Resection of the Primary Colorectal Cancer Is Not Necessary in Nonobstructed Patients with Metastatic Disease

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ABSTRACT
Asymptomatic patients with metastatic colorectal cancer do not routinely need to undergo resection of the primary tumor. Although several retrospective analyses suggest that patients who undergo resection of the primary tumor live longer, most of these reviewed data prior to the advent of modern polychemotherapy and are subject to considerable bias, as patients who were considered able to undergo surgery likely had better overall prognoses than those who were not. In addition to significant prolongation of overall survival, current combinations of systemic chemotherapeutic agents and targeted agents have allowed improved local and distant tumor control, decreasing the likelihood of local tumor-related complications requiring colon resection. The Oncologist 2009;14:963–969

INTRODUCTION: METASTATIC COLORECTAL CANCER
In 2009, there will be approximately 150,000 new diagnoses of colorectal cancer (CRC) in the United States. In that same time period, approximately 49,960 will die from cancer of the colon and rectum. Between 20% and 25% of patients diagnosed with CRC will present with metastases at the time of initial diagnosis [1]. Therefore, appropriate management of patients who present with metastatic disease from a synchronous colorectal cancer is a significant oncologic issue.

Modern polychemotherapy combined with targeted agents has improved median survival from less than 1 year with single-agent fluoropyrimidines to almost 2 years [2]. Nonetheless, less than 10% of patients diagnosed with metastatic CRC (mCRC) are alive at 5 years, with most patients dying from their cancer [1]. Consequently, in patients with a limited life expectancy, in addition to improving survival, the potential morbidity of treatment and the treatment’s impact on patient quality of life must be considered.

In patients with symptomatic primary CRC, the goals of resection of the primary lesion are to decrease cancer-related morbidity related typically to bleeding, obstruction, or perforation. In addition, in selected patients, resection of...
all sites of metastatic disease can offer improvement in long-term survival. Surgical resection rapidly palliates symptomatic primary colon lesions. However, resection of the colon in mCRC patients is associated with a 1%–6% perioperative mortality [3–6] and postoperative morbidity of 20%–30% [3, 6, 7]. In patients who have resectable stage I, II, or III cancer, any perioperative mortality and morbidity is balanced by the potential for cure, but in patients with incurable cancer, the benefit, if it exists, is much more modest. In particular, two groups of patients can be identified who benefit most from a nonsurgical initial approach. First are those patients with bulky, aggressive metastatic disease who require immediate relief of symptoms by systemic therapy. Second is the patient with limited liver metastases, for whom neoadjuvant therapy followed by hepatic resection is often favored over concurrent colectomy and hepatic metastasectomy.

**Retrospective Analyses**

No prospective randomized clinical trials exist to guide treatment in patients with asymptomatic primary colorectal lesions and diffuse metastatic disease at presentation. Several retrospective analyses report a benefit from primary cancer resection; these are summarized in Table 1. Although each of these studies reports a numerically higher survival for patients who underwent resection compared with patients who did not, the analyses are subject to substantial selection bias. Patients were not randomly assigned to treatment groups; rather, they were treated based on the standard practice of their physician. The choice to perform surgery on a given patient reflected a lower burden of disease, higher performance status, and younger age. This selection bias is reflected in, but not completely elucidated by, reported differences in population characteristics, partly summarized in the fifth column of Table 1. As a consequence of these differences, patients selected for surgery likely had a better prognosis and their survival advantage may be unrelated to surgery.

Retrospective studies concluding against resecting the asymptomatic primary tumor suffer from these same confounding factors. Indeed, two of the studies [10, 11] must be credited for not only recognizing and discussing these biases, but going so far as to conclude that their data did not support resection despite numerically higher survival in the resected group. These studies are summarized in Table 2.

**Response of Primary Tumor to Chemotherapy**

Patients given chemotherapy in the preceding retrospective trials mostly received regimens of single-agent fluoropyrimidine therapy. Modern chemotherapy regimens incorporating the novel cytotoxic agents oxaliplatin and irinotecan as well as the biologic agents bevacizumab and cetuximab have improved both response rates and survival. The negative consequence of delaying chemotherapy to allow for surgery may therefore be increased in an era of better chemotherapy. Furthermore, if chemotherapy is able to better shrink the primary lesion, the risk/benefit ratio of surgical morbidity to palliative benefit may lean further toward risk than before. Table 3 summarizes the outcome results of several of the key trials that define the standard of care for modern chemotherapy. A discussion of the details of these studies is beyond the scope of this review; rather, the table aims to demonstrate the high efficacy of state-of-the-art chemotherapy.

