Role of Repeated Hepatectomy in the Multimodal Treatment of Hepatic Colorectal Metastases

Aziz Ahmad, MD; Steven L. Chen, MD, MBA; Anton J. Bilchik, MD, PhD

Hypothesis: Multimodal treatment consisting of repeated hepatectomy and adjuvant systemic chemotherapy for liver-confined recurrence of colorectal cancer can yield long-term survival comparable with that associated with primary hepatectomy.

Design: Retrospective analysis.

Setting: A prospective database at a tertiary referral cancer center.

Patients: Review of 274 consecutive liver resections identified 64 patients who underwent resection of hepatic colorectal metastases without ablation followed by adjuvant irinotecan hydrochloride- or oxaliplatin-based systemic chemotherapy.

Main Outcome Measures: Median and 5-year overall and disease-free survival after primary and repeated hepatectomy.

Results: At median follow-up of 40 months, median and 5-year overall survival after hepatectomy were 60 months and 53%, respectively; median and 5-year disease-free survival were 33 months and 25%, respectively. Multivariate analysis showed that less than 1 year between colectomy and liver resection (P = .001), more than 3 metastases (P = .001), no repeated hepatectomy (P = .01), and lymph node–positive primary colon cancer (P = .02) were independently predictive of worse survival. Of 28 patients (44%) with liver-confined recurrence, 19 (30%) underwent repeated hepatectomy; at median follow-up of 38 months, median and 5-year overall survival after repeated hepatectomy were 48 months and 44%, respectively. No risk factors were identified in multivariate analysis. In patients with recurrence, median and 5-year overall survival measured from primary hepatectomy were 70 months and 73%, respectively, with repeated hepatectomy vs 43 months and 43%, respectively, without repeated hepatectomy (P =.03).

Conclusion: Multimodal treatment of recurrent colorectal cancer confined to the liver should begin with consideration of repeated hepatectomy.

Arch Surg. 2007;142:526-532

Surgical resection is the only proven therapy for long-term survival in patients with hepatic colorectal metastases confined to the liver. Reports of 5-year survival after resection have improved from 30% to 40% several years ago to as high as 58% in recent series. Credit has been given to a multimodal approach that involves more sensitive preoperative imaging techniques, intraoperative detection of occult disease by means of ultrasonography, improvements in anesthesia, better surgical techniques, and more effective systemic treatment. As survival has increased, mortality has dropped to less than 3% at most experienced centers. These improvements have coincided with an increasingly aggressive surgical approach in patients whose size, number, or distribution of lesions might previously have rendered them ineligible for resection.

Even after curative resection, recurrence of disease can be expected. Up to 70% of patients will develop recurrence; an estimated 30% of these recurrences will be confined to the liver. Hepatic recurrence has been shown to be associated with factors such as the size, number, and distribution of metastases. As the number of patients undergoing aggressive resection continues to increase, isolated hepatic recurrence will become an increasingly frequent presentation.

Treatment of recurrent hepatic metastases includes systemic therapy, hepatic artery infusion, radiofrequency ablation (RFA), and repeated hepatectomy. In the past, repeated resection was avoided owing to the concern about the increased morbidity of repeated operation, but institutions experienced in hepatic surgery have shown that the morbidity rate of repeated hepatic resection is similar to that of primary resection. Up to 30% of resections for hepatic colorectal metastases are now repeated hepatectomies. Studies of survival after repeated hepatec-
tomy vary widely, some showing limited success and others showing success similar to that of primary hepatic resection. Also, little is known about the utility of the newer systemic agents after hepatic resection.

We conducted a retrospective analysis of all patients at the John Wayne Cancer Institute at St John’s Hospital who underwent resection of hepatic colorectal metastases confined to the liver during a 6-year period. All patients during this period were treated in a multimodal manner with irinotecan hydrochloride– or oxaliplatin-based systemic chemotherapy in addition to surgery. Survival and risk factors after primary hepatectomy and repeated hepatectomy were analyzed to determine the value of repeated hepatic resection in patients with recurrent hepatic colorectal metastases.

