Cryosurgical Ablation and Radiofrequency Ablation for Unresectable Hepatic Malignant Neoplasms

A Proposed Algorithm

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Some say the world will end in fire,
Some say in ice.
From what I’ve tasted of desire
I hold with those who favor fire.
But if it had to perish twice,
I think I know enough of hate
To know that for destruction ice
Is also great
And would suffice.

Robert Frost, “Fire and Ice” (Harper’s, December 1920)

Background: Thermal ablation of unresectable hepatic tumors can be achieved by cryosurgical ablation (CSA) or radiofrequency ablation (RFA). The relative advantages and disadvantages of each technique have not yet been determined.

Hypothesis: Radiofrequency ablation of malignant hepatic neoplasms can be performed safely, but is currently limited by size. Cryosurgical ablation, while associated with higher morbidity, is more effective for larger unresectable hepatic malignant neoplasms.

Design: Retrospective analysis of prospective patient database.

Patients and Methods: Between July 1992 and September 1999, 308 patients with liver tumors not amenable to curative surgical resection were treated with CSA and/or RFA (percutaneous, laparoscopic, celiotomy). No patient had preoperative evidence of extrahepatic disease. All patients underwent laparoscopy with intraoperative ultrasound if technically possible. Both RFA and CSA were performed under ultrasound guidance. Resection, as an adjunctive procedure, was combined with ablation in certain patients.

Results: Laparoscopy identified extrahepatic disease in 12% of patients, and intraoperative hepatic ultrasound identified additional lesions in 33% of patients, despite extensive preoperative imaging. Radiofrequency ablation alone or combined with resection or CSA resulted in reduced blood loss (P<.05), thrombocytopenia (P<.05), and shorter hospital stay compared with CSA alone (P<.05). Median ablation times for lesions greater than 3 cm were 60 minutes with RFA and 15 minutes with CSA (P<.001). Local recurrence rates for lesions greater than 3 cm were also greater with RFA (38% vs 17%).

Conclusions: Laparoscopy and intraoperative ultrasound are essential in staging patients with hepatic malignant neoplasms. Radiofrequency ablation when combined with CSA reduces the morbidity of multiple freezes. Although RFA is safer than CSA and can be performed via different approaches (percutaneously, laparoscopically, or at celiotomy), it is limited by tumor size (<3 cm). Percutaneous RFA should be considered in high-risk patients or those with small local recurrences.

PATIENTS AND METHODS

Between July 1992 and September 1999, 308 patients underwent CSA or RFA of primary and metastatic hepatic malignant neoplasms at the John Wayne Cancer Institute, Santa Monica, Calif, or the Cancer Center at Century City Hospital, Los Angeles, Calif. From July 1992 through October 1997, all study patients were treated with CSA alone or in combination with resection. In November 1997, RFA was incorporated as an alternative or adjunct to CSA and/or non-curative resection. Patients selected for either ablative procedure had no evidence of extrahepatic disease but were not candidates for curative surgical resection due to the location or size of hepatic lesions and/or the presence of hepatic dysfunction. All patients underwent extensive preprocedural evaluation, including spiral computed tomography (CT), magnetic resonance imaging, and fludeoxiglucone F 18 positron emission tomography as indicated. Hepatic function was assessed through laboratory indicators of synthetic function and Childs-Pugh classification.

Laparoscopy was undertaken, when possible, to rule out extrhepatic disease. All parietal and visceral peritoneal surfaces, the lesser sac, omentum, and all viscera were examined. Sequential laparoscopic ultrasonographic examination of all segments of the liver was performed using a flexible 7.5-MHz ultrasonic probe (Aloka Inc, Wallingford, Conn). If laparoscopy was not possible because of extensive adhesions, inability to obtain an appropriate pneumoperitoneum, or other technical reasons, a complete open exploration was undertaken and IOUS performed using a handheld ultrasonic probe.

