

## Original Investigation

# Long-term Outcomes Following Tumor Ablation for Treatment of Bilateral Colorectal Liver Metastases

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**IMPORTANCE** Ablative therapies extend the capability of delivering potentially curative treatment for bilateral hepatic colorectal metastases.

**OBJECTIVE** To compare the long-term effectiveness of ablation with that of resection in patients with bilateral hepatic colorectal metastases.

**DESIGN** Review of a prospective database of 2123 operative cases of hepatic colorectal metastases.

**SETTING** A large institution with expertise in ablation and resection.

**PATIENTS** Patients with bilateral colorectal liver metastases undergoing operation with a curative intent. A total of 141 patients had been treated with bilateral resection (BR) and 95 had undergone ablation.

**INTERVENTIONS** Radiofrequency or microwave ablation alone or in combination with resection (A/R) compared with BR.

**MAIN OUTCOMES AND MEASURES** We compared tumor characteristics and operative and postoperative outcomes using  $\chi^2$  or Wilcoxon tests as appropriate and assessed overall survival differences between the 2 groups using the log-rank test.

**RESULTS** During the study, 141 patients were treated with BR and 95 patients with A/R. The A/R group was a significantly poorer prognostic group than the BR group as judged by the Clinical Risk Score ( $P < .01$ ). There was no difference in median operative time (A/R: 280 minutes, BR: 282 minutes;  $P = .52$ ), but a lower blood loss (A/R: 300 mL, BR: 500 mL;  $P < .01$ ) and a shorter length of stay (A/R: 7 days, BR: 9 days;  $P < .01$ ) was achieved in the A/R group. Long-term outcome was not significantly different between the groups (5-year overall survival, A/R: 56%, BR: 49%;  $P = .16$ ).

**CONCLUSIONS AND RELEVANCE** Treatment of bilateral, multiple hepatic metastases with combined resection and ablation was associated with improved perioperative outcomes without compromising long-term survival compared with bilateral resection. Ablative therapies extend the capability of delivering potentially curative treatment for bilateral hepatic colorectal metastases.

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Resection of colorectal metastases confined to the liver improves the overall survival of patients and offers the potential for cure.<sup>1-5</sup> Patients with bilateral liver metastases are less likely to be resectable with conventional techniques. Strategies for managing patients with bilateral liver metastases include multiple simultaneous liver resections, staged approaches to resection (with or without portal vein embolization), or attempts at reducing tumor burden using systemic or local chemotherapy.<sup>6,7</sup>

In the past decade, ablative techniques have emerged as an option to locally treat liver tumors including colorectal liver metastases. The role of ablation in patients with colorectal liver metastases is unclear. Previous series have suggested that ablation yields an improvement in survival compared with chemotherapy alone for unresectable metastases but is inferior to resection for resectable metastases.<sup>8</sup> A recent attempt to establish clinical practice guidelines concluded that there was insufficient evidence on which to base guidelines, with wide variability in 5-year survival (15%-55%) and a compelling need for more research to determine the efficacy and usefulness of ablation.<sup>9</sup>

Given the challenges to treating patients with bilateral colorectal liver metastases, ablative techniques may increase the number of patients eligible to be treated with a potentially curative intent. The objective of this study was to compare perioperative and long-term outcomes in patients with bilateral colorectal liver metastases treated with ablation with or without resection (A/R) to patients treated with the historical gold standard of bilateral resection (BR).

## Methods

Patients operatively treated for bilateral, multiple colorectal liver metastases between 1999 and 2008 were identified from a prospectively maintained database containing demographic, clinical, operative, pathologic, and follow-up data. Prior to 2004, patients with resectable bilateral colorectal metastases underwent bilateral resection in either a 1-stage or 2-stage approach. Surgeons at our institution began using ablation (primarily radiofrequency ablation) more frequently in 2004. In general, patients with bilateral colorectal metastases undergo BR if sufficient parenchyma can be safely preserved. Patients with borderline resectable metastases or with unresectable metastases amenable to complete treatment with ablation undergo ablation alone or in combination with resection.

To minimize the bias from patient selection that has occurred in the more contemporary period, we compared patients treated by ablation alone or in combination with resection from 2004-2008 (A/R group) with cases treated by conventional BR from 1999-2003 (BR group). Some of the patients in this study were included in prior reports on outcomes of metastatic colorectal cancer at our institution. The institutional review board at Memorial Sloan-Kettering Cancer Center approved this study.