METHODS

We reviewed the medical records of 274 consecutive patients who underwent hepatic surgery at the John Wayne Cancer Institute at St John’s Hospital between January 1, 1997, and December 31, 2003. Only patients who underwent complete resection of hepatic colorectal cancer metastases confined to the liver and received adjuvant systemic chemotherapy were included. Adjunctive ablative procedures were an exclusion criterion. The treatment plan for the primary hepatic resection in all patients was determined after a history and physical examination, laboratory analysis (blood cell counts, chemistries, liver function tests, and serum tumor markers), and radiologic evaluation. All the patients underwent spiral computed tomography (CT) with intravenous contrast, and selected patients underwent magnetic resonance imaging or positron emission tomography (PET) to determine the extent of liver disease and to rule out extrahepatic disease. Patients whose disease was considered unresectable were referred for systemic treatment.

In all operative cases laparoscopic examination of the abdomen was attempted to identify any extrahepatic disease. Cellotomy was performed if laparoscopy was not possible. When there was no evidence of extrahepatic disease, intraoperative ultrasonography of the liver was performed to search for any radiologically occult disease. If metastases proved to be unresectable, RFA was performed with or without resection if the patient would be left clinically free of disease; otherwise surgery was aborted. Parenchymal transection was performed using the clamp crushing technique, sparing as much functional liver as possible. Types of resections included wedge, segmentectomy, and lobectomy.

All the patients received irinotecan- or oxaliplatin-based chemotherapy after recovery from primary hepatic surgery. Chemotherapy was administered for at least 6 months as tolerated. Blood was tested for tumor markers approximately 1 week after the operation, every 3 months for 2 years, and every 6 months thereafter; CT was undertaken every 6 months for 2 years and yearly thereafter.

If recurrence was found on follow-up, patients were further evaluated for the possibility of repeated resection if the recurrence was confined to the liver. Computed tomographic biopsy was used to confirm an uncertain diagnosis; more recently, PET was performed to further determine the extent of disease. If recurrent disease seemed to be resectable, patients were offered surgery with curative intent. If recurrent disease could not be completely resected, patients were offered systemic therapy and were reevaluated for surgery at 6- to 8-week intervals. The response to systemic therapy was recorded as partial (>50% reduction in tumor size), stabilization of disease (≤50% reduction in tumor size), or progression of disease (increase in tumor size). Patients were offered surgery as soon as all disease was deemed resectable. Patients who did not become candidates for repeated resection were considered for ablation or continued systemic treatment as tolerated and effective; those who underwent ablative procedures were excluded from analysis of survival after repeated hepatectomy. Patients who underwent repeated hepatectomy or received adjuvant systemic treatment according to their previous response and as tolerated.

Overall survival (OS) and disease-free survival were determined from the time of primary hepatectomy and from the time of repeated hepatectomy. Complications after primary and repeated hepatectomy were recorded and compared. Postoperative mortality was defined as any death within the first 30 days after hepatectomy or before discharge from the hospital.

All data were entered into a database program (Microsoft Excel; Microsoft Inc, Redmond, Wash). SPSS version 13.0 (SPSS Inc, Chicago, Ill) was used for statistical analysis. Groups were compared using analysis of variance and χ² tests. The Kaplan-Meier method was used to evaluate OS and disease-free survival; significance was determined using the log-rank test. Cox proportional hazards model was used to evaluate the prognostic importance of the following risk factors: increasing age, sex, number and size of lesions, tumor status of the lymph nodes resected with the primary tumor, preoperative carcinoembryonic antigen level, interval between colon resection and primary hepatectomy or between primary hepatectomy and repeated hepatectomy, presence of bilobar disease, and complications during surgery.

RESULTS

Of 274 patients who underwent hepatic surgery for colorectal metastases at John Wayne Cancer Institute between January 1, 1997, and December 31, 2003, 64 had metastases confined to the liver and received adjuvant irinotecan- or oxaliplatin-based chemotherapy. This study group comprised 33 men and 31 women; their median age was 63 years (range, 28-85 years). Of the 64 patients, 45 had been diagnosed as having node-positive primary colon cancer. The median number of hepatic metastases per patient was 3 (range, 1-9); the median size of each tumor was 4 cm (range, 1-12.5 cm). Operative procedures included 37 wedge resections, 19 segmentectomies, 35 lobectomies, and 1 trisegmentectomy. The mean interval between colectomy and the primary hepatectomy was 16.7 months. Liver metastases were synchronous with the primary colon cancer in 27 patients (42%); 38 (59%) had liver metastases within 1 year after colon resection. Bilobar metastases were present in 13 patients (20%).

