoms, and predicted life expectancy after surgery. The goal of palliative surgery is to relieve symptoms, prevent more distressing symptoms, and possibly provide psychological benefit for the patient who feels that the “cancer” has been removed. General health and well-being may be improved, and there is some evidence that life is prolonged in specific cases. Our study suggests that younger patients (<65 years) without carcinomatosis or extensive hepatic metastases should tolerate a resection of the primary tumor with minimal morbidity and reasonable success. In patients with less extensive stage IV disease, early (elective) resection of the primary lesion may prevent the need for urgent surgical resections at a later time, when the patient is less fit, the disease more widespread, and the patient in extremis. If the liver tumor burden is excessive, or in the setting of carcinomatosis, resection is unlikely to benefit the patient and is associated with a high risk of postoperative complications. Patients in this setting are probably better served by focusing on the disseminated component of their disease and instituting systemic treatment early on in their course, reserving surgery for when and if symptoms from the primary tumor are substantial. As always, the surgeon must individualize decision making for each patient, taking into account patient goals, family goals, and the risks and benefits of all available treatment options.

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REFERENCES


DISCUSSION

James E. Goodnight, Jr, MD, PhD, Sacramento, Calif: Dr Rosen and his coauthors have addressed a question that we all face not uncommonly, whether to resect a primary colon cancer in the face of stage IV disease. They have asked the right question. In a disease that by and large we cannot cure, how can we as surgeons help?

As I read the manuscript in a drive for simplification in the management of a complex disease, their answer is straightforward. Resect the primary colon tumor except when there is extensive liver disease, ie, greater than 50% replacement of the liver, and/or there is extensive carcinomatosis, based on the short survival of the patients in theirs and others’ series. In most other cases there is an opportunity to extend survival, decrease the chance of bowel obstruction, and prevent bleeding. From there we go to footnotes.

Stage IV colon carcinoma is an extremely difficult disease on which to make generalizations. As the authors point out, it
is a disease that, despite a single staging designation, is a very heterogeneous disease. At one end of the spectrum are resectable liver metastases that have well-defined indications for resection with a reasonable expectation of cure. Even in synchronous metastases, there is little argument about what to do except whether or not at this time to add intra-arterial chemotherapy.

At the other end of the spectrum are the severely ill patients just described for whom resection of the primary adds little to their care. I am continually struck in this disease and in others, such as melanoma, of the variety and different behavior of liver metastatic clones. In this disease, the worst of all appears to be the one that likes to live in the bowel wall and produces the phenomenon that we see clinically as carcinomatosis. Besides the problems of tumor burden, this clone appears to impair bowel motility. In situations of bulky tumor and/or carcinomatosis, it is often difficult to decide what to do. My impression is that the patient gets one good operation, and that is probably done early on with resection of the primary.

With notable exceptions, we probably fool ourselves when we go in again to treat bowel obstruction after the patient has already had one good operation. I would be interested in the authors' thoughts on this.

I would like to address 4 questions to the authors in this very fine paper. (1) Except for the very elderly (a term which certainly becomes nebulous as I age), I would not have expected age to be as much of a factor in survival as your series suggests. Were you surprised at this finding? (2) As you point out, systemic chemotherapy was a factor in survival. I will presume not, but were there generalizable selection criteria for systemic chemotherapy? (3) My third question is, in my own hands I have not been pleased with the results from resecting combined liver and lung metastases in this disease. How do you manage this particular problem? (4) Then, finally, returning to the thesis of your paper, I like the way a similar question was phrased in a paper years ago on bile duct carcinoma. Sven Bengmark at that time asked in his particular paper what approach would result in the patient spending the fewest of his remaining days in the hospital. Therefore, I might ask the same question that you have addressed in the paper, that excluding resectable liver metastases, given the other stage IV manifestations, what approach to resection of the primary colon cancer in stage IV disease will allow the patients to spend the fewest of their remaining lifespan in the hospital?

