Hypothesis: Bowel resection followed by chemotherapy is a better management strategy than immediate chemotherapy in asymptomatic patients with colorectal cancer and unresectable liver-only metastases at presentation.

Design: Retrospective study.

Setting: University hospital.

Patients: Sixty-five consecutive symptom-free colorectal cancer patients with unresectable synchronous metastases confined to the liver undergoing bowel tumor resection plus systemic chemotherapy (42 patients [resection group]) or chemotherapy first (23 patients [chemotherapy group]).

Main Outcome Measures: Long-term survival and identification of prognostic indicators of outcome.

Results: In the resection group, the mean and median overall survival times were shown to be significantly better than those in the chemotherapy group (P = .03). Performance status, basal serum levels of lactic dehydrogenase and alkaline phosphatase, percentage of liver involvement, potentially curative resection of the bowel tumor, and type of treatment (resection vs chemotherapy) were demonstrated to be the only variables significantly correlated with long-term survival. On multivariate analysis, performance status, extent of liver involvement, and type of treatment were shown to be the only covariates independently associated with survival rate. The rate of liver metastasis downstaging with subsequent curative hepatic resection was clearly associated with good performance status, limited liver involvement, and resection of the bowel tumor.

Conclusions: Achieving complete cure in asymptomatic colorectal cancer patients with unresectable synchronous liver-only metastases appears to be mostly the result of shrinkage and resection of hepatic metastases. In patients with good performance status and limited liver involvement, bowel tumor resection appears to be the best treatment option for this purpose.


See Invited Critique at end of article

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argued that bowel tumor resection may result in high mortality and morbidity rates and delay systemic chemotherapy and proposed immediate administration of systemic chemotherapy, with surgery reserved for treatment of tumor complications or, if tumor shrinkage occurs, for a potentially curative resection. Thus, the best treatment strategy for asymptomatic CRC patients with unresectable liver-only metastases still remains unclear, warranting additional investigations.7,18

In this study, we report on our experience on treatment of asymptomatic CRCs with unresectable metastases confined to the liver. Specifically, we retrospectively compared clinical outcome in patients undergoing bowel tumor resection plus chemotherapy (resection group) with that in patients treated with chemotherapy first (chemotherapy group), in an effort to identify selection criteria for the most beneficial treatment of these patients.

## METHODS

### PATIENTS

Clinical records from 33 consecutive patients with stage IV bowel cancer and unresectable liver-only metastases were retrospectively selected from the database of the Division of Surgical Oncology from January 4, 1995, to December 23, 2005. These patients had hepatic metastases judged unresectable because of invasion of major liver pedicles (metastatic disease adjacent to or involving all 3 hepatic veins, and/or the portal vein bifurcation, and/or the retrohepatic vena cava, and/or the vascular structures of the opposite lobe) or intrahepatic dissemination (bilar disease) requiring a liver resection potentially capable of jeopardizing postoperative liver function. Eight of these 33 patients (25%) were symptomatic and needed immediate surgical exploration to manage tumor complications. Among the remaining 25 asymptomatic or relatively symptom-free patients (ie, complaining only of constitutional symptom such as fatigue or anorexia), 3 received only supportive care because of very poor general conditions, and the remainder underwent resection of the bowel tumor. The 42 remaining patients represented the resection group of this study.

The chemotherapy group consisted of 23 asymptomatic or relatively symptom-free CRC patients with unresectable liver-only metastases who had refused surgery and were thus treated with chemotherapy first. These patients were treated by the medical oncology team in our department during the study period. Their clinical records were retrieved from the medical oncology database.

All tumors were staged on evaluation of findings of physical examination, routine laboratory tests, and diagnostic imaging (including complete colonoscopy with biopsy, abdominal ultrasonography, chest and abdomen computed tomography, scintigraphic bone scan, and, more recently, whole-body magnetic resonance imaging and fludeoxyglucose F18-labeled positron emission tomography).