We calculated the Clinical Risk Score (CRS) for each patient included in the analysis.<sup>10</sup> The CRS is a prediction tool

consisting of 5 clinical variables: node-positive primary cancer, disease-free interval less than 12 months, multiple liver metastasis, largest diameter of any liver metastasis greater than 5 cm, and preoperative serum carcinoembryonic antigen level greater than 200 ng/mL. Based on CRS, patients were grouped into 2 categories: low CRS (0, 1, or 2) and high CRS (3, 4, or 5).

We compared baseline patient and tumor characteristics, operative time, blood loss, length of hospital stay, and 30-day mortality between patients in the 2 groups using the  $\chi^2$  test for categorical variables and the Wilcoxon test for continuous variables. We assessed overall survival differences between the 2 groups using the log-rank test. All statistical tests were 2 sided, and we considered  $P < .05$  indicative of statistically significant differences.

## Results

During the defined study periods, 141 patients were treated with BR and 95 patients underwent ablation, either alone ( $n = 9$ ) or in combination with resection ( $n = 86$ ). The median age was 62 years, with no difference between groups (Table 1). More patients treated with the combined approach had colon primary cancers compared with the resected group, and patients treated with ablation were more likely to undergo simultaneous colorectal resection (23% vs 4%). Patients treated with a combined strategy in general had a higher CRS, primarily attributed to shorter disease-free intervals (Figure 1). In contrast, patients treated with resection had higher carcinoembryonic antigen (CEA) levels, number of tumors, and size of largest tumor.

Operative time was similar between the 2 groups, while blood loss was significantly greater in patients treated with BR (Table 2). Three patients (2.1%) died within 30 days of operation in the resection group compared with 1 patient in the A/R group. The median length of stay was 9 days following resection and 7 days following ablation with or without resection ( $P < .001$ ).

The median follow-up in patients treated with resection was 44 months and 23 months in patients treated with the combined approach. Overall survival at 3 years was 67% in the BR group and 77% in the A/R group; after 5 years, overall survival was 49% and 56%, respectively ( $P = .16$ , Figure 2).

## Discussion

This comparative analysis of patients with bilateral colorectal liver metastases demonstrates the perioperative and long-term safety of a combined ablative strategy compared with the conventional gold standard of BR. Patients treated with ablation, either alone or in combination with resection, had less intraoperative blood loss, similar perioperative mortality, shorter length of hospitalization, and similar overall 5-year survival.

The long-term survival in patients treated with the combined approach in this study is particularly encouraging given their high-risk clinical characteristics. More than half of patients in the A/R group presented with a CRS of 3 or greater com-

Table 1. Characteristics of Patients Included in the Study

	No. (%)		P Value
	Bilateral Resection (n = 141)	Ablation ± Resection (n = 95)	
Female	62 (47)	41 (43)	.53
Age, median (IQR), y	61.4 (53.6-69.2)	63.0 (53.6-71.0)	.43
Primary in colon	94 (70)	78 (82)	.03
Simultaneous colorectal resection	6 (4)	22 (23)	<.001
Primary nodal status			.25
N0	43 (31)	40 (42)	
N1	62 (45)	36 (38)	
N2	32 (23)	19 (20)	
Disease-free interval, median (IQR), mo	8.9 (2.4-19.9)	0 (0-0)	<.001
CEA, median (IQR), ng/mL	29.2 (7.9-166.3)	7.9 (2.9-28.3)	<.001
No. of tumors, median (IQR)	4.0 (2.0-5.0)	3.0 (2.0-4.0)	.005
Size of largest tumor, median (IQR), cm	4.1 (2.5-6.0)	2.3 (1.5-3.6)	<.001
Clinical Risk Score, >2	42 (31)	46 (51)	.003
Ablation alone	NA	9 (9)	NA
Ablation ± resection		86 (91)	
Ablation			
Radiofrequency	NA	88 (91)	NA
Microwave		9 (9)	

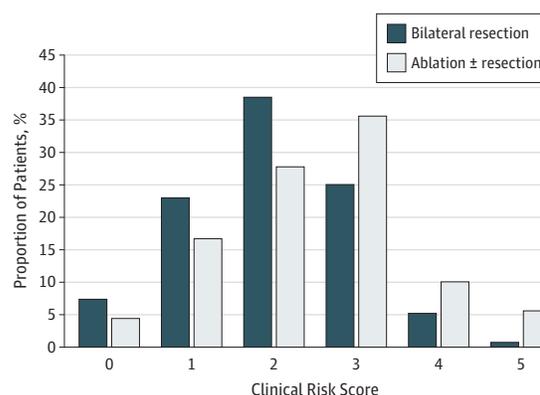
Abbreviations: CEA, carcinoembryonic antigen; IQR, interquartile range; NA, not available.

pared with 31% of patients who underwent BR. This difference was predominantly driven by the shorter disease-free interval in patients who underwent ablation. The median disease-free interval in this group was zero, indicating that most patients presented with synchronous liver metastases. In contrast, patients who underwent BR had larger tumor burden, evidenced by the higher number of metastases, size of the largest metastasis, and CEA level. In the more contemporary time frame, patients with high tumor burden were appropriately selected for resection rather than ablation; therefore, they were noticeably absent from this group.

