ORIGINAL ARTICLE

First-Line Chemotherapy vs Bowel Tumor Resection Plus Chemotherapy for Patients With Unresectable Synchronous Colorectal Hepatic Metastases

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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.

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COLORECTAL CANCER (CRC) is the third most prevalent cancer in the world, with more than 940 000 cases and nearly 500 000 deaths occurring annually worldwide.[1] Almost 20% to 25% of patients with CRC (hereinafter referred to as CRC patients) present with distant metastases at the time of diagnosis.[2,3] The liver is involved in 80% to 90% of the cases, and in almost 50% it is the only site of metastasis.[4] From 10% to 30% of CRC patients with newly diagnosed disease and liver-only deposits have resectable metastases at presentation. In such instances, resection of the primary tumor with immediate or delayed hepatic resection is the only potentially curative option with a low mortality rate and 5-year survival rates of 18% to 46%.[5,6] However, an estimated 70% to 90% of these patients have unresectable hepatic metastases.[7] In such cases, surgery is a necessary indication in symptomatic patients with tumor complications such as intestinal obstruction, perforation, or hemorrhage, whereas

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therapeutic options for asymptomatic or relatively asymptomatic patients (nearly 80% of all cases) are still debated.[8-10] Some authors recommend resection of the bowel tumor followed by systemic chemotherapy to perform correct abdominal tumor staging, prevent tumor complications, and potentially improve patients' status and efficacy of chemotherapy through tumor load reduction.[3,11-13] In recent studies, other authors[14-17] have

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 53 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 (bilobar disease) requiring a liver resection potentially capable of jeopardizing postoperative liver function. Eight of these 53 patients (15%) were symptomatic and needed immediate surgical exploration to manage tumor complications. Among the remaining 45 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),[19] 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 pathological 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 χ^2 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.

RESULTS

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

Table 1. Clinical Characteristics of 65 Asymptomatic Colorectal Cancer Patients With Unresectable Liver-Only Metastases[a]

Characteristics	Resection Group (n=42)	Chemotherapy Group (n=23)	*P* Value[b]
Age, mean (SD) [range]	62 (13) [28-84]	59 (14) [28-82]	.39[c]
Sex			
Male	28	15	.87
Female	14	8	
Site of the bowel tumor			
Right colon	12	6	.90
Left colon	23	12	
Rectum	7	5	
Performance status			
0	13	6	.90
1	18	11	
2	11	6	
0/1	31	17	.77
CEA level, ng/mL			
≤3.5	12	5	.76
>3.5	30	18	
CA 19-9 level, U/mL			
≤37	15	4	.20
>37	27	19	
LDH level, U/L			
≤450	16	10	.87
>450	26	13	
ALP level, U/L			
≤128	27	14	.99
>128	15	9	
Liver involvement[d]			
H1, <25%	16	9	.89
H2, 25%-50%	11	7	
H1 and H2, 0%-50%	27	16	.87
H3, >50%	15	7	
Chemotherapy			
Until 2001	14	9	.84
After 2001	28	14	
Starting delay, d, mean (SD) [range]	35 (6) [25-44]	8 (2) [6-12]	<.001[c]
Grade 3-4 toxicity	19	10	.89

Abbreviations: ALP, alkaline phosphatase; CA 19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; LDH, lactate dehydrogenase.

SI conversion factors: To convert ALP and LDH to microkatals per liter, multiply by 0.0167.

[a] Because all colorectal cancers showed moderate histologic differentiation (G2) and infiltrating tumor growth pattern, these variables were excluded from statistical analyses. Unless otherwise indicated, data are expressed as number of patients.

[b] Unless otherwise indicated, calculated using the χ^2 test with Yates correction.

[c] Calculated using the unpaired *t* test.

[d] H1, H2, H3, and their respective percentages indicate the percentage of whole liver volume replaced by tumor.