Liver metastases were staged according to the degree of hepatic parenchymal replacement by tumor (ie, H1, <25%; H2, 25%-50%; and H3, >50% of whole liver volume) by means of computer-aided analysis of computed tomography with a dedicated software. In the resection group, all patients underwent resection of the bowel cancer; no explorative laparotomy or colon bypass was performed in these patients. First-line systemic chemotherapy based on intravenous fluorouracil plus folinic acid or, after 2001, fluorouracil, folinic acid, and oxaliplatin or fluorouracil, folinic acid, and irinotecan hydrochloride was started immediately after diagnosis in the chemotherapy group and at least 3 weeks after surgery in the resection group. The response to systemic therapy was evaluated every 3 months and metastases were restaged with regard to their resectability. A switch to second-line chemotherapy, with the eventual addition of new biological therapies such as bevacizumab and cetuximab, was decided in cases of partial response (metastatic reduction <25%) or disease progression. All of the patients were available for follow-up and the statistical analysis was completed by July 31, 2006.

The main characteristics of the patient population are summarized in Table 1. In the resection group, extent of the primary tumor and nodal status (T and N variables of the TNM staging system),16 degree of histologic differentiation (well, moderate, or poor), tumor growth pattern (expanding or infiltrating),20 number of resected nodes, tumor size, curative or noncurative resection of the bowel tumor (defined as macroscopic and microscopic removal of the tumor, free resection margins, absence of peritoneal diffusion, and lymphadenectomy extended beyond involved nodes at the postoperative pathologic examination), and postoperative complications were also recorded. Finally, in the chemotherapy group, the complication rate related to unresected bowel tumors was recorded.

## STATISTICAL ANALYSIS

We used the BMDP statistical package (BMDP Statistical Software Inc, Los Angeles, California) to perform statistical analysis. In all analyses, the significance level was specified as P < .05. The equality of group means and comparisons between proportions were analyzed by using the unpaired t test and x2 test with the Yates correction, respectively. Univariate statistical analysis related to survival was determined by the log-rank test (Mantel-Cox). Curves were plotted using the product-limit method (Kaplan-Meier) and analyzed using the generalized Savage test or the Mantel-Cox test (BMDP1L; BMDP Statistical Software, Inc). The independent significance of prognostic variables related to overall survival was determined by multivariate analysis, using the Cox proportional hazards model. The level of significance was obtained by means of a score test (BMDP2L; BMDP Statistical Software, Inc). Finally, a stepwise multivariate analysis was performed to generate a model of the best linear combination of variables able to predict overall survival.

The 2 groups were well matched with regard to clinical characteristics (Table 1). In the resection group, 4 patients (9.5%) underwent noncurative resection of the bowel tumor owing to diffuse nodal and/or peritoneal spreading. No postoperative mortality was recorded. Nine patients (21.4%) experienced slight postoperative complications. All patients could be discharged from hospital and were able to undergo systemic chemotherapy as scheduled.

The mean (SD) follow-up time was 21 (15) months (range, 5-61 months; median, 16 months). None of the patients was readmitted because of bowel obstruction or other late complications of surgery. During follow-up, 28 patients (67%) died of disease within 5 to 47 months after tumor resection, whereas 14 patients are still alive. Of interest, 5 of the surviving patients (12% of the resection group) underwent curative hepatic resection after metastasis downstaging by means of chemotherapy, and they are disease free at 12, 17, 37, 43, and 61 months after bowel
Female 14 8