This study is strengthened by the high quality of the data. All patients were treated at a single institution with extensive experience caring for patients with colorectal liver metastases. Data were prospectively collected and follow-up was complete. We chose to focus on overall survival as an indicator of long-term efficacy because it is objective and of most importance to patients.

The conclusions from this study are most limited by the selection bias inherent in this comparison. The optimal study design to address this question would be a prospective, randomized clinical trial. Unfortunately, surgeons have been relatively unsuccessful at assessing the efficacy of new technologies with randomized trials and this technology is no exception. Technologies instead are generally introduced into general practice and rapidly adopted as part of standard care. A randomized trial would be particularly difficult to conduct in this setting because the selection of patients for ablation or resection seems intuitive. In general, patients with multiple tumors confined to one region of the liver or with large solitary metastases should undergo resection. Ablation in these settings would be, at best, inefficient and, at worst, ineffective. In contrast, ablation may play a role for patients with a limited number of small metastases deep within the hepatic parenchyma. In this scenario, abla-

Figure 1. Risk Score Distribution



Distribution of Clinical Risk Score among patients treated with bilateral resection or ablation with or without resection (P = .002).

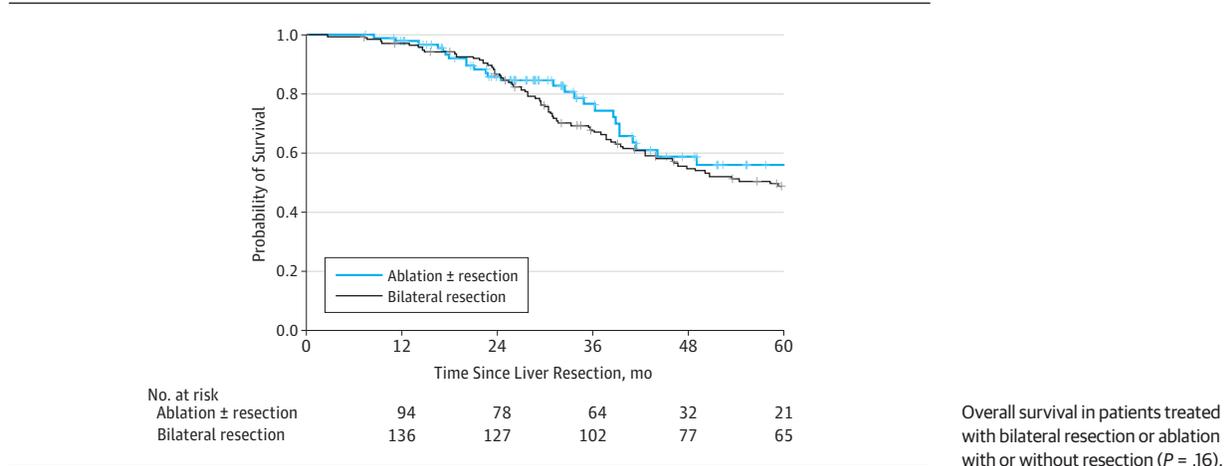
Table 2. Operative and Perioperative Outcomes in Patients Treated With Bilateral Resection or Ablation ± Resection

	Median (IQR)		P Value
	Bilateral Resection (n = 141)	Ablation ± Resection (n = 95)	
Total operative time, min	282 (238-336)	280 (219-330)	.52
Intraoperative blood loss, mL	500 (300-1000)	300 (200-420)	<.001
30-d mortality, No. (%)	3 (2)	1 (1)	.52
Length of stay, d	9 (7-11)	7 (6-9)	<.001

Abbreviation: IQR, interquartile range.

tion allows for optimal parenchymal preservation and extends potentially curative treatment to patients who might otherwise be deemed unresectable.

