Role of Intraoperative Thermoablation Combined With Resection in the Treatment of Hepatic Metastasis From Colorectal Cancer

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Hypothesis: Thermoablation, either cryosurgical ablation (CSA) or radiofrequency ablation (RFA), combined with resection is effective in the treatment of extensive bilobar colorectal metastasis.

Design: Retrospective analysis of a prospective hepatobiliary surgical database.

Setting: Tertiary care referral center.

Patients: Consecutive patients with colorectal hepatic metastases selected for surgical treatment.

Interventions: All patients underwent hepatic resection combined with CSA or RFA.

Main Outcome Measures: Local recurrence rates at ablation sites, overall survival, disease-free survival, and hepatic disease–free survival.

Results: Between January 1, 1998, and December 31, 2003, 665 patients with colorectal metastases underwent hepatic resection. Of these, 39 (5.9%) had additional intraoperative thermoablative procedures (19 RFA, 20 CSA). There was 1 (3%) postoperative death not directly associated with the ablation, and the total morbidity rate was 41% (16 of 39). No RFA-related complication occurred; however, 3 patients developed an abscess at cryoablation sites. Actuarial 3-year survival was 47% for the entire group, with a median follow-up of 21.1 months (range, 0.5-71.4 months). The median disease-free survival was 12.3 months (range, 8.4-16.2 months). Overall, the local in situ recurrence rate according to number of ablated tumors was 14% for RFA and 12% for CSA. Tumor size correlated directly with recurrence ($P = .02$) in RFA-treated lesions.

Conclusions: Ablation combined with hepatic resection is rarely necessary or applicable. However, in selected patients whose tumors were otherwise unresectable, additional use of ablation allows effective clearance of disease. In these patients with extensive bilobar disease, recurrence rates are high, but long-term survival is encouraging and may be improved with aggressive postoperative chemotherapy.

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In the United States, colorectal cancer is the third most common type of cancer in both men and women. Approximately one-quarter of patients present with synchronous liver metastases, and an additional 35% to 45% of patients will develop hepatic metastases during the course of their disease.1 Most patients have disseminated disease and, if untreated, have a median survival of less than 1 year. With modern chemotherapy, median survival has increased to more than 20 months.2 For the minority of patients with disease confined to the liver, hepatic resection remains the only potentially curative therapy and is safe, with mortality rates of less than 5% in high-volume centers.3-5 However, most patients with liver-only metastases are not candidates for resection because of bilobar disease that is not amenable to complete extirpation. In an attempt to increase resectability, novel approaches such as neoadjuvant chemotherapy, preoperative portal vein embolization, and 2-stage hepatectomy have been used. Despite these strategies, not all metastases are safely resectable with anatomic and/or wedge resections. Interstitial thermoablative techniques involving freezing (cryosurgical ablation [CSA]) or radiofrequency ablation (RFA) allow parenchyma-sparing treatment of hepatic tumors in such circumstances.

Cryosurgical ablation devices cause tumor cell death by ice crystal formation during rapid freezing, with resultant destruction of normal cellular structures. Several studies6-9 have demonstrated significant long-term survival after CSA in selected patients; however, the instrumentation has

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been cumbersome and substantial complication rates have been reported.\textsuperscript{9-11} Radiofrequency ablation is currently the most commonly used ablative technique, and a number of studies have shown that it is safe.\textsuperscript{10-14} As a result of its technical simplicity and safety, RFA is gaining popularity as the preferred modality for local ablation of unresectable tumors in many centers. During RFA, thermal energy from alternating current in the radiofrequency range is conducted to surrounding tissue, resulting in desiccation, microvascular injury, and coagulative necrosis. Either technique can be performed percutaneously, laparoscopically, or via laparotomy. Few reports describe outcomes in patients undergoing hepatic resection combined with simultaneous thermoablative techniques.\textsuperscript{8,10-12,15-17}

The purpose of this study was to review our experience with patients undergoing partial hepatectomy combined with intraoperative thermoablation, as well as to analyze the utility and outcome of this strategy.

**METHODS**

We used a prospectively maintained hepatobiliary surgery database to identify a total of 665 patients with colorectal hepatic metastases resected at Memorial Sloan-Kettering Cancer Center from January 1, 1998, through December 31, 2003. Of this total, 39 patients (5.9%) who underwent hepatic resection combined with additional thermoablative procedures (RFA in 19 and CSA in 20) are the subject of this study. Institutional review board approval for this study was obtained, and data collection adhered to regulations of the Health Insurance Portability and Accountability Act.