At median follow-up of 40 months after primary hepatectomy, median and 5-year OS were 60 months and 53%, respectively, for the 64 patients. Median and 5-year disease-free survival were 33 months and 25%, respectively (Figure 1). Univariate analysis showed that a short interval between colectomy and liver resection, multiple metastases, and no repeated hepatectomy were associated with decreased OS (Table 1). Multivariate analysis confirmed the importance of these 3 factors and also identified node-positive colon cancer as an independent risk factor associated with worse OS (Table 2).

Of the 64 patients, 40 (63%) developed recurrence at any site and 28 (44%) had liver-confined recurrence. Of the 28 patients with liver-confined recurrence, 19 underwent repeated hepatectomy; the remaining 9 patients had diffuse or large metastases that could not be treated with resection alone. These patients either had
Table 1. Univariate Analysis of Risk Factors Associated With Decreased Survival After Primary Hepatectomy

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increasing age</td>
<td>.67</td>
</tr>
<tr>
<td>Male sex</td>
<td>.25</td>
</tr>
<tr>
<td>&gt;3 Lesions*</td>
<td>.005</td>
</tr>
<tr>
<td>Largest lesion &gt;5 cm</td>
<td>.08</td>
</tr>
<tr>
<td>Node-positive colon cancer</td>
<td>.64</td>
</tr>
<tr>
<td>Interval between colon resection and hepatectomy &lt;1 y*</td>
<td>.04</td>
</tr>
<tr>
<td>Carcinoembryonic antigen &gt;100 ng/mL</td>
<td>.69</td>
</tr>
<tr>
<td>Bilobar disease</td>
<td>.53</td>
</tr>
<tr>
<td>No repeated hepatectomy*</td>
<td>.01</td>
</tr>
<tr>
<td>Complication during hepatectomy</td>
<td>.31</td>
</tr>
</tbody>
</table>

*Independent risk factor associated with worse overall survival.

Table 2. Multivariate Analysis of Risk Factors Associated With Decreased Survival After Primary Hepatectomy

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Hazard Ratio</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increasing age</td>
<td>0.34</td>
<td>.55</td>
</tr>
<tr>
<td>Male sex</td>
<td>2.86</td>
<td>.06</td>
</tr>
<tr>
<td>&gt;3 Lesions*</td>
<td>4.62</td>
<td>.001</td>
</tr>
<tr>
<td>Largest lesion &gt;5 cm</td>
<td>0.96</td>
<td>.32</td>
</tr>
<tr>
<td>Node-positive colon cancer*</td>
<td>4.47</td>
<td>.02</td>
</tr>
<tr>
<td>Interval between colon resection and hepatectomy &lt;1 y*</td>
<td>11.90</td>
<td></td>
</tr>
<tr>
<td>Carcinoembryonic antigen &gt;100 ng/mL</td>
<td>0.18</td>
<td>.67</td>
</tr>
<tr>
<td>Bilobar disease</td>
<td>0.84</td>
<td>.35</td>
</tr>
<tr>
<td>No repeated hepatectomy*</td>
<td>11.10</td>
<td>.001</td>
</tr>
<tr>
<td>Complication during hepatectomy</td>
<td>0.44</td>
<td>.05</td>
</tr>
</tbody>
</table>

*Independent risk factor associated with worse overall survival.

adjunctive ablative procedures or surgery was aborted, which excluded them from analysis of survival after repeated hepatectomy. Nine of the 19 patients who underwent repeated hepatectomy received a second round of systemic chemotherapy before resection in an attempt to downsize the metastases; the other 10 patients underwent repeated hepatectomy without additional chemotherapy after recurrence was discovered. Repeated hepatectomy consisted of 14 wedge resections, 4 segmentectomies, and 1 lobectomy. The median size of recurrence was 3 cm (range, 1-5.3 cm), and the median number of tumors per patient was 1 (range, 1-5).