Figure 2. Probability of Survival



We attempted to address the inherent selection bias as much as possible by selecting patients who underwent BR from the time frame prior to the adoption of ablation at our institution. As a result, this group represents a broadly representative group of patients with bilateral metastases, rather than patients who were specifically selected not to receive ablation. Although the 2 groups are not perfectly matched (Table 1), the higher CRS in the ablation group suggests that, if anything, the long-term results should favor the resection group. The comparable long-term survival despite this potential bias is reassuring. Furthermore, although systemic treatment of patients with colorectal liver metastases has improved during this period, the incremental benefit has been modest, with overall survival in the absence of surgery between 20% and 30% at 3 years.<sup>11,12</sup> The 3-year survival in patients who underwent ablation in this study was 77%, 3 times that of these contemporary patients treated with chemotherapy only. Follow-up in the ablation group was shorter than in the resection group given the different periods, thus, longer follow-up ideally including patterns of recurrence would be beneficial.

This study contributes to the growing body of literature confirming the safety and efficacy of ablation in the treatment of colorectal liver metastases. Abdalla and colleagues<sup>8</sup> from the MD Anderson Cancer Center reported their experience in a series of patients with metastases confined to the liver. With a me-

dian follow-up of 21 months, patients who underwent resection achieved better 3-year survival than patients who underwent ablation (73% vs 40%). However, the authors reserved ablative strategies for patients deemed unresectable at the time of laparotomy, making it difficult to compare outcomes in these heterogeneous groups. In a similar study from the Cleveland Clinic, 234 patients who were not candidates for resection underwent laparoscopic ablation.<sup>13</sup> Five-year survival in this group of patients was only 18%; however, a significant proportion of patients had extrahepatic disease and most patients had been treated extensively with chemotherapy prior to operation. The authors concluded that survival in these patients would be near zero and that the use of ablation in this group achieves a survival advantage. Our study builds on these findings by limiting inclusion to patients with bilateral liver metastases in whom ablation was more liberally adopted with excellent long-term outcomes. Future research may compare these patients with a larger group of patients treated with ablation alone, perhaps including a percutaneous ablation group.

In summary, treatment of bilateral hepatic colorectal metastases with a combined ablative strategy yields good perioperative outcomes and does not compromise long-term overall survival. Ablative therapies may extend the capability of delivering potentially curative treatment for patients with bilateral hepatic colorectal metastases.

#### ARTICLE INFORMATION

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**Acquisition of data:** Jarnagin and Tuorto.

**Analysis and interpretation of data:** Karanicolas, Gonen, Allen, and D'Angelica.

**Drafting of the manuscript:** Karanicolas, Gonen, Tuorto, Allen, D'Angelica, and Fong.

**Critical revision of the manuscript for important intellectual content:** Karanicolas, Jarnagin, DeMatteo, and D'Angelica.

**Statistical analysis:** Karanicolas and Gonen.

**Administrative, technical, and material support:** Tuorto.

**Study supervision:** Allen, DeMatteo, D'Angelica, and Fong.

**Conflict of Interest Disclosures:** None reported.

**Previous Presentation:** This study was presented at the American College of Surgeons Hepatobiliary Paper Session; October 6, 2010; Washington, DC.

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## Invited Commentary

## To Ablate or Not to Ablate?

Karen L. Sherman, MD; David J. Bentrem, MD, MS

**Karanicolas and colleagues<sup>1</sup> report** a retrospective single-institution experience of combined tumor ablation and resection vs resection alone in the treatment of a highly selected group of patients with bilateral hepatic colorectal metastases. They identified that patients treated with a combined approach had decreased operative



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blood loss and length of stay; however, they had similar operative time, 30-day mortality, and 5-year overall survival. The authors concluded that treatment with a combined approach was associated with improved perioperative outcomes, although similar 5-year overall survival.

The authors are to be commended for their contribution in further defining the role of ablation in the treatment of colorectal hepatic metastases. Although resection is the gold standard treatment modality, the evidence for the use of radiofrequency ablation, either alone or in conjunction with surgery,

is less well defined.<sup>2</sup> The available literature consists primarily of institutional series with both resectable and unresectable disease, heterogeneous outcome measures, and contradictory results, making it difficult to draw conclusions. For example, the analysis by Abdalla et al<sup>3</sup> of 358 patients with primarily unilateral colorectal hepatic metastases treated with ablation, resection, or both demonstrated improved overall survival among those who underwent resection alone over those who underwent a combined resection and ablation approach. Direct comparative studies remain necessary to better clarify the treatment effect of ablation on outcome.

Still, ablation is increasingly being used in patients with resectable and unresectable colorectal hepatic metastases.<sup>4</sup> As treatment intensity and the costs at the end of life continue to escalate,<sup>5</sup> we must continue to evaluate the outcomes, overall costs, out-of-pocket costs, and patient quality of life to provide more complete information regarding treatment options when counseling patients with advanced disease.

## ARTICLE INFORMATION

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