All patients routinely underwent preoperative abdominal and pelvic computed tomographic (CT) scans, chest roentgenograms or chest CT, and colonoscopy. Other imaging studies such as ultrasonography, magnetic resonance imaging, and positron emission tomography (PET) were obtained at the discretion of the treating surgeon. Preoperative chest CT and PET scanning was performed in 34 (87%) and 21 (54%) patients, respectively. Liver function was evaluated with standard serum biochemical tests and Childs-Pugh classification. No patient with biochemical evidence of cirrhosis was included in this series.

A standardized approach to hepatic resection was used and has been previously published.\textsuperscript{18} Briefly, this method involves low central venous blood pressure, vascular control, and parenchymal transection using a clamp-crushing technique under intermittent Pringle maneuver. Intraoperative ultrasound (IOUS) was carried out in all patients and was also used to guide placement of the CSA and RFA probes. Inflow arrest was not routinely performed for ablations. The RFA was administered by means of a 15-gauge needle with a retractable curved electrode configuration (RITA Medical Systems Inc, Mountain View, California). The formation of the typical hypercohesive lesion was followed by IOUS. The CSA was performed by means of insulated cryoprobes (Accuprobe; Cryomedical Sciences Inc, Rockville, Maryland). Multiple probes were used for lesions larger than 3 cm. Tumor freezing was also monitored by IOUS until the ice ball enveloped the tumor with a 1-cm margin of normal tissue. Each lesion was treated with 2 cycles of cryoablation to a temperature of $-190^\circ$, with passive thawing for several minutes between cycles and after the final freeze cycle. Both techniques were used according to the manufacturer’s instructions.

**DEFINITIONS AND STATISTICAL ANALYSIS**

Resections were defined according to the Couinaud classification.\textsuperscript{19} Resection of segments 4 through 8 is an extended right hepatectomy; resection of segments 2 through 5 and 8 is an extended left hepatectomy. A right hepatectomy is resection of segments 5 through 8; a left hepatectomy is resection of segments 2 through 4. Major hepatectomy was defined as resection of 3 or more segments. The largest resection was labeled the primary procedure and additional smaller resections and ablations were labeled secondary procedures. Bilobar tumor involvement was defined as tumor(s) involving any segments of the left and right hemiliver. Failure of ablative treatment was defined as incomplete ablation as judged by IOUS. In situ recurrence was defined as radiologic (CT or magnetic resonance imaging) and/or histologic (needle biopsy) detection of recurrent tumor at the original ablation site during follow-up. Radiologic proof was evaluated by sequential imaging demonstrating progression of disease.

Synchronous disease was defined as the identification of liver metastases within 1 year from the date of resection of the primary colorectal carcinoma. All complications and deaths within 30 days of surgery were considered postoperative morbidity and mortality.

Complications were graded on a scale of 1 to 5 according to a previously published grading system.\textsuperscript{20} Grade 1 complications are those that require only supportive care. Grade 2 complications require moderate interventions such as intravenous medications or prolonged tube feeding. Grade 3 complications require invasive surgical or radiologic intervention. Grade 4 complications produce chronic disability, and grade 5 complications result in death. Grades 1 and 2 were grouped as minor complications and grades 3 to 5 as major complications.

We used SPSS statistical software, version 12 (SPSS Inc, Chicago, Illinois), for data analysis. Categorical variables were compared using chi test and continuous variables by Wilcoxon rank sum test. Survival comparisons were performed by the Kaplan-Meier method and the log-rank test. Results are reported as median with range unless otherwise stated. Survival data were measured from the time of resection of the hepatic metastases.

**RESULTS**

**DEMOGRAPHICS AND INDICATIONS FOR INTRAOPERATIVE ABLATION**

The median age at the time of hepatectomy was 56 years (range, 29-78 years), and 28 of the 39 patients (72%) were male. In 31 patients (79%), intraoperative RFA or CSA was used for centrally located tumors on the contralateral side of the primary resection that could not be safely removed by resection. Six patients (15%) had extensively diseased parenchyma (5 had steatosis and 1 had cirrhosis due to alcohol abuse) precluding further resection, and 2 additional patients (5%) had tumor proximity to the inferior vena cava precluding a margin-negative resection.