Between November 1997 and September 1999, 68 patients underwent RFA of 181 hepatic lesions. Radiofrequency ablation was performed laparoscopically, percutaneously, or at celiotomy using an 13-gauge needle with a retractable curved-electrode configuration (RITA Medical Systems Inc, Mountain View, Calif) (Figure 1). The needle was guided to the center of the lesion using IOUS. Seven times were deployed, and 50 W of alternating current was delivered to achieve a temperature greater than 90°C for at least 8 minutes. The formation of the typical hyper-echoic lesion was followed by IOUS. Following ablation, the probe tract was cauterized as the RFA needle was withdrawn. For lesions larger than 2.5 cm, multiple overlapping ablations were performed. If laparoscopy was not possible because of extensive previous surgery, RFA was undertaken at celiotomy. Combinations of RFA, CSA, and/or resection were undertaken at celiotomy as indicated, particularly in patients with multiple (>3) lesions. If operation was contraindicated by the patient’s overall medical status, RFA was performed percutaneously under CT scan or ultrasound guidance. Patients with CSA recurrences often were treated by percutaneous RFA.

Between July 1992 and September 1999, 254 patients underwent CSA of 762 hepatic lesions. Cryosurgical ablation was performed at celiotomy using insulated cryoprobes (Accuprobe; Cryomedical Sciences Inc, Rockville, Md). Cylindrical probes were inserted into the lesion and their position confirmed with IOUS. Multiple probes were used for lesions larger than 3 cm. Liquid nitrogen was circu- lated at temperatures no greater than −195°C. Tumor freezing was monitored by ultrasonography until the ice ball enveloped the tumor with a 1-cm margin of normal tissue. Probe tracts were packed with absorbable gelatin sponge (Gelfoam) for hemostasis.

Blood cell count and liver function tests were assessed immediately postoperatively and the next morning. Patients undergoing additional procedures were treated appropriately. A baseline CT scan was obtained 1 week postoperatively. Tumor markers and CT were used to follow up patients at 3 months and then at 6-month intervals. Preoperative and postoperative data for all patients were entered into a prospective database. Length of hospital stay, blood transfusion requirements, major complications (extensive bleeding, bile duct injury, abscess, symptomatic pleural effusion), and recurrences were compared between treatment groups using the t test for numeric variables and the Fisher exact test for categorical variables.

RESULTS

Radiofrequency ablation was performed alone in 40 patients (Figure 2 and Figure 3), with resection in 14, CSA in 9, and both CSA and resection in 5 patients...
Cryosurgical ablation was performed alone in 159 patients and with resection in 81 patients (CSA group). The following is the breakdown of the 308 patients who underwent RFS, CSA, or combination therapy:

<table>
<thead>
<tr>
<th>Modalities</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>RFA group</td>
<td></td>
</tr>
<tr>
<td>RFA alone</td>
<td>40</td>
</tr>
<tr>
<td>RFA and resection</td>
<td>14</td>
</tr>
<tr>
<td>RFA and CSA</td>
<td>9</td>
</tr>
<tr>
<td>RFA, CSA, and resection</td>
<td>5</td>
</tr>
<tr>
<td>Subtotal</td>
<td>68</td>
</tr>
<tr>
<td>CSA group</td>
<td></td>
</tr>
<tr>
<td>CSA alone</td>
<td>159</td>
</tr>
<tr>
<td>CSA and resection</td>
<td>81</td>
</tr>
<tr>
<td>Subtotal</td>
<td>240</td>
</tr>
</tbody>
</table>

The 308 patients included 168 men and 140 women, and their median age was 63 years (range, 30-84 years). Median postoperative follow-up was 16 months (range, 1-77 months) for the 240 patients in the CSA group (CSA with or without resection) and 9 months (range, 1-22 months) for the 68 patients in the RFA group. Lesion diameter ranged from 1 to 22 cm for CSA (median, 5 cm) and 0.5 to 9 cm for RFA (median, 2 cm). The median number of lesions treated was 3 (range, 1-16) for CSA and 2 (range, 1-13) for RFA. Lesion types are outlined in Table 1.