48

20

24

H2, 25%-50% 11 7

H3, 12

After 2001 28 14

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diagnosis to the start of chemotherapy was 8(2) days median, 12 months). The mean (SD) interval from the
treatment time was 16 (12) months (range, 5-45 months;
range, 6-12 days; median, 8 days), which was signifi-
cantly shorter than that observed in the resection group,
as expected. Seven patients (30%) had severe complica-
tions related to unresected bowel tumor. Two colon per-
 perforations, 1 intestinal hemorrhage, and 1 bowel obstruc-
tion required emergency surgery. Three cases of intestinal
obstructions were initially managed with endoscopic stent
placement, but 2 patients required surgery owing to bowel
perforation or stent dislocation. In these 7 patients, com-
 plications occurred 3, 7, 9, 10, 14, 16, and 22 months
(mean, 11 months; median, 10 months) after the initial
diagnosis. In 3 of these patients, a reduction in the size
of metastatic liver lesions was obtained by chemother-
apy, although they still remained unresectable. Surgi-
cal mortality and morbidity rates were 14% (1 patient
died of septic shock after bowel perforation), and 43%
(3 patients showed prolonged intestinal paralysis, pleu-
ral effusion, and wound infection), respectively. All but
3 patients were able to continue systemic chemother-
apy. Twenty-one patients (91%) died of disease,
whereas 2 patients were still alive 37 and 43 months af-
after the start of chemotherapy. The first is alive with un-
surpassable disease in the liver and stented bowel tumor;
the second, after shrinkage of liver metastases, under-
went successful synchronous curative resection of the
bowl tumor and chemotherapy (both groups), extent of liver involvement, and per-
formance status (Table 2), although the small sample
size did not allow reaching a significant difference.
In the whole series, age, sex, site of tumor bowel, basal
serum levels of carcinoembryonic antigen and carbohy-
drate antigen 19-9, degree of histologic differentiation,
tumor growth pattern, and different treatment schedu-
les (before and after 2001) were not significantly asso-
ciated with overall survival.
Likewise, in the resection group, tumor size, T and N staging of bowel tumor, number of resected nodes, and postoperative complications were not shown to correlate with the long-term outcome. Although patients administered novel chemotherapeutic agents, such as oxaliplatin or irinotecan, displayed no better survival rates than patients administered fluorouracil-based chemotherapy only, it has to be emphasized that the 4-year actuarial survival rate was 40% in the former and 3% in the latter (46% and 7%, respectively, in the resection group and 22% and 0%, respectively, in the chemotherapy group). On the contrary, performance status, basal serum levels of lactic dehydrogenase and alkaline phosphatase, percentage of liver involvement, potentially curative resection of the bowel tumor, and type of treatment (resection vs chemotherapy) were demonstrated to be the only variables significantly correlated with long-term survival (Table 3). On multivariate analysis, performance status, liver involvement, and modality of primary treatment were shown to be the only covariates independently associated with survival rate. Patients in the chemotherapy group had a 2-fold increased risk of

| Table 2. Curative Hepatic Resection Rate in Asymptomatic Colorectal Cancer Patients With Unresectable Liver-Only Metastases |
|---|---|---|
| Whole Series (N=65) | Resection Group (n=42) | Chemotherapy Group (n=23) |
| **No. of Patients** | **cHR, No. (%)** | **No. of Patients** | **cHR, No. (%)** | **No. of Patients** | **cHR, No. (%)** |
| Total | 65 | 6 (9.2) | 42 | 5 (11.9) | 23 | 1 (4.3) |
| Liver involvement<sup>a</sup> | | | | | |
| H1, < 25% | 25 | 4 (16.0) | 16 | 3 (18.8) | 9 | 1 (11.1) |
| H2, 25%-50% | 18 | 2 (11.1) | 11 | 2 (18.2) | 7 | 0 |
| H1 and H2, 0%-50% | 43 | 6 (13.9) | 27 | 5 (18.5) | 16 | 1 (6.3) |
| H3, > 50% | 22 | 0 | 15 | 0 | 7 | 0 |
| Performance status | | | | | |
| 0 | 19 | 4 (21.1) | 13 | 4 (30.8) | 6 | 0 |
| 1 | 29 | 2 (6.9) | 18 | 1 (5.6) | 11 | 1 (9.1) |
| 2 | 17 | 0 | 11 | 0 | 6 | 0 |
| 0/1 | 48 | 6 (12.5) | 31 | 5 (16.1) | 17 | 1 (5.9) |

Abbreviation: cHR, curative hepatic resection rate.  
<sup>a</sup>H1, H2, H3, and their respective percentages indicate the percentage of whole liver volume replaced by tumor.