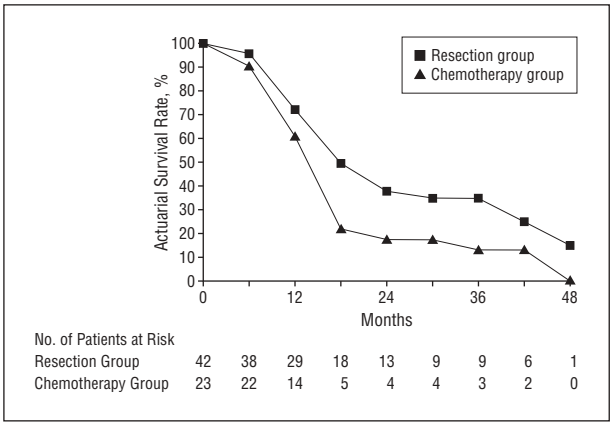

Figure 1. Actuarial survival curves in 65 patients with asymptomatic colorectal cancer and unresectable liver metastases treated with resection of the bowel tumor and chemotherapy (resection group; n=42) or with chemotherapy first (chemotherapy group; n=23). A significant difference was shown between the 2 groups (*P*=.03).

resection (2 patients underwent a successful hepatic second resection for liver recurrence). The remaining 9 patients are still being administered systemic chemotherapy. The mean and median overall survival times were 26 and 15 months, respectively; the 1- to 4-year actuarial survival rates were 72%, 38%, 35%, and 15% (**Figure 1**).

In the chemotherapy group, the mean (SD) follow-up time was 16 (12) months (range, 5-45 months; median, 12 months). The mean (SD) interval from the diagnosis to the start of chemotherapy was 8 (2) days (range, 6-12 days; median, 8 days), which was significantly shorter than that observed in the resection group, as expected. Seven patients (30%) had severe complications related to unresected bowel tumor. Two colon perforations, 1 intestinal hemorrhage, and 1 bowel obstruction 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, complications 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 chemotherapy, although they still remained unresectable. Surgical mortality and morbidity rates were 14% (1 patient died of septic shock after bowel perforation), and 43% (3 patients showed prolonged intestinal paralysis, pleural effusion, and wound infection), respectively. All but 3 patients were able to continue systemic chemotherapy. Twenty-one patients (91%) died of disease, whereas 2 patients were still alive 37 and 43 months after the start of chemotherapy. The first is alive with unresectable disease in the liver and stented bowel tumor; the second, after shrinkage of liver metastases, underwent successful synchronous curative resection of the bowel tumor and hepatic deposits. The mean and median overall survival time were 17 and 12 months, respectively; the 1- to 4-year actuarial survival rates were 61%, 17%, 13%, and 0%, respectively (Figure 1).

Overall, a curative hepatic resection after shrinkage of initially unresectable liver metastases was possible in 6 patients and it appeared to be dependent on the type of treatment (5 in the resection group and 1 in the chemotherapy group), extent of liver involvement, and performance 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 carbohydrate antigen 19-9, degree of histologic differentiation, tumor growth pattern, and different treatment schedules (before and after 2001) were not significantly associated with overall survival.

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[a]						
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.
[a]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[a]
Performance status					.01
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					.02
≤450	26	27.3	19.5 (13-38)	0.74	
>450	39	17.9	12.0 (10-14)	1.28	
ALP, U/L					<.001
≤128	41	29.8	22.8 (14-45)	0.66	
>128	24	11.6	10.0 (8-12)	2.29	
Liver involvement[b]					<.001
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[c]					.02
Yes	38	28.0	21.5 (13-47)	2.83	
No	4	10.1	5.9 (5-9)	0.90	
Treatment					.03
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.
SI conversion factors: To convert ALP and LDH to microkatals per liter, multiply by 0.0167.
[a]Calculated by means of the log-rank test.
[b]H1, H2, H3, and their respective percentages indicate the percentage of whole liver volume replaced by tumor.
[c]Includes resection group only.

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 4. Cox Proportional Hazards Model and Stepwise Multivariate Analysis Related to Overall Survival in 65 Asymptomatic Colorectal Cancer Patients With Unresectable Liver-Only Metastases

Prognostic Factor	Coefficient	Hazard Rate (95% CI)	*P* Value
Cox Proportional Hazards Model			
Performance status >1	1.1571	3.18 (2.49-3.86)	.01
LDH >450 U/L	0.3020	1.35 (0.73-1.97)	.33
ALP >128 U/L	0.8273	2.28 (1.20-3.36)	.13
Liver involvement H3, 50% of whole liver volume	1.7525	5.76 (4.69-6.84)	<.001
No curative resection	0.5079	1.66 (0.95-2.36)	.15
Treatment chemotherapy first	1.3653	3.91 (2.83-4.99)	<.001
Stepwise Multivariate Analysis			
Performance status	0.71	1.22 (0.75-1.70)[a]	.39
Liver involvement	25.90	4.65 (3.73-5.56)[a]	<.001
Treatment	8.61	2.78 (2.37-3.20)[a]	.003

Abbreviations: ALP, alkaline phosphatase; CI, confidence interval; LDH, lactate dehydrogenase.