William W. Turner, Jr, MD, Jackson, Miss: I was intrigued by the increased survival time in the patients with rectal carcinoma, and I wonder how those patients were managed in terms of their primary tumors. Theodore X. O’Connell, MD, Los Angeles, Calif: It seems that one of your recommendations is to do synchronous liver resections for patients with metastatic disease to the liver. However, I don’t think the data from the paper really substantiates this conclusion, since this is not a randomized study but a retrospective review. It really comes down to a post hoc proper hoc type of argument. Obviously, it is the same with the chemotherapy. The patients who had hepatic resection probably were patients who were younger, in better shape, and had tumors that could be resected, and these are compared to patients with more extensive disease.

Frederic E. Eckhauser, MD, Ann Arbor, Mich: The authors use the term substantial tumor burden in decrying an aggressive approach for selected patients. I wonder if you would comment about the techniques that you employed for staging patients, more specifically, the use of laparoscopy in determining which patients perhaps might be candidates for nonoperative management. With the advent of endoscopic laser recanalization and coagulation techniques to control obstruction and bleeding, there obviously is a subset of patients whose survival is sufficiently short that a nonoperative approach might be warranted. I wonder if you would comment on that.

Dr Posner: Dr Goodnight, with respect to age, you asked if we were surprised by our findings. I guess the answer is yes and no. Obviously, these elderly patients are different than other cancer patients who do not present with significant metastatic disease. Patients who are elderly are at somewhat of a disadvantage when they come in with extensive disease outside of their primary site and undergo, although technically, a straightforward operation. For them, it may not be simple in terms of recovery and long-term outcome. So we were somewhat surprised, but, on the other hand, these patients are at a significant disadvantage.

In terms of systemic chemotherapy and who would receive it following treatment surgically; in our institution our medical oncologists are very aggressive in treating these patients. Many of them go on phase I or II trials in an attempt to answer meaningful questions. But I do know that the vast majority of these patients, although they have substantial metastatic disease, most of them have a reasonable performance status and can tolerate chemotherapy. In an era where our systemic regimens are becoming more effective, it may be that survival will increase over time.

In terms of combined liver and lung resection, you have to be very, very selective in this group of patients. There is reasonable data that suggest that patients with limited disease, either to the liver, to lung, or to combined liver and lung, still may benefit from aggressive resection since there is no other curative therapy available.

The question regarding our approach to allowing the patient to be in the hospital for the “fewest days,” this review was mainly done in an era where laparoscopy in the management of patients with colorectal cancer was not common. In this day and age, that type of approach would be more ideal than laparotomy if feasible and if not considering an aggressive surgical approach for their metastatic disease.

Dr Turner, with regard to the increased survival for rectal cancer patients, I do not have a great explanation for that. All of these patients obviously received an operation for their primary tumor and frequently, even in the setting of metastatic disease, the radiation oncologist would consider offering them additional therapy in an attempt to prevent them from developing the horrible symptoms from a local recurrence. It is hard to believe that that necessarily impacts on their survival. They may well have a different pattern of metastases, which may suggest why they obtain an improved survival.

Dr O’Connell, in terms of your question regarding resection of synchronous hepatic metastases, I agree with you. This is a retrospective review, and we all understand the biases and limitations of a retrospective review. The most compelling argument to be aggressive in these patients is that when you look at historical data that has been published in the 1960s, our survival is actually no different for synchronous hepatic resection than those patients. They still may be biologically different. In terms of chemotherapy, I agree with you that patients who are more fit are more likely to receive chemotherapy, and therefore you would expect their survival to be better.

Dr Eckhauser, with regard to the substantial tumor burden that we talked about, I agree with you that there is a place in this day and age to consider nonoperative therapy in those patients with extensive carcinomatosis and/or extensive hepatic metastases. Endoscopic laser treatment as well as stent placement may have a role in the treatment of these patients in select circumstances.