At median follow-up of 38 months after repeated hepatectomy, median and 5-year OS were 48 months and 44%, respectively. Median and 5-year disease-free survival were 23 months and 26%, respectively (Figure 2). Five patients were 5-year survivors; 7 patients were alive without evidence of disease at 15, 24, 29, 31, 43, 44, and 48 months, respectively; 1 patient was alive with disease at 12 months; and 6 patients died of disease. Univariate analysis identified multiple lesions and a short interval between primary and repeated hepatectomy as independent risk factors for decreased survival (Table 3). In multivariate analysis, only the latter factor approached significance for decreased survival (hazard ratio, 0.016; P = .10).

Median and 5-year OS after primary hepatectomy were significantly higher in the 19 patients who underwent repeated hepatectomy than in the 45 patients who did not undergo repeated hepatectomy (70 months and 73% vs 43 months and 43%, respectively; P = .03) (Figure 3). Of the 19 patients who underwent repeated hepatectomy, 4 had a third resection and 2 had a fourth resection. The number of patients and the length of follow-up did not allow further analysis of these patients.

After primary hepatectomy there was 1 death (2%); this patient succumbed to postoperative liver failure. There were no postoperative deaths after repeated hepatectomy. After primary hepatectomy there were 17 complications in 13 patients, for a complication rate of 20%. Complications included 3 right upper quadrant abscesses, 1 bile leak, 3 wound infections, 1 case of pneumonia, 3 pleural effusions, 2 cases of sepsis, 2 cases of deep venous thrombosis, and 2 patients with Clostridium difficile colitis. After repeated hepatectomy there were 4 complications in 3 patients, for a complication rate of 21%. Complications included 1 abscess, 2 pleural effusions, and 1 wound infection. Median blood loss was 400 mL for primary and repeated hepatectomy; only 4 patients required blood transfusion during surgery (3 after primary hepatectomy and 1 after repeated hepatectomy).

No single factor can explain the increase in survival rates after resection of hepatic colorectal metastases. Instead, a multimodal approach is credited with producing more long-term survivors. High-resolution CT and PET have resulted in better patient selection because of improved ability to detect extrahepatic disease. The use of low–central venous pressure anesthesia has decreased blood loss during surgery. A better understanding of liver anatomy, the use of vascular staplers, and hemostatic agents have led to lower perioperative morbidity and mortality rates. Intraoperative ultrasound can find metastases that are missed on preoperative workup to further ensure curative resection. Systemic chemotherapy with irinotecan- and oxaliplatin-based regimens has been shown to prolong survival in nonsurgical candidates and convert a proportion of initially unresectable patients into candidates for curative resection. The newer systemic agents are commonly used, but little is known about their utility after hepatic resection. Improved

Figure 1. Overall (OS) and disease-free (DFS) survival from the time of primary hepatectomy.
survival has led to a more aggressive approach to patients who may have not been considered in the past to be candidates for resection. Even with this aggressive approach, morbidity and mortality rates have continued to decrease; most major medical centers report mortality of 0% to 5%.

We found that more than 3 metastases, less than 1 year between colon resection and primary hepatectomy, and node-positive colon cancer were associated with decreased survival (P = .001, .001, and .02, respectively). Although the lymph node status of the primary colon cancer was not significant on univariate analysis, it became significant on multivariate analysis because of its close association with the development of hepatic metastases within 1 year after colon resection. These characteristics have been linked to poor outcome in many studies. Nineteen patients (30%) had more than 3 metastases, 38 (59%) had an interval from colon resection to primary hepatectomy less than 1 year, and 47 (73%) had lymph node–positive colon cancers. Even with the high proportion of patients who had risk factors for decreased survival, the present 5-year survival of 53% and mortality of 2% are similar to those of other recent series. The present results justify a continued aggressive approach to all patients with disease.

Despite the improvement in surgical management, recurrence remains a major problem. The reported rate of recurrence after resection of hepatic colorectal metastases is 50% to 70%; 30% of these recurrences are confined to the liver. Of the 40 patients (63%) in the present study whose disease recurred after primary hepatectomy, 28 (44%) had recurrences confined to the liver. Our higher rate of liver-only recurrence may reflect the use of PET combined with CT to identify and exclude patients with extrahepatic disease. The higher rate of recurrence confined to the liver allowed 19 (30%) of the 64 patients to undergo successful repeated hepatectomy compared with 10% to 15% reported in other studies.

In candidates for repeated resection there has been concern about increased morbidity and mortality with repeated operation. Several studies have shown that morbidity and mortality rates are similar to those associated with primary hepatic resection. Our series confirms this; there were no deaths, and the complication rate was similar to that after primary hepatectomy (21% vs 20%, respectively).