Of the 68 patients in the RFA group, 26 had laparoscopic RFA, 16 had percutaneous RFA, and 26 underwent RFA at celiotomy. Despite extensive preoperative imaging, extrahepatic disease was identified in 7 (12%) of 59 patients undergoing laparoscopy before RFA and in 25 (13%) of 190 patients undergoing CSA. Further surgical treatment was therefore not performed in these patients. Also, IOUS demonstrated additional intrahepatic lesions not identified on preoperative imaging studies in 17 (33%) of 52 patients undergoing RFA and in 72 (30%) of 240 patients undergoing CSA. These additional lesions were ablated.

Length of the procedure, duration of hospitalization, and morbidity were significantly less for the 40 patients undergoing RFA alone than for the 139 patients undergoing CSA alone (P<.001) (Table 2). The mortality rates, however, were similar between these 2 groups (2.5% and 3%, respectively). Local recurrence rates were also similar (P=.62).

When the morbidity of treatment for patients with multiple (>3) lesions was examined (Table 3), there was significantly more blood loss and thrombocytopenia associated with CSA alone than with RFA alone or RFA in combination with CSA or resection. This suggests that RFA reduces the morbidity of multiple freezes. On the other hand, when the outcomes of patients with large (>3 cm) lesions were examined (Table 4), the rate of local recurrence was higher with RFA than with CSA,
and there were several complications in this subgroup of patients. One RFA patient was taken back to the operating room for bleeding (7%). Three RFA patients developed hepatic abscesses (23%) compared with 7% for CSA patients ($P = .08$). In one case, a severely cirrhotic man who underwent multiple ablations for a 9-cm hepatoma developed a delayed intrahepatic abscess 5 months following RFA. This abscess was successfully treated with percutaneous drainage, and at last follow-up (15 months) the patient was free of disease. Two other patients developed acute hepatic abscesses following multiple percutaneous RFAs of 4.5- and 5-cm lesions. Another patient (7%) developed a bile duct stricture that required endoscopic stent placement subsequent to RFA of a metastasis adjacent to the left bile duct and portal vein. The one death in the RFA group (8%) followed diaphragmatic necrosis and hepatic abscess from multiple percutaneous RFAs of a large lesion. Finally, the number and duration of ablations for large lesions were significantly less for CSA than for RFA ($P .001$).

At a median follow-up of 12 months, 28 patients (41%) treated with RFA have developed progression of disease at other sites and 5 (7%) have developed local disease recurrence (5 recurrences [3%] of 181 treated lesions). Fourteen (20%) have died of progression of disease. At a median follow-up of 28 months, 158 patients (66%) treated with CSA have developed progression of disease recurrence (36 recurrences [5%] of 762 treated lesions) (Figure 4).

This study, which represents the largest series of liver ablations for unresectable hepatic malignant neoplasms reported to date, covers a 7-year period during which we developed criteria for a multimodality operative approach. Although we have had considerable success using CSA for patients with unresectable hepatic metastases, it is evident that the incidence of major complications is high (17% in the present study) and directly proportional to the volume of liver frozen. To minimize the amount of tissue frozen, we incorporated the use of RFA for smaller lesions. When compared with CSA alone, RFA plus CSA and/or resection reduced morbidity, thrombocytopenia, and blood transfusions. Target temperatures were easily reached when both ablative techniques were used simultaneously.

Although RFA can be performed percutaneously or laparoscopically, the former increases the recurrence and complication rates. We favor a laparoscopic approach because it can identify extrahepatic disease without the morbidity of celiotomy. Moreover, the insufflation and direct vision provided by laparoscopy facilitate ablation of superficial liver tumors while avoiding injury to adjacent organs (percutaneous ablation of a superficial lesion resulted in a skin burn in one of our patients). In our study, laparoscopy identified peritoneal metastasis missed by extensive preoperative imaging in 12% of patients. Also, IOUS identified additional intrahepatic lesions in 33% and 30% of patients undergoing RFA and CSA, respectively. This finding is similar to results reported by others.