**PATIENT AND TUMOR CHARACTERISTICS**

In 33 patients (85%), the primary colorectal tumor was associated with regional lymph node metastases. The median preoperative carcinoembryogenic antigen level at the time of partial hepatectomy was 46 ng/mL (the conversion of carcinoembryogenic antigen to micrograms per
liter is a 1-to-1 conversion) (range, 3-5395 ng/mL) and 10 patients (26%) had a level greater than 200 ng/mL. Thirty-three patients (85%) presented with synchronous hepatic metastases. Neoadjuvant chemotherapy was administered in 33 patients (85%), for a median time of 9.8 months (range, 1-20 months). Adjuvant chemotherapy after hepatic resection was given to 38 patients (97%). Hepatic arterial infusion pumps were placed in 33 patients (85%) at the time of partial hepatectomy. The median number of hepatic metastases was 5 (range, 2-14), and 31 patients (79%) had 4 or more tumors. The median size of the largest metastasis was 3 cm (range, 1-15 cm), and 11 patients (28%) had tumors larger than 5 cm. A bilobar distribution of tumors was present in 38 patients (97%). Extrahepatic resections were performed in 6 patients (15%). Two of the 6 (33%) were because of local extension, 1 of which was true histologic invasion. Five patients (13%) underwent simultaneous hepatic resection and resection of the primary colorectal tumor. Portal vein embolization was performed preoperatively in 7 patients (18%) thought to have an inadequate future liver remnant. The surgical margins were histologically involved in 12 patients (31%), and 2 patients (5%) had residual peritoneal disease.

### SURGICAL RESECTIONS AND ABLATIVE PROCEDURES

As a primary procedure, a total of 20 (51%) major resections were performed, of which 7 (18%) were extended hepatectomies, 11 (28%) were hemihepatectomies, and 2 (5%) were segmentectomies (≥3 segments combined). Nineteen patients (49%) underwent minor hepatectomies with segmental and/or wedge resections as the primary procedure. Simultaneous CSA was performed in 20 patients (51%) and RFA in 19 patients (49%). The combinations of resections and ablations are summarized in Table 1. A total of 70 tumors were ablated: 36 (51%) by RFA and 34 (49%) by CSA. There was no difference in median tumor size of the ablated tumors between CSA and RFA. Four of 36 tumors (11%) in the RFA group and 3 of 34 (9%) in the CSA group had direct contact with a large vessel. There were no intraoperative failures in the CSA group; 1 patient with a 6-cm lesion who underwent RFA was considered to have an intraoperative failure (Table 2).

### INTRAOPERATIVE AND POSTOPERATIVE OUTCOME

The median operative time was 307 minutes (range, 150-470 minutes), and the median duration of the Pringle maneuver was 35 minutes (range, 0-77 minutes). The median intraoperative estimated blood loss was 500 mL (range, 50-2000 mL). The median number of units of packed red blood cells and fresh frozen plasma transfused per patient was 0 for both (range, 0-4 U). Overall, 13 patients (33%) received a postoperative blood transfusion. The median postoperative hospital stay was 7 days (range 2-102 days). The use of intraoperative CSA was associated with a higher blood loss (Table 3).

### Table 1. Distribution of Surgical Procedures

<table>
<thead>
<tr>
<th>Secondary Procedure</th>
<th>Major Resection (n=20)</th>
<th>Minor Resection (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RFA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alone</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>With wedge</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>9 (45)</td>
<td>10 (53)</td>
</tr>
<tr>
<td>CSA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alone</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>With wedge</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>With wedge and segmentectomy</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>11 (55)</td>
<td>9 (47)</td>
</tr>
</tbody>
</table>

Abbreviations: CSA, cryosurgical ablation; RFA, radiofrequency ablation.

### Table 2. Characteristics of Ablated Tumors

<table>
<thead>
<tr>
<th></th>
<th>RFA (n=19)</th>
<th>CSA (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total No. of ablated tumors</td>
<td>36 (51)</td>
<td>34 (49)</td>
</tr>
<tr>
<td>(% of all ablated tumors)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of ablated tumors per patient, No. of patients</td>
<td>1</td>
<td>13</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Median (range)</td>
<td>1 (1-7)</td>
<td>1 (1-4)</td>
</tr>
<tr>
<td>Ablated tumor size, cm (median [range])</td>
<td>2 (1-6)</td>
<td>2 (1-5)</td>
</tr>
<tr>
<td>Contact with large vessels, No. (%)</td>
<td>4 (11)</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Intraoperative failure rate, No. (%)</td>
<td>1 (3)</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: CSA, cryosurgical ablation; RFA, radiofrequency ablation.