Reported data on the long-term benefit of repeated hepatectomy are inconsistent. Chu et al showed 5-year survival of only 23% and median survival of 16 months after primary resection, and Fong et al reported 5-year survival of 34% and median survival of 37 months after repeated resection. The present 5-year survival of 44% and median survival of 48 months after repeated hepatectomy are similar to the 5-year survival of 41% and median survival of 46 months reported by Adam et al. The different survival rates in these studies indicate the potential importance of adjuvant systemic chemotherapy. In the present study and the study by Adam et al, all the patients received systemic chemotherapy after primary and repeated hepatic resection. In contrast, neither Chu et al nor Fong et al reported chemotherapy as part of the patient’s multimodal treatment after most primary and repeated hepatectomies. The present study is unique in that the patients did not undergo ablative procedures in addition to resection. Univariate analysis showed that only multiple lesions and less than 1 year between primary and repeated hepatectomy were risk factors associated with decreased survival. The lymph node status of the primary colon cancer was not a significant factor in OS after repeated hepatectomy as it was for primary hepatectomy. One reason may be that patients eligible for repeated hepatectomy might have had more favorable tumor biology.

Table 3. Univariate Analysis of Risk Factors Associated With Decreased Survival After Repeated Hepatectomy

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increasing age</td>
<td>.25</td>
</tr>
<tr>
<td>Male sex</td>
<td>.64</td>
</tr>
<tr>
<td>&gt;1 lesion*</td>
<td>.04</td>
</tr>
<tr>
<td>Largest lesion &gt;5 cm</td>
<td>.77</td>
</tr>
<tr>
<td>Node-positive colon cancer</td>
<td>.58</td>
</tr>
<tr>
<td>Interval between primary hepatectomy and repeated hepatectomy &lt;1 y*</td>
<td>.01</td>
</tr>
<tr>
<td>Carcinoembryonic antigen &gt;100 ng/mL</td>
<td>.90</td>
</tr>
<tr>
<td>Bilobar disease</td>
<td>.47</td>
</tr>
<tr>
<td>Complication during repeated hepatectomy</td>
<td>.69</td>
</tr>
</tbody>
</table>

*Independent risk factor associated with worse overall survival.
Newer systemic agents, such as irinotecan, oxaliplatin, and bevacizumab, improve response and survival rates.33 Still, long-term survival is rare when these combined regimens are used alone.22,26,27 Ongoing prospective trials will determine whether there is a benefit to chemotherapy given before or after hepatic resection in patients with resectable disease. Because we did not compare the present data with groups that did not receive chemotherapy before or after hepatic resection, conclusions on any survival benefit cannot be made. In the present study the benefit of repeated hepatectomy even in those receiving systemic treatment is supported by a subgroup of 9 patients who received a second round of irinotecan- or oxaliplatin-based chemotherapy before repeated hepatectomy in an attempt to down-size metastases (data not shown). Two of the 9 patients became surgical candidates only after initiation of chemotherapy, an approach shown to be successful in retrospective data published by Adam et al.8 The other 7 patients were candidates for resection but received systemic therapy initially for other reasons (eg, high risk of surgery, potentially insufficient liver volume, or patient preference). Although systemic treatment reduced tumor volume more than 50% in only 1 of these patients (alive with disease at 12 months of follow-up), the other 6 patients still enjoyed long-term survival after repeated hepatectomy.

There has been concern that newer chemotherapeutic agents may cause damage to the liver and limit surgical options. Changes such as steatosis, steatohepatitis, sinusoidal fibrosis, and veno-occlusive lesions have been shown in the livers of patients treated with oxaliplatin or irinotecan.28-30 Gross changes observed during surgery include edema, a spongiform consistency to the liver, and a blue discoloration of the liver parenchyma (“blue liver syndrome”).30 Although the newer chemotherapeutic agents have not been definitively proved to increase surgical morbidity, complete resection should be undertaken as soon as possible to minimize the potential toxic effects of systemic therapy.30 In the present patients this approach has avoided insufficient hepatic reserve and has allowed us to achieve a postoperative morbidity rate comparable with that reported in the literature.3