| Table 3. Univariate Analysis Related to Overall Survival in 65 Asymptomatic Colorectal Cancer Patients With Unresectable Liver-Only Metastases |
|---|---|---|---|---|
| | No. of Patients | Mean Survival Time, mo | Median Survival Time (95% CI), mo | Hazard Rate | P Value<sup>a</sup> |
| Performance status | | | | | |
| 0 | 19 | 29.2 | 20.1 (13-44) | 0.69 |
| 1 | 29 | 20.8 | 14.0 (12-23) | 0.96 |
| 2 | 17 | 13.2 | 7.4 (6-14) | 1.91 |
| LDH, U/L | | | | | |
| ≤ 450 | 26 | 27.3 | 19.5 (13-38) | 0.74 |
| > 450 | 39 | 17.9 | 12.0 (10-14) | 1.28 |
| ALP, U/L | | | | | |
| ≤ 128 | 41 | 29.8 | 22.8 (14-45) | 0.66 |
| > 128 | 24 | 11.6 | 10.0 (8-12) | 2.29 |
| Liver involvement<sup>b</sup> | | | | | |
| H1, < 25% | 25 | 35.3 | 36.6 (20-52) | 0.47 |
| H2, 25%-50% | 18 | 20.4 | 13.9 (13-23) | 0.99 |
| H3, > 50% | 22 | 9.4 | 8.5 (6-10) | 3.35 |
| Curative resection of the bowel tumor<sup>c</sup> | | | | | |
| Yes | 38 | 28.0 | 21.5 (13-47) | 2.83 |
| No | 4 | 10.1 | 5.9 (5-9) | 0.90 |
| Treatment | | | | | |
| Resection | 42 | 26.3 | 15.2 (12-38) | 0.82 |
| Chemotherapy | 23 | 16.9 | 12.3 (11-14) | 1.43 |

Abbreviations: ALP, alkaline phosphatase; CI, confidence interval; LDH, lactate dehydrogenase.  
<sup>a</sup>SI conversion factors: To convert ALP and LDH to microkatal per liter, multiply by 0.0167.  
<sup>b</sup>Calculated by means of the log-rank test.  
<sup>c</sup>H1, H2, H3, and their respective percentages indicate the percentage of whole liver volume replaced by tumor.  
<sup>c</sup>Includes resection group only.
COMMENT

Treatment options for asymptomatic or relatively symptom-free CRC patients with unresectable liver-only metastases are still debated.9,10 For several decades tumor resection followed by chemotherapy has been considered the treatment of choice because it allows precise definition of the tumor stage (peritoneal carcinomatosis or other misdiagnosed metastases), treatment of associated symptoms, prevention of local complications, provision of psychological benefit for the patients who believe that the cancer has been completely removed, and, finally, performance of a reduction of neoplastic masses.9,12 In particular, tumor debulking was considered very important because it could result in more effective postoperative morbidity rates, high frequency of tumor complications requiring emergency surgery in patients who did not undergo resection, and significantly different 2-year survival rates between patients undergoing tumor resection and patients treated with chemotherapy.13,18 However, excluding a case-matched study,17 the remaining trials compared nonhomogeneous patient populations, thus complicating interpretation of results. Therefore, it is still unclear how to best treat these patients, considering that even the most recent strategy proposed by Mentha et al14 requires further validation.9,10

To overcome the limits intrinsic to noncomparative series, patients included in this study were all treated at the same institution and had matched clinical and tumor characteristics when subgrouped according to treatment op-
tion. In the resection group, surgery allowed more precise staging of abdominal disease, as in 4 cases, for instance, where it turned out to be noncurative owing to preoperative undiagnosed diffuse cancer spreading. The postoperative complication rate was low and chemotherapy could be administered to all patients after 3 weeks. Mean and median survival times and the actuarial survival rate were significantly better than those recorded in the chemotherapy group and in previous series dealing with patients undergoing systemic chemotherapy first.14-17 Although these latter patients could benefit from a shorter interval from the diagnosis to the start of chemotherapy, the complication rate related to unresected tumor was not negligible, frequently requiring emergency surgery with high postoperative morbidity. Along with good performance status and limited liver involvement, tumor resection was shown to be an independent variable associated with survival rate. Of interest, the best model to predict long-term survival included curative tumor resection along with a hepatic replacement volume of 50% or less of the whole liver. To our knowledge, this is the first time that tumor resection has been demonstrated to be an independent prognostic factor in stage IV CRC patients.