Radiofrequency ablation was not as effective as CSA for large (>3 cm) lesions. Larger lesions are more amenable to CSA, because multiple probes can be placed simultaneously and the hypoechoic changes are easily visualized by ultrasound. Even when multiple overlapping RFAs were performed, recurrence rates for large lesions were 38% after RFA compared with 17% after CSA. This may be attributed to poor visualization under IOUS or inadequate ablation between the overlapping ablation zones. Moreover, because larger lesions required several overlapping ablations, RFA treatment time was significantly longer than the 15 minutes required for a single CSA (Figures 2 and 3).

### Table 2. Outcomes of Patients Undergoing Radiofrequency Ablation (RFA) Alone vs Cryosurgical Ablation (CSA) Alone

<table>
<thead>
<tr>
<th>Variable</th>
<th>RFA Alone (n = 40)</th>
<th>CSA Alone (n = 159)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital stay, mean ± SD, d</td>
<td>2 ± 1</td>
<td>8 ± 3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Length of procedure, mean ± SD, h</td>
<td>2.5 ± 1</td>
<td>4.5 ± 2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Blood loss, mean ± SD, mL</td>
<td>40 ± 20</td>
<td>800 ± 200</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Thrombocytopenia, %</td>
<td>0</td>
<td>70</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Pleural effusion, %</td>
<td>0</td>
<td>80</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hepatic abscess, No. (%)</td>
<td>3/40 (7.5)</td>
<td>11/159 (7)</td>
<td>NS*</td>
</tr>
<tr>
<td>Bile duct injury, No. (%)</td>
<td>1/40 (2.5)</td>
<td>7/159 (4)</td>
<td>NS*</td>
</tr>
<tr>
<td>Local recurrence rates, No. (%)</td>
<td>4/40 (10)</td>
<td>24/159 (15)</td>
<td>NS*</td>
</tr>
<tr>
<td>Intensive care unit stay, mean ± SD, d</td>
<td>0</td>
<td>2 ± 1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Death, No. (%)</td>
<td>1/40 (2.5)</td>
<td>5/159 (3)</td>
<td>NS</td>
</tr>
</tbody>
</table>

*NS indicates not significant.

### Table 3. Clinical Outcomes of Ablation of Multiple (>3) Hepatic Lesions: Comparison of Cryosurgical Ablation (CSA) vs Radiofrequency Ablation (RFA) or Combination Therapy

<table>
<thead>
<tr>
<th>Variable</th>
<th>CSA Group (n = 130)</th>
<th>RFA and CSA Combination (n = 14)</th>
<th>RFA Alone (n = 14)</th>
<th>CSA Alone (n = 9)</th>
<th>RFA and Resection (n = 14)</th>
<th>CSA and Resection (n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital stay, mean ± SD, d</td>
<td>8 ± 3</td>
<td>2 ± 1*</td>
<td>6 ± 2</td>
<td>5.2 ± 2*</td>
<td>6.5 ± 2</td>
<td>5.6 ± 2</td>
</tr>
<tr>
<td>Blood loss, mean ± SD, mL</td>
<td>800 ± 160</td>
<td>40 ± 15*</td>
<td>450 ± 100†</td>
<td>320 ± 70*</td>
<td>500 ± 150†</td>
<td>250 ± 150†</td>
</tr>
<tr>
<td>Thrombocytopenia, No. (%)</td>
<td>117/130 (90)</td>
<td>0/14 (0)†</td>
<td>3/9 (33)†</td>
<td>3/14 (21)†</td>
<td>2/5 (40)†</td>
<td>0/5 (0)†</td>
</tr>
<tr>
<td>Complications, No. (%)</td>
<td>22/130 (17)</td>
<td>0/14 (0)†</td>
<td>0/9 (0)</td>
<td>0/14 (0)†</td>
<td>0/5 (0)</td>
<td>0/5 (0)</td>
</tr>
</tbody>
</table>