Because primary hepatectomy decreases hepatic reserve, repeated hepatectomy cannot be as extensive. In this study, the median number and size of tumors removed were 1 and 3 cm, respectively, during repeated hepatectomy compared with 3 and 4 cm, respectively, during primary hepatectomy. The percentage of wedge resections was correspondingly higher during repeated vs primary hepatectomy (74% vs 42%), a finding reported by other researchers.8,11,25 These differences emphasize the importance of preserving as much parenchymal tissue as possible during the primary resection; evidence shows that outcome is not changed by the type of resection as long as margins are at least 1 cm.31,32

In no case was RFA used for completely resectable disease. Radiofrequency ablation has been associated with high local recurrence rates and has not been shown to have the survival benefit of resection.33 Still, RFA may be the only chance for long-term survival in patients with metastases not amenable to resection.3

Few studies have reported a long-term survival benefit in select patients undergoing repeated hepatectomy. A recent article by Wei et al34 showed 5-year survival of 52% after primary resection. Improved survival in the present study may in part be due to the more limited disease in those undergoing repeated hepatectomy and the exclusion of patients treated with ablative procedures. Also, the use of adjuvant chemotherapy after primary and repeated hepatectomy may extend disease-free intervals and prevent further spread of metastatic disease more effectively than either chemotherapy or hepatectomy alone. The 5-year survival rate for these select patients with large, multiple, and bilobar metastases is comparable with the 71% reported for patients with a solitary liver lesion.34

In conclusion, multimodal treatment has led to improved survival after resection of hepatic colorectal metastases. As survival rates have increased, surgeons have become more aggressive in their attempts to resect metastases. Most patients will eventually develop recurrence of their disease. In select patients whose recurrence is confined to the liver, repeated hepatectomy may offer the best chance of long-term survival. Because of the potential hepatic toxic effects of newer systemic agents, resection should be offered as soon as metastases are deemed resectable. Because the risk and survival benefit approximate those of primary hepatic resection, repeated hepatectomy should be the initial consideration in the multimodal treatment of recurrent hepatic colorectal cancer metastases.

Accepted for Publication: January 23, 2006.
Correspondence: Anton J. Bilchik, MD, PhD, John Wayne Cancer Institute, 2200 Santa Monica Blvd, Santa Monica, CA 90404 (bilchika@jwci.org).
Author Contributions: Study concept and design: Ahmad, Chen, and Bilchik. Acquisition of data: Ahmad. Analysis and interpretation of data: Ahmad, Chen, and Bilchik. Drafting of the manuscript: Ahmad and Bilchik. Critical revision of the manuscript for important intellectual content: Bilchik. Statistical analysis: Chen. Study supervision: Bilchik.
Financial Disclosure: None reported.
Funding/Support: This study was supported by funding from the Rod Fasone Memorial Cancer Fund, Henry L. Guenther Foundation, William Randolph Hearst Foundation, Davidow Charitable Fund, Harold J. McAlister Charitable Foundation, Compaq Computer/Judy and Sandy Litvack, Joseph B. Gould Foundation, John Wayne Cancer Institute Auxiliary, Wrather Family Foundation, Patricia C. Brown Foundation, Family of Robert Novick, Samueli Foundation, and Ruth Weil.
Previous Presentation: This paper was presented at the 114th Annual Meeting of the Western Surgical Association; November 14, 2006; Los Cabos, Mexico; and is published after peer review and revision. The discussions that follow this article are based on the originally submitted manuscript and not the revised manuscript.

REFERENCES


**DISCUSSION**

William C. Chapman, MD, St Louis, Mo: Before I begin, I need to disclose that I am one of a number of cofounders of a company, Pathfinder Therapeutics, which has been formed to conduct a clinical trial investigating the use of image guidance in liver surgery, which I will not discuss today. As an aside, we presented our initial experiences in this area in 1999 at this meeting and were fortunate to receive the Bradley J. Aust Award for that presentation, which we were very proud of. We subsequently received several NIH [National Institutes of Health] grant awards to further develop this area and are now preparing our clinical trial.

For this paper today and this report, Dr Ahmad and his colleagues from the John Wayne Cancer Institute in Santa Monica report their encouraging experience performing repeated resections in 19 out of 274 patients who initially received hepatic resection at their center and were followed over a 7-year time period. Importantly, the authors discuss and demonstrate excellent long-term survival in these 19 patients, with median survival of 70 months and a 5-year OS rate of 73% when taken from the time of initial resection.