However, shrinkage of liver deposits to allow curative hepatic resection is crucial to obtain long disease-free survival in patients with unresectable liver-only metastases at presentation.10,25 In previous reports, potentially curative treatment of downstaged liver metastases ranged from 1.9% to 9% in patients treated with chemotherapy first15,17,23; conversely, these percentages were higher (15.6%-29%) in patients undergoing curative bowel resection.17,26,27 In the present series, the curative hepatic resection rate was almost 3-fold higher in the resection group than in the chemotherapy group; patients with limited hepatic involvement who underwent resection had a significantly better survival rate than those with comparable liver involvement who did not, suggesting that debulking of primary tumor may improve outcome of postoperative chemotherapy.13 Recently, an increased hepatic resection rate (33.3%) has been reported with an aggressive approach that includes curative bowel resection followed by hepatic arterial infusion and systemic chemotherapy28; this percentage is expected to exceed 40% by extending surgical material support: Galizia, Lieto, Castellano, Imperatore, Pinto, and Zamboli. Analysis and interpretation of data: Galizia, Lieto, Imperatore, Pinto, and Zamboli. Drafting of the manuscript: Galizia, Lieto, and Ordutia. Critical revision of the manuscript for important intellectual content: Galizia, Lieto, Ordutia, Castellano, Imperatore, Pinto, and Zamboli. Statistical analysis: Galizia and Imperatore. Administrative, technical, and material support: Galizia, Lieto, Ordutia, Castellano, and Pinto. Study supervision: Castellano and Zamboli.

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CONCLUSIONS

Novel surgical and chemotherapeutic treatment options could change our attitude toward asymptomatic CRC patients with unresectable liver-only metastases by giving us the tools to pursue prolonged survival, improved quality of life, and even complete cure. Bowel tumor resection allows precise disease staging, avoids complications related to unresected colon cancer, does not prevent postoperative therapy, appears to promote metastatic shrinkage and improved antitumor therapy, and allows aggressive surgery toward metastatic sites. According to our experience and those of others,2,11,13 such a treatment option is feasible for patients showing good performance status, metastatic liver involvement of less than 50% of the whole hepatic volume, and conditions for potentially curative resection of bowel tumor. In the remaining patients, chemotherapy first is preferable as palliative treatment while waiting to switch to curative surgery of distant metastases.

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**INVITED CRITIQUE**

The optimal management strategy for asymptomatic patients presenting with unresectable stage IV colorectal cancer remains controversial. Whether or not resection of the primary tumor provides a benefit to the patient of survival or prevention of secondary complications remains to be conclusively addressed. Many have devoted retrospective studies to this question, including the report by Galizia and colleagues, who make a compelling argument for proceeding with resection of the primary tumor before initiating chemotherapy. In their report, patients treated medically suffered a significant rate of secondary complications attributable to the primary tumor. Galizia et al ultimately concluded that resection of the primary tumor should be undertaken to reduce the risk of severe complications related to the unresected bowel tumor and to provide better median survival times. Although some authors such as Ruo et al report similar findings and support the surgery-first approach, others report that complication rates as low as 3% to 5% can be achieved without surgery first. Indeed, a review of the literature demonstrates that one can support surgery followed by chemotherapy or chemotherapy alone as treatment for this group of patients (i.e., equipoise).

It is fortunate that this debate has not escaped Laurence McCahill, MD, and Nicholas J. Petrelli, MD, who are leading a clinical trial effort to resolve the debate. NSABP C-10 is a phase 2 trial that specifically addresses the safety and efficacy of treating patients up front with fluorouracil, leucovorin calcium, and oxaliplatin plus bevacizumab in those patients presenting with an asymptomatic primary colon cancer in the setting of unresectable metastatic disease. We look for results from this trial to lead the way toward providing evidence and identifying a best practice.

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