The efficacy of neoadjuvant chemotherapy suggests that the high response rates reported in chemotherapy trials are not limited to metastatic sites. For example, in 2006, Chau et al. published a report of a phase II study evaluating the effect of neoadjuvant chemotherapy on 77 patients with poor-risk rectal cancer [17]. Neoadjuvant chemotherapy was followed by chemoradiotherapy, total mesorectal excision, and adjuvant chemotherapy. Enrolled patients received 12 weeks of capecitabine and oxaliplatin prior to capecitabine with radiation. During the neoadjuvant chemotherapy, patients were assessed for evidence of rectal bleeding, pelvic pain, tenesmus, diarrhea, and constipation. The objective response rate after 12 weeks of neoadjuvant capecitabine and oxaliplatin was 88%, and 86% of the patients with symptoms had symptomatic improvement. Specifically, pelvic pain/tenesmus was decreased in 71% of patients, 90% had improvement in diarrhea/constipation, 100% had reduced rectal bleeding, and 93% had weight stabilization or weight gain. The median time to symptom resolution was 32 days. These results were compared with the 28% response rate in the previously reported study of neoadjuvant protracted infusion 5-fluorouracil and mitomycin-C, also in patients with rectal cancer [18].

**Palliation of Intestinal Complications by Nonsurgical Methods**

Endoscopic techniques may be very effective in managing intestinal hemorrhage or malignant obstruction. Endoluminal stents inserted by surgeons, gastroenterologists, or interventional radiologists are able to restore patency in many patients with malignant bowel obstruction. In a report by Camuñéz et al., more than 90% of stents remained patent for 6 months or more following placement [19]. Clinically significant bleeding is present in only 10% of patients with mCRC [2] and endoscopic laser therapy, cryotherapy, radi-
### Table 1. Retrospective studies of patients with metastatic colorectal cancer supporting the benefit of resection of the primary tumor

<table>
<thead>
<tr>
<th>Study</th>
<th>n (Initial resection/no initial resection)</th>
<th>Perioperative morbidity (surgery group)/Later surgery needed (no surgery group)</th>
<th>Survival, resected vs. not resected</th>
<th>Key differences in population characteristics, resected vs. not resected</th>
<th>Key concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ruo et al. (2003) [4]</td>
<td>209</td>
<td>20.5% 29%</td>
<td>16 mo 9 mo</td>
<td>● Site in right colon -46% R -28% NR</td>
<td>● Imbalances in patient characteristics.</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td>● Single site metastatic disease -68% R -53% NR</td>
<td>● Patients with liver-only disease included in analysis; some of the patients in the surgical arm may have been cured via metastasectomy. Importance of this imbalance confirmed in analysis of prognostic factors showing extent of liver disease as only significant prognostic variable.</td>
</tr>
<tr>
<td></td>
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<td>● Met to liver only -56% R -41% NR</td>
<td>● Chemotherapy used in the NR group was predominantly 5-FU without oxaliplatin, irinotecan, or biologic agents.</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>● Comorbidity -32% R -20% NR</td>
<td>● No data available on comorbidity.</td>
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<td></td>
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<td></td>
<td></td>
<td>● LDH above normal -52% R -64% NR</td>
<td>● No data available on need for surgery for symptom control.</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>● Use of chemotherapy -58% R -42% NR</td>
</tr>
<tr>
<td>Cook et al. (2005) [8]</td>
<td>17,657</td>
<td>Not reported</td>
<td>11 mo 2 mo</td>
<td>● Med age -67.1 R -70.3 NR</td>
<td>● 64% of patients in NR group presented with symptoms of uncontrolled bleeding, obstruction, or perforation. 23 of 47 required a procedure that included nonresective surgery in 17.</td>
</tr>
<tr>
<td></td>
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<td>● Site primary R -R colon 75.3% -L colon 73.0% -Rectum 45.6%</td>
<td>● No data on performance status.</td>
</tr>
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<td></td>
<td></td>
<td>● No data on many important comorbidities not presented.</td>
</tr>
<tr>
<td>Konyalian et al. (2007) [9]</td>
<td>62</td>
<td>14% R 20% NR (17/47 NR patients had nonresective surgery) 0% but 4.3% later required stent</td>
<td>375 days 138 days</td>
<td>● Use of chemotherapy -58% R -42% NR</td>
<td>● Data on many important comorbidities not presented.</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>● Data on many important comorbidities not presented.</td>
</tr>
<tr>
<td>Galizia et al. (2008) [6]</td>
<td>42</td>
<td>43% 30%</td>
<td>26 mo 17 mo</td>
<td>● Rate of complete hepatic resection -11.9% R -4.3% NR</td>
<td>● 4/42 patients in R group were brought to surgery with curative intent and found to have metastases at surgery; they likely had a lower burden of disease.</td>
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<tr>
<td></td>
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<td>● Complete hepatic metastasectomy can be curative. More patients received complete hepatic resection in the resection group, perhaps secondary to the last bullet point.</td>
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<td>● Low response rate to chemotherapy likely reflects use of older regimens; better results can be expected with modern regimens.</td>
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</tbody>
</table>