### Table 3. Clinical Outcome Measures by Ablation Technique

<table>
<thead>
<tr>
<th></th>
<th>RFA (n=19)</th>
<th>CSA (n=20)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major hepatectomy, No. (%)</td>
<td>9 (47)</td>
<td>11 (55)</td>
<td>.75</td>
</tr>
<tr>
<td>EBL, median (range), mL</td>
<td>300 (50-1000)</td>
<td>500 (200-2000)</td>
<td>.04</td>
</tr>
<tr>
<td>PRBCs, median (range), U</td>
<td>0 (0-3)</td>
<td>0 (0-4)</td>
<td>.14</td>
</tr>
<tr>
<td>LOS, median (range), d</td>
<td>7 (2-102)</td>
<td>8 (6-22)</td>
<td>.13</td>
</tr>
</tbody>
</table>

Abbreviations: CSA, cryosurgical ablation; EBL, estimated blood loss; LOS, length of stay; PRBCs, packed red blood cells; RFA, radiofrequency ablation.
Median follow-up for survivors was 21.1 months (range, 0.5-71.4 months). At the time of last follow-up, 13 patients (33%) were dead of disease, 15 (38%) were alive with disease, and 11 (28%) had no evidence of disease. Actuarial 3-year survival was 47%, with a mean survival (median was not reached) of 45.8 months (range, 35.8-55.9 months) for the entire group as measured from the time of hepatic resection (Figure 1). Tumor size of 5 cm or more was associated with a worse survival ($P = .005$).

There was a trend toward worse survival in patients with a positive resection margin ($P = .07$). Nodal status of the primary, tumor number, and preoperative carcinoembryonic antigen level were not associated with survival in this patient cohort. The number and size ($> 2$ cm) of the ablated lesions and their proximity to major vessels were not associated with overall survival.

The median disease-free survival measured from the time of hepatic resection for the 37 patients with complete gross resection was 12.3 months (range, 8.4-16.2 months), with actuarial disease-free survival of 52% at 1 year, 20% at 2 years, and 8% at 3 years (Figure 2). The median hepatic disease-free survival was 15 months (range, 11-19 months), and 22 patients (56%) had hepatic recurrence at the time of last follow-up (Figure 3). Overall, disease recurred in 29 of the 37 patients with complete gross resection (78%), and 8 patients (22%) had no recurrence at last follow-up. The local in situ recur-

### Table 4. Morbidity and Mortality by Ablation Technique

<table>
<thead>
<tr>
<th></th>
<th>RFA (n=19)</th>
<th>CSA (n=20)</th>
<th>Total (N=39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morbidity</td>
<td>6 (32)</td>
<td>10 (50)</td>
<td>16 (41)</td>
</tr>
<tr>
<td>Minor complications</td>
<td>5 (26)</td>
<td>4 (20)</td>
<td>9 (23)</td>
</tr>
<tr>
<td>Major complications</td>
<td>1 (5)a</td>
<td>6 (30)b</td>
<td>7 (18)</td>
</tr>
<tr>
<td>Ablation related</td>
<td>0</td>
<td>3 (15)c</td>
<td>3 (8)</td>
</tr>
<tr>
<td>Interventions (surgical or radiologic)</td>
<td>1 (5)</td>
<td>6 (30)</td>
<td>7 (18)</td>
</tr>
<tr>
<td>Mortality</td>
<td>1 (5)</td>
<td>0</td>
<td>1 (3)</td>
</tr>
</tbody>
</table>

Abbreviations: CSA, cryosurgical ablation; RFA, radiofrequency ablation.

a Sepsis.
b Small-bowel obstruction in 1 patient, abscess and pleural effusion in 4, and fluid collection and pleural effusion in 1.
c Abscess in all 3 patients.

Figure 1. Kaplan-Meier survival plot of overall survival.

Figure 2. Kaplan-Meier survival plot of disease-free survival excluding 2 patients with residual disease.

Figure 3. Kaplan-Meier survival plot of hepatic disease-free survival excluding 2 patients with residual disease.
Hepatic resection is generally accepted as the standard of care and the only potential for cure in patients with limited and resectable colorectal cancer metastases confined to the liver. With more effective chemotherapy and general advancements in surgical technique, hepatic resection is playing an increasingly important role in treating patients with extensive disease, although the benefit is still unknown in this subgroup. Despite novel strategies to increase resectability, the tumors in most patients are technically unresectable, and techniques such as RFA and CSA have been implemented to clear all hepatic disease in these patients. The use of CSA was more common in the past, but its popularity has declined since the advent of RFA, which is simpler to use. However, the more recent argon-based CSA system is much less cumbersome than the older liquid nitrogen system and probably no more complicated to use than RFA devices. Either technique can be applied percutaneously or laparoscopically or at open operation. Thermoablation combined with resection for extensive bilobar disease has become popular, although only a few series with small numbers of patients have evaluated the utility of this strategy.