This is a very important point and one that needs to be repeated. namely, that after hepatic resection of colorectal metastases, patient follow-up is important and not just to document a recurrence for which there are no further therapeutic options but rather to identify patients for whom further surgical therapy may be possible. This point is not always considered, especially by medical oncologists who most frequently follow these patients.

There are several aspects of this manuscript that I would like the authors to clarify.

1. As we have heard, the authors stress the role of systemic chemotherapy, particularly irinotecan and oxaliplatin, as potentially facilitating the improvements and outcomes seen in this series and suggest that in some cases it may even be considered in patients with hepatic recurrence. However, of the 9 patients who received systemic therapy prior to hepatic resection only 3 had significant responses to therapy. In addition, the authors point out the potential hepatic toxicity that this may entail and clearly limit the ability for successful resection. So, again, please clarify what you are suggesting and what strategy ought to be considered by the medical oncologist following such a patient. In my view, we really don't know whether systemic therapy prior to hepatectomy given as a neoadjuvant strategy is beneficial, but may learn so as a result of the EORTC [European Organization for Research and Treatment of Cancer] trial, which has now accrued over 300 patients randomized to either immediate hepatic resection or delayed surgery after initial systemic therapy. Until we have these results, I think we have to be cautious about recommending the use of these therapies, especially in patients with potentially resectable disease.

2. What is your stance on the use of ablative therapy? In the past, the John Wayne Cancer Institute has played a leading role in the use of ablative therapy, initially cryoablation, and more recently RFA as a treatment strategy for metastatic colorectal cancer, but you seem to be distancing yourself from this therapy in this manuscript. Under what circumstances should this be used, and what about the use of percutaneous RFA?

3. You highlight the improvements in diagnostic imaging which have contributed to improved patient outcomes, including CT/PET and MR [magnetic resonance imaging]. However, 9 out of the 28 patients (32%) who were selected for repeated hepatectomy were unable to undergo successful resection. What about these 9 cases prevented the resection, and shouldn't this have been able to be detected preoperatively?
4. Your statistical analysis states that not undergoing repeated hepatectomy is associated with decreased long-term survival. This would suggest that patients who have a primary liver resection should actually hope for a second recurrence in the liver that is resected. I just don’t think that that is really the case. Could you clarify this further for us?

5. I would suggest that you may reexamine your statistical analysis. You report in univariate analysis that node-positive colorectal cancer was not associated with long-term survival, and this was at a P value of .60, not even close, yet you report in multivariate analysis that this is an important variable.

**Dr Bilchik:** The treatment of metastatic colon cancer has clearly evolved over the past few years. More systemic drugs have been approved in the past 5 years than for any other malignancy, and who would have thought that response rates of up to 80% in patients with widespread metastatic disease would be possible? The bar has, therefore, been elevated by our medical oncology colleagues, and it is, therefore, incumbent upon us as surgeons to carefully evaluate the role of these drugs either before or after hepatectomy, a procedure that we know to be the only curative option.

In the absence of a prospective randomized trial, it is difficult to determine whether the improvement in survival is a consequence of more aggressive hepatectomy or the additive systemic therapy in eradicating micrometastatic disease. Fortunately, as you mentioned, a prospective randomized trial has been completed by Dr Nordslinger (EORTC [European Organization for Research and Treatment of Cancer] No. 40983), and the survival data should be available in the next year or 2. I do think, however, that the systemic therapy in our study did impact survival because this was a high-risk group with 60% of patients developing liver metastasis within a year of primary colectomy.

There is also no doubt that patient selection played an important role in our study. The use of PET imaging as described by Dr Strasberg at your institution has largely eliminated unnecessary hepatectomies by excluding patients with extrahepatic disease. It also improves the chance of early detection of hepatic recurrence. With careful staging and effective systemic therapy, 30% of patients undergoing primary resection could subsequently undergo repeated resection and still achieve survival similar to that seen after primary hepatectomy. This is not meant to suggest that recurrence is a favorable prognostic factor, since 38% of patients in the primary hepatectomy group are still disease free at a mean follow-up of 3 years.