*Significance at $P < .05$ vs CSA.
†Significance at $P < .01$ vs CSA.
The volume of ablation during RFA can be increased by restricting hepatic inflow using the Pringle maneuver. In a similar report that used in vivo porcine liver, Goldberg et al demonstrated an increase in RFA lesion size with pharmacologic reduction of blood flow. Volume of ablation also can be increased by infusing 0.9% isotonic sodium chloride solution or 5% hypertonic saline solution through a needle electrode. The cooling tip increases the area of conduction around the needle tip by reducing the coagulation zone. However, until these probes have been completely evaluated, CSA should still be considered more effective for ablating large unresectable hepatic lesions. Cryosurgical ablation is also preferable for use at the site of resection when a lesion has been excised with less than 1-cm margins of normal tissue. Liquid nitrogen circulated through a paddle probe can achieve a 2- to 3-cm margin of cell destruction. The configuration of current RFA electrodes does not permit this type of margin ablation.

In the series of Curley et al, 123 patients underwent RFA of hepatic tumors. Approximately three quarters of the patients had RFA performed at celiotomy with a Pringle maneuver, whereas one quarter had percutaneous RFA. The local recurrence rate was only 1.8% (3 of 169 treated lesions), with a median follow-up of 15 months. Our overall RFA recurrence rate on a per lesion basis was a comparable 2.8% (5 of 181 treated lesions).

In the absence of studies comparing ablation and resection in patients with hepatic metastases, RFA and CSA should be considered adjuncts to resection and used as a primary modality only in patients with poor liver function or bilobar unresectable lesions. We propose the following algorithm for these patients: (1) laparoscopy when possible to exclude extrahepatic disease; (2) laparoscopicIOUS to evaluate intrahepatic tumor volume; (3) RFA on multiple lesions 3 cm or smaller; (4) laparoscopic RFA with multiple overlapping ablations for lesions larger than 3 cm in high-risk patients or those with severe hepatic dysfunction; (5) celiotomy and CSA of lesions larger than 3 cm in patients who are candidates for general anesthesia; (6) simultaneous RFA and CSA for small (≤3 cm) and large (>3 cm) lesions, respectively, and consideration of hepatic artery infusion and pump placement in appropriate patients; and (7) percutaneous RFA for patients with disease recurrences and in those who cannot tolerate general anesthesia (Figure 4).

Although this retrospective study represents a heterogeneous group of patients, it clearly suggests the value of a flexible, multifaceted approach to unresectable hepatic malignant neoplasms. The goal for these patients is to prolong life without significant operative morbidity. Since most patients with hepatic metastases develop progressive disease, studies evaluating the role of ablation with adjuvant therapy are clearly needed. In a recent study, we demonstrated that intrahepatic floxuridine after CSA significantly improved survival in patients with metastatic colon cancer compared with CSA alone. Although a randomized trial comparing resection and ablation is unlikely, CSA and RFA provide effective methods of tumor destruction. Resection, when possible, remains the standard for management of hepatic tumors. However, a surgeon experienced with the multimodality approach to hepatic tumors (resection, RFA, and/or CSA) is well suited to provide the most appropriate treat-