Previous publications have shown that RFA does not increase perioperative morbidity significantly when added to hepatic resection. In contrast, serious adverse events have been reported for CSA, including the cryoshock syndrome, hemorrhage following ice ball cracking, and hepatic abscess. A few retrospective studies comparing RFA with CSA found higher rates of complications, blood loss, and length of stay in patients treated with CSA.

The efficacy of thermoablative techniques is influenced by various tumor-related factors, including number, size, and proximity to larger vessels. Treatment of large liver tumors (>3 cm) with RFA remains a significant challenge. To minimize recurrence and failure rates, new electrodes with larger coagulation zones and the use of hepatic inflow occlusion have been reported to increase the ablated volume. However, size continues to be strongly associated with local failure. Larger lesions are more amenable to CSA because multiple probes can be placed simultaneously and the hypoechogenic changes are easily visualized by ultrasound. The use of CSA is also preferable for margin enhancement when a lesion has been excised with suboptimal margins, and CSA is currently the only described method of achieving long-term survival in patients with involved margins.

In our series, in which we reviewed records of a large cohort of patients, ablative techniques were rarely used as an adjunct to resection (6%), underscoring our general philosophy of treating colorectal hepatic metastases by resection whenever possible. In certain situations, however, intraoperative thermoablation is helpful to completely clear disease that would otherwise be unresectable. The patients in this series had a high tumor load, and nearly all had bilobar distribution of multifocal disease. Therefore, the main indication for using intraoperative RFA or CSA was centrally located tumors on the contralateral side of the primary resection that could not be resected while preserving a sufficient functional liver remnant. The other indication for intraoperative thermoablation was the presence of extensively diseased parenchyma where major resections were not considered safe and maximal preservation of normal parenchyma was necessary.

The use of RFA did not add morbidity, and complications specifically related to RFA were not found. However, 3 patients treated with CSA did develop postoperative ablation-site abscesses. The use of CSA was associated with clinical outcome measures such as higher blood loss. This finding cannot be ascribed to the extent of the resection procedures because there was no significant difference between the RFA- and CSA-treated patients in this regard. The overall perioperative morbidity rate was consistent with previous findings from our group in large numbers of patients.

With regard to efficacy, the local in situ recurrence rates at ablation sites were comparable to those in other studies and show that local control with ablation techniques is feasible at an open operation. Tumor size was associated with recurrence in RFA-treated tumors, demonstrating that tumor size is an ongoing limitation for this technique. The only intraoperative ablation failure was in a 6-cm RFA-treated lesion. Overall recurrence rates were similar between CSA- and RFA-treated tumors, and this likely reflects the similarly advanced nature of the tumors in both groups. Other series comparing intraoperative RFA and CSA have found differences in outcome between the groups, but these studies, like ours, are limited by their retrospective nature.

Despite local efficacy of these techniques, the overall and hepatic recurrence rates were high. Three-year disease-free survival was 8%, and 56% had hepatic recurrence at the time of last follow-up. Overall survival, however, was acceptable, with an actuarial survival of nearly 50% at 3 years. These findings are likely a reflection of tumor biology in that these patients all had multiple bilobar tumors. Undoubtedly, better preoperative staging will ultimately improve outcomes by identifying patients with occult extrahepatic metastases. Nearly all of our patients underwent preoperative chest CT, but only 54% had PET scans, and increased use of PET in these high-risk patients may improve patient selection. A recent publication comparing outcomes after hepatic resection combined with RFA and resection alone suggested an improved outcome associated with resection alone. The selection bias between these 2 groups, which almost certainly had an influence on outcome, was not addressed in detail and is perhaps impossible to discern in a retrospective study. Our results must be seen in the context of effective systemic chemotherapy; 85% received adjuvant therapy and nearly all received adjuvant chemotherapy. In recent years, chemotherapy for colorectal cancer has improved, and combinations of fluorouracil-based chemotherapy with irinotecan hydrochloride and oxaliplatin have increased response rates and survival in advanced disease. The encouraging survival seen...
Ablative techniques combined with hepatic resections are rarely used at our institution. However, in selected cases that were otherwise unresectable, the additional use of those techniques allowed complete clearance of disease. Rather than an alternative to resection, ablative techniques are regarded as a complement to hepatectomy and as an additional means to achieve tumor eradication when complete resection is not possible. Because of its technical simplicity and safety, RFA is the preferable technique, although its limitation in treating large tumors remains a problem. Therefore, CSA may have a role in treating larger tumors. The outcome of these patients is limited by the biological characteristics of the tumor and the necessity for adjuvant therapy.

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