Abbreviations: 5-FU, 5-fluorouracil; LDH, lactate dehydrogenase; Med, median; Met, metastases; mo, months; NR, not resected; R, resected.
ation therapy, and photodynamic therapy may be effective in controlling bleeding symptoms [20, 21]. Radiation therapy is also useful in palliating perineal pain from local invasion seen in some patients with locally advanced rectal cancer.

In the event that nonsurgical methods are unsuccessful, operative interventions, including colonic diversion, laparoscopic or open colectomy, or abdominoperineal resection, may be performed. In the recently published Memorial Sloan-Kettering Cancer Center (MSKCC) study, 16 patients underwent emergent surgery following the initiation of chemotherapy [22]. Of those, two (12.5%, or 0.8% of the total study population) died in the 30 days following surgery. Median survival of patients who underwent emergent surgery was 6 months, compared with 13 months for the 152 patients who did not require any intervention for their primary cancer.

**PROSPECTIVE TRIALS EVALUATING THE VALUE OF PRIMARY RESECTION**

Unfortunately, no randomized controlled trials have been reported to provide level I evidence to answer this question.

### Table 2. Retrospective studies of patients with metastatic colorectal cancer refuting the benefit of resection of the primary tumor

<table>
<thead>
<tr>
<th>Study</th>
<th>n (Initial surgery/Not initially resected)</th>
<th>Key differences in population characteristics</th>
<th>Survival, resected vs. not resected</th>
<th>Perioperative morbidity (surgery group)/Later surgery needed (no surgery group)</th>
<th>Key concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scoggins et al. (1999) [3]</td>
<td>66/23</td>
<td>● Rectal site of primary -21.2% R&lt;br&gt;-47.8% NR&lt;br&gt;● Use of radiation or chemoradiation -0% R&lt;br&gt;-43.5% NR</td>
<td>14.5 mo&lt;br&gt;16.6 mo</td>
<td>30.3%&lt;br&gt;4.6%</td>
<td>● 10 patients in NR group received radiation or chemoradiation. The NR group contained 11 patients with rectal cancer; radiation is particularly effective for local control of this site.</td>
</tr>
<tr>
<td>Tebbutt et al. (2003) [10]</td>
<td>280/82</td>
<td>● Gender -40% female R&lt;br&gt;-27% female NR&lt;br&gt;● Performance status ≥2 -20% R&lt;br&gt;-38% NR&lt;br&gt;● Rectal site of primary -33% R&lt;br&gt;-46% NR&lt;br&gt;● Mean alkaline phosphatase -179 U/l R&lt;br&gt;-329 U/l NR&lt;br&gt;● Mean albumin -38.7 g/l R&lt;br&gt;-34.5 g/l NR&lt;br&gt;● Mean CEA -809 g/l R&lt;br&gt;-3139 g/l NR</td>
<td>14.0 mo&lt;br&gt;8.2 mo</td>
<td>13.2% obstruction&lt;br&gt;5% total needed repeat surgery&lt;br&gt;13.4% obstruction&lt;br&gt;9.8% total needed surgery</td>
<td>● Unresected group included patients whose primary tumors were symptomatic. &lt;br&gt;● Surgical group included patients who were not known to harbor metastatic disease until the time of surgery. &lt;br&gt;● Multiple imbalances in known prognostic factors.</td>
</tr>
<tr>
<td>Stelzner et al. (2005) [11]</td>
<td>128/58</td>
<td>Demographic details of R vs. NR groups not presented.</td>
<td>11.4 mo&lt;br&gt;4.6 mo</td>
<td>11.7% surgical mortality R</td>
<td>● Surgery performed whenever possible. Reasons for inclusion in NR group included advanced tumor spread, multiple concomitant disease, and patient choice. &lt;br&gt;● 42/58 patients in NR group were operated without resection for intestinal diversion, formation of a colostomy, or diagnostic laparotomy.</td>
</tr>
</tbody>
</table>