<table>
<thead>
<tr>
<th>Variable</th>
<th>RFA Group (n = 13)</th>
<th>CSA Group (n = 140)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median follow-up, mo</td>
<td>9</td>
<td>16</td>
<td>. .</td>
</tr>
<tr>
<td>Recurrence, No. (%)</td>
<td>5/13 (38)</td>
<td>23/140 (17)</td>
<td>.06</td>
</tr>
<tr>
<td>Duration of ablation,</td>
<td>60 ± 10</td>
<td>15 ± 2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>mean ± SD, min</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. (range) of ablations</td>
<td>6 (4-14)</td>
<td>1 (1-2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Bleeding, No. (%)</td>
<td>1/13 (8)</td>
<td>11/140 (8)</td>
<td>&gt;.99</td>
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<tr>
<td>Abscess, No. (%)</td>
<td>3/13 (23)</td>
<td>10/140 (7)</td>
<td>.08</td>
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<td>Respiratory failure, No. (%)</td>
<td>1/13 (8)</td>
<td>7/140 (5)</td>
<td>.86</td>
</tr>
<tr>
<td>Bile duct injury, No. (%)</td>
<td>1/13 (8)</td>
<td>6/140 (4)</td>
<td>.47</td>
</tr>
<tr>
<td>Deaths, No. (%)</td>
<td>1/13 (8)</td>
<td>4/140 (3)</td>
<td>.36</td>
</tr>
</tbody>
</table>

*CSA group indicates CSA with or without resection; RFA group, RFA with or without CSA and/or resection.

Figure 4. A, Marginal recurrence of cryosurgical ablation (CSA) at the confluence of hepatic veins within segments 4A and 8. B, Computed tomography–guided percutaneous radiofrequency ablation (RFA), one of several overlapping ablations. C, Computed tomographic scan 1 week after percutaneous RFA showing uniform low density in a region larger than the area of recurrent disease (arrow). D, Computed tomographic scan 3 months after RFA demonstrating reduction in the ablation size with no evidence of recurrence (arrow).
ment(s) to the wide spectrum of patients who present with hepatic malignant neoplasms.

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REFERENCES


DISCUSSION

Fred E. Eckhauser, MD, Ann Arbor, Mich: Dr Bilchik and colleagues report an extensive experience using ablative techniques including radiofrequency ablation (RFA) and cryosurgery (CSA) to treat unresectable hepatic malignancies. The study population consisted of 308 patients treated over a 7-year period. Both laparoscopy and IOUS were utilized to identify and exclude patients from additional treatment and to detect occult lesions that might alter intraoperative treatment. A number of outcome predictors were analyzed, including hospital length of stay, length of procedure, estimated intraoperative blood loss, major complications, and local recurrence. RFA was safer overall than CSA when judged by these parameters, and local recurrence rates were similar at 10% and 15%, respectively. The advantages observed with RFA were even greater among patients with multiple, that is greater than 3, lesions. By comparison, RFA was less effective than CSA in patients with large lesions greater than 3 cm judged by a 2-fold higher rate of local recurrence. The authors suggest that RFA and CSA should be viewed as complementary adjuncts to be used alone or in combination with hepatic resection, depending on the number and location of lesions and the degree of liver dysfunction. I have several questions for the authors. First, the study population is quite heterogeneous, with two thirds of the patients having colorectal metastases and the remaining one third having a variety of conditions, including primary hepatic malignancies, neuroendocrine tumors, and an "other" category of lesions such as breast, lung, and stomach primary malignancies with liver metastases. First, do the survival and local recurrence results hold up if one analyzes these 2 disparate groups separately? Second, does the etiology of the underlying condition predict the risk of complications or is this a reflection of the technology employed and the patient's hepatic reserve at the time of intervention? Third, the authors suggest that hepatic artery infusion pumps may be considered in appropriate patients. Given the recent data available from 2 major studies evaluating resection alone or combined with hepatic artery pump placement, I would be interested in hearing the authors selection criteria for utilization of hepatic artery infusion pumps in this setting.

Stephen Stain, MD, Pasadena, Calif: Your group has been doing CSA now for nearly 7 years. In your manuscript, I find no comment about survival. I realize most reports in the literature comment only about local recurrence, but if ablation is truly a useful modality, you need to know whether there is a survival benefit. Your median follow-up was only 16 months; was that because patients are dying, you are not following them up, or they are being lost for other reasons? Could you give us some specific recommendations for patients with tumors greater than 5 cm or more than 3 lesions? Do you think those really...
are appropriate for ablative therapy, or are they truly incurable patients?