SI conversion factors: To convert ALP and LDH to microkatals per liter, multiply by 0.0167.

[a] Indicates 95% CI of the hazard rate of cancer-related death associated with more than 50% liver involvement (H3) and chemotherapy first.

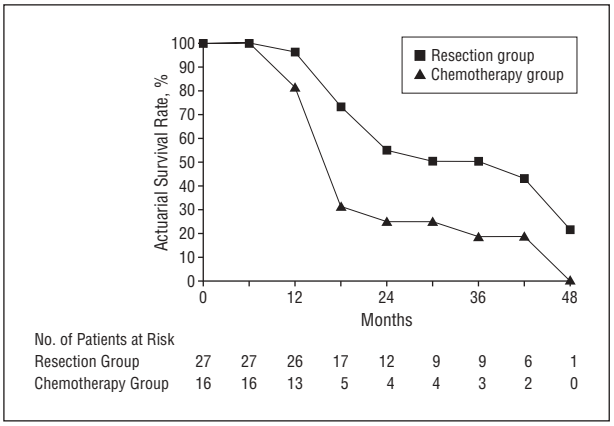

Figure 2. Actuarial survival curves in 43 patients with asymptomatic colon cancer and unresectable liver metastases involving less than 50% of the whole liver. Significantly different survival rates (*P*=.006) were shown between patients treated with resection of the bowel tumor and chemotherapy (resection group; n=27) and those treated with chemotherapy first (chemotherapy group; n=16).

cancer-related death than patients undergoing resection of bowel tumor. Metastatic seeding involving more than 50% of the whole liver was associated with a 5-fold increased risk of cancer death than more limited hepatic spread. After backward elimination, performance status was removed from the model; stepwise regression selected liver involvement and type of treatment as the best combination of variables capable of predicting long-term survival (**Table 4**). On the basis of the model generated by the stepwise process, a 4-year survival rate was plotted stratifying for liver involvement and treatment strategy. The mean and median survival times and the 4-year survival rate for 27 patients with H1 to H2 liver involvement undergoing potentially curative bowel tumor resection were 34.5 and 25.0 months and 21.5%, respectively. These figures were significantly better than those observed in 16 patients in the chemotherapy group who had H1 and H2 liver involvement (mean and median survival times, 20.6 and 13 months, respectively; 4-year survival rate, 0%) (**Figure 2**).

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.[8,12] In particular, tumor debulking was considered very important because it could result in more effective postoperative chemotherapy, as previously demonstrated for advanced renal cell and ovarian cancers.[21,22] Major drawbacks of this approach are high postoperative mortality and morbidity rates, poor control of symptoms when these are related to metastases, and, in particular, a remarkable delay in starting chemotherapy.[17,23] To avoid delayed chemotherapy, Sarela et al[23] first suggested modifying the general approach taken with these patients by immediately starting chemotherapy so as to treat systemic disease and to identify responders to chemotherapy who would have a better prognosis. Major drawbacks of this nonoperative treatment are the low percentage of responders, lack of long-term survivors, and risk of intestinal complications caused by unresected CRCs requiring, in turn, emergency surgery with high mortality and morbidity rates owing to chemotherapy-induced immunosuppression.[7]

Thus far, only 6 trials have compared the following 2 modalities of treatment: tumor resection followed by systemic chemotherapy, or systemic chemotherapy first with surgery only in case of complications or metastases that become amenable to curative resection. In 4 series, high postoperative morbidity rates, low rates of emergency surgery for tumor complications, and equivalent median survival times suggested that asymptomatic CRC patients with unresectable metastases could be safely treated without tumor resection.[14-17] On the contrary, 2 other reports showed low 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 al[24] 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 first[15,17,23]; 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 chemotherapy[28]; this percentage is expected to exceed 40% by extending surgical frontiers of distant metastases and using more effective novel immunochemotherapeutic agents such as bevacizumab and cetuximab.[27,29] Thus, to obtain a long disease-free survival, aggressive chemotherapy that eventually includes hepatic arterial infusion, major hepatectomies, and resections of other involved organs such as lung and brain must be anticipated.[25,28,30] In this scenario, immediate bowel tumor resection will allow shifting the focus of treatment toward distant metastatic sites that will eventually require aggressive surgery.

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,[1-4] 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[1] report similar findings and support the surgery-first approach, others report that complication rates as low as 3% to 15% can be achieved without surgery first.[2-4] 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 (ie, 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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