Abbreviations: CEA, carcinoembryonic antigen; mo, months; NR, not resected; R, resected.
However, one trial is ongoing. National Surgical Adjuvant Breast and Bowel Project (NSABP) C-10, a phase II trial of 5-fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) chemotherapy plus bevacizumab for patients with unresectable stage IV colon cancer and a synchronous asymptomatic primary tumor, has been designed to prospectively accrue 90 patients with unresected primary colon tumors and radiographically confirmed, surgically unresectable metastases. The primary aim of the study is to determine the rate of major morbidity for patients who are treated with mFOLFOX6 with bevacizumab, without resection of the primary tumor. Major morbidity will be defined as any event related to the intact primary tumor necessitating surgery or resulting in patient death. Additional aims of this study are to evaluate local complications and determine the rate of specific events related to the intact primary tumor requiring hospitalization or a major intervention, but not requiring surgery. In addition to overall survival, the study will monitor the rate of grade 3 or 4 toxicities related to study therapy prior to disease progression. The trial is powered to determine outcomes related to the primary tumor, with an incidence of events less than 25% considered a therapeutic success. In addition, documentation will be made of how many patients with initially unresectable metastases develop resectable disease. Accrual is ongoing [23].

**DISCUSSION**

Prospective randomized clinical trials support the use of systemic polychemotherapy in patients with diffuse metastases from mCRC. Patients who are fit enough to receive modern chemotherapeutic regimens that combine standard antineoplastic agents with targeted therapy have a median survival close to 2 years [2]. Response rates in the first-line setting with modern combination chemotherapy range from more than 20% with 5-fluorouracil and leucovorin, to more than 50% with FOLFOX and 5-fluorouracil, leucovorin, and irinotecan (FOLFIRI) [24, 25]. The addition of bevacizumab improves response rates of combination chemotherapeutic regimens in most phase III trials [26–28], as does the addition of cetuximab [13, 14, 29, 30]. In patients who receive a combination of chemotherapy and biologic therapy, there is an increased risk of grade 3 or 4 toxicities. For example, in the retrospective BRiTE registry, patients with an intact primary tumor had a slightly increased risk (3.4%) of gastrointestinal perforations [31]. However, as in other bevacizumab trials, both perforations as well as sites of bleeding could occur at sites away from the original tumor. Therefore, resecting the primary tumor would not eliminate the risk of perforation or bleeding. Targeting the metastases as well as the primary tumor with systemic therapy is likely to offer the greatest benefit to a patient with unresectable cancer.

Bevacizumab is commonly added to primary chemotherapy for metastatic CRC. All of the available studies with bevacizumab precluded entry by patients who had an identified bleed within the preceding 6 months. Therefore, prospective data for the use of bevacizumab in patients with a bleeding primary CRC are not available. However, in the MSKCC study [22], bevacizumab was incorporated into the first-line therapy for 112 (48%) patients. No episodes of intractable bleeding that required surgery were documented. Therefore, in the setting of unresected primary CRC, barring uncontrolled bleeding, the potential benefit of bevacizumab-based polychemotherapy outweighs the small risk of bleeding or perforation.

There is no evidence that response rates of the primary tumor are inferior to that of the metastases; on the contrary, the data from Chau et al. in a prospective trial demonstrate that primaries may be even more responsive than metastatic disease [17]. In asymptomatic patients, potential complications from an intact primary tumor range from 10% to 20% for intestinal obstruction, 4% for gastrointestinal hemorrhage, and 4% for fistula formation [3, 4, 10, 32]. In the study by Tebbutt et al., the risk of colonic obstruction was 13%, whether the tumor was resected or not, because patients who underwent surgery may develop adhesions that