Also let me clarify for you that it was not 19 out of 274 who underwent repeated hepatic resection in our study but rather 19 out of 64 patients. Patients were only selected for this study if they received irinotecan or oxaliplatin-based chemotherapy.

Regarding your question on RFA, we typically use it as an adjunct to hepatectomy or percutaneously in high-risk patients. Most studies reporting high recurrence rates do so using first-generation technology. With more sophisticated technology and better intraoperative imaging, this is likely to decrease. Despite this, recurrence rates, as we have reported, for tumors greater than 3 cm are still unacceptably high. I agree with you that careful consideration should be given to avoid ablation in these patients, particularly if they have resectable disease. In fact, we have recently shown that the 5-year survival was 20% and the median survival 25 months in patients undergoing ablation and resection, significantly less than the 53% five-year survival after resection alone.

The P value you are referring to (.60) in the univariate analysis for node-positive colon cancer became positive in multivariate analysis because every patient who developed liver metastases within 1 year had node-positive colon cancer.

Regarding downsizing or downsizing liver metastasis with neoadjuvant chemotherapy, we did only have a limited number of patients in this study to make any meaningful conclusions, but we and others have found that up to 20% of patients with unresectable disease can undergo resection. An increasing problem, however, that we face is the overtreatment with chemotherapy leading to much sicker livers, which ultimately may preclude patients from curative resection. I therefore agree with you that resectable tumors should be considered for early resection, and patients receiving neoadjuvant chemotherapy should be evaluated at regular intervals in a multidisciplinary fashion and referred for resection after 3 to 4 cycles of chemotherapy or as soon as the tumors become resectable.

**Thomas A. Stellato, MD, Cleveland, Ohio:** Can you tell us a little bit about the primary tumors? Was there a difference in the margin status between those patients who did not have recurrence and those who did have recurrence?

**Dr Bilchik:** In this study all patients had a negative pathologic margin, although sometimes close. There was no difference in margin status in those with recurrence. Recent reports have demonstrated that even a 1-cm margin is adequate because of low local recurrence rates.

**Alden H. Harken, MD, Oakland, Calif:** When patients are evaluated for major surgical stress, it is the other organs that dictate acute and long-term survival. We all recognize that liver function tests (LFTs) don’t reflect it. You have already indicated that the chronic use of chemotherapeutic agents really depletes hepatocellular function. What do you do to assess liver function? We all recognize that LFTs are a blunt tool; salure, is it galactose clearance? You must have some strategy for assessing liver function that can help us when we assess somebody for a cardiac or an abdominal aortic aneurysm. It is frequently the liver that nails us.

**Dr Bilchik:** We have entered a very complex era in hepatic surgery with these novel systemic agents, particularly since there is no specific pathological feature that clearly defines the changes seen. This has become a subject of much debate among the pathologists. Steatosis, steatohepatitis, sinusoidal obstructive features, and cirrhosis have all been described. There is also conflicting data as to whether irinotecan- or oxaliplatin-based therapy is more toxic to the liver. Regardless, there is general consensus that the hepatotoxicity is generally related to the length of time on chemotherapy. Hence, patients should be considered for early resection. Unfortunately, there is also no preoperative biochemical parameter that is useful in predicting hepatotoxicity. Surgeons often describe a blue, congested, spongy liver that bleeds more. Most times these patients have normal liver function test results. More studies are therefore needed to improve our strategies for preoperative evaluation, particularly for those patients who have received extensive preoperative chemotherapy.

**Robert Sticca, MD, Grand Forks, ND:** Of the 28 patients who were considered candidates for repeated resection, 19 of them had resection. You then compared the survivals between those and the other 9 who did not have resection. Do you think that there is a selection bias in those 19 patients, as they are probably the ones with smaller tumors, or that the tumor was in an anatomical location that allowed resection?

It is also surprising that in the 9 patients who did not undergo resection, you had a 43% 5-year survival rate. Did those patients undergo either additional systemic therapy or RFA or some other method of treatment, as their survival rate was much higher than 1 would expect without further treatment?

**Dr Bilchik:** The 19 patients who had resection clearly had lesions that were in resectable locations. The 9 patients did in fact undergo ablation with systemic therapy. The 43% 5-year survival is for all 21 patients with recurrence who did not have a repeated hepatectomy.

**Financial Disclosure:** Dr Chapman is a company founder of Pathfinder Therapeutics, Inc.