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>RR</th>
<th>OS</th>
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</thead>
<tbody>
<tr>
<td>N016966: FOLFOX or XELOX + bevacizumab [12]</td>
<td>899</td>
<td>38%</td>
<td>21.3</td>
</tr>
<tr>
<td>FOLFOX-4 + cetuximab [13]</td>
<td>337</td>
<td>46% (61% in <em>kRAS</em> wild type)</td>
<td>N/A</td>
</tr>
<tr>
<td>CRYSTAL: FOLFIRI + cetuximab [14]</td>
<td>1198</td>
<td>47% (59% in <em>kRAS</em> wild type)</td>
<td>24.9</td>
</tr>
<tr>
<td>BRiTE tumor registry, bevacizumab past progression group [15]</td>
<td>642</td>
<td>48%</td>
<td>31.8</td>
</tr>
<tr>
<td>GONO: FOLFOXIRI [16]</td>
<td>122</td>
<td>60%</td>
<td>22.6</td>
</tr>
</tbody>
</table>

Abbreviations: FOLFIRI, 5-fluorouracil, leucovorin, and irinotecan; FOLFOX, 5-fluorouracil, leucovorin, and oxaliplatin; FOLFOXIRI, leucovorin, 5-fluorouracil, oxaliplatin, and irinotecan; GONO: Gruppo Oncologico Nord Ovest; N/A, not available; OS, overall survival; RR, relative risk; XELOX, capecitabine and oxaliplatin.
cause bowel obstruction or obstruction due to peritoneal recurrences [10]. Resection of an asymptomatic primary tumor risks surgical complications and may postpone the administration of chemotherapy that may offer systemic (as opposed to just local) control. Most of the published retrospective studies reflect systemic treatment prior to the availability of oxaliplatin, irinotecan, bevacizumab, panitumumab, or cetuximab. In addition, these retrospective studies do not address case selection bias, availability or administration of active chemotherapeutic agents, the performance status, or a prospective evaluation of the initial burden of metastatic disease. Most patients will succumb to metastatic disease before developing symptoms from their unresected primary colorectal lesion [3]. In patients with a limited life expectancy, the morbidity and mortality of unnecessary surgery or surgery that does not improve quality of life or survival should be carefully evaluated, preferably in prospective, multicenter clinical trials. With the availability of effective combination chemotherapy and biologic agents, systemic therapy for the treatment of life-threatening metastases should be paramount.

**CURRENT RECOMMENDATIONS**

(a) Patients with evidence of perforation, significant obstruction, or uncontrolled bleeding should undergo resection of the symptomatic lesion.

(b) Patients who are not fit to undergo surgery, or who decline surgery, should undergo endoscopic management with stents or ablation to palliate symptoms.

(c) Patients with potentially resectable metastases should undergo resections of the primary tumor and the metastases (typically, sequentially).

(i) Chemotherapy may be administered preoperatively to assess the natural history of the underlying malignancy.

(ii) If disease is controlled with chemotherapy, resection of primary and secondary lesions should be considered [33].

(d) In patients who have diffuse, metastatic CRC with unresectable metastases, modern polychemotherapy with targeted agents will offer disease control without the mortality and morbidity of surgery directed at the primary lesion.

**REFERENCES**


16. Falcone A, Ricci S, Brunetti I et al. Phase III trial of infusional fluorouracil,
leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: the Gruppo Oncologico Nord Ovest.


18 Chau I, Allen M, Cunningham D et al. Neoadjuvant systemic fluorouracil and mitomycin C prior to synchronous chemoradiation is an effective strategy in locally advanced rectal cancer.


20 Sarela AI, Guthrie JA, Seymour MT et al. Non-operative management of the primary tumour in patients with incurable stage IV colorectal cancer.


21 Dohmoto M, Hunerbein M, Schlag PM. Palliative endoscopic therapy of rectal carcinoma.


24 de Gramont A, Figer A, Seymour M et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer.


25 Tournigand C, Andre T, Achille E et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GER-COR study.


26 Hurwitz H, Fehrenbacher L, Novotny W et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer.


29 Cunningham D, Humblet Y, Siena S et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer.


30 Sobrero AF, Maurel J, Fehrenbacher L et al. EPIC: phase III trial of cetuximab plus irinotecan after fluoropyrimidine and oxaliplatin failure in patients with metastatic colorectal cancer.


32 Petrelli NJ. Expressing the prochemotherapy position on treatment of synchronous colorectal metastases in the asymptomatic patient.


33 Mentha G, Majno PE, Andres A et al. Neoadjuvant chemotherapy and resection of advanced synchronous liver metastases before treatment of the colorectal primary.