Philip D. Schneider, MD, Sacramento, Calif: At Davis, we did our first RFA in 1990, and it has been a joint effort between John McGahan, who is a superior ultrasonographer, and the Surgical Oncology Division at Davis. At the time we started, you have to remember that there was a disappointing, some would say catastrophic, experience at Allegheny Hospital with CSA, which not only made it difficult to evaluate the results of CSA but it made it impossible for some of us to get insurance coverage for our patients because the data was so disparate. We started our RFA program with a very conservative approach like Glenn Steele and T.S. Ravikumar had advocated with CSA. We have learned a few things. We have now increased the infarct size up to a credible 3 to 4 cm, and we still struggle with ultrasound as the monitoring technique for ablation whether it is CSA or RFA. Ultrasound is excellent for staging, and we agree with the authors on that account, but it is difficult to safely evaluate the treatment of lesions or the RFA lesions with ultrasound, particularly laparoscopic ultrasound. It does not give one the degrees of freedom to do this safely or completely. The big danger, along with unanticipated injuries, is that you will undertreat patients and, thereby, do them a disservice. What do you do technically to ensure a good RFA burn? Has your group had any experience with open MRI? Second, what conceivable, what possible rationale could the authors have for treating patients with more than 5 lesions? Neuroendocrine metastases aside, this is irrational, and it does a real disservice to the technique and to the patients undergoing treatment.

Theodore X. O’Connell, MD, Los Angeles, Calif: The first question is that even though they start off saying this is a comparison between CSA and RFA, this is hardly a randomized study and is really comparing apples and oranges, since obviously the CSA patients are the ones with the larger lesions and RFA the smaller lesions. Are the results due to differences in the size of the lesions rather than technique used? Second, although in their study RFA was done only in unresectable patients, why couldn’t it be done in patients with small 2-cm hepatomas that are resectable to avoid surgery altogether? My third concern mimics Dr Stain’s and Dr Schneider’s question: what are your survival data for patients with greater than 4 lesions? Are you really doing these patients any good, or are you just freezing and heating up their livers to look like Swiss cheese?

Ronald G. Latimer, MD, Santa Barbara, Calif: I would like to know what the authors thought of the PET [positron emission tomographic] scanning? This is becoming a very hot issue among our nuclear medicine people for staging, and I would like to see what their correlation is with laparoscopic staging and PET scanning.

William C. Chapman, MD, Nashville, Tenn: Could you tell us something about how you factor in adjacent major vascular structures? In those patients with tumors greater than 3 cm in size, you report a local recurrence rate of 17% and 38% of CSA and RFA, respectively. This would seem to represent a very high and perhaps unacceptable result for patients undergoing standard resection, but, in reality, these are typically the exact patients we see that are unresectable for involvement of adjacent vascular structures. How do you factor that into your preoperative assessment? Could you also tell us the number of patients that you have seen and treated with standard surgical resection without CSA or RFA during this same time interval of assessment?

Herand Abdcarian, MD, Chicago, Ill: Although the recurrence rate in this study is fairly low, 10% and 15%, most studies show a recurrence rate as high as 30%. The recurrence seems to be higher the larger the number of lesions and the shorter the interval from primary cancer to metastases. I would like to get the feeling of the authors about an adjunct insertion of hepatic artery catheter for infusion, as this concept is again being resurrected.

Don Melvin Morris, MD, Albuquerque, NM: Which is the preferred technique in your hands for dealing with lesions next to the vena cava and why?

John Smith, MD, Wichita, Kan: As the new generation of probes and generators come on line, do you think you will see a further shift toward RFA from CSA?

Arthur Donovan, MD, Pasadena: You referred to the recent discussion and review article in Annals of Surgery on this subject. In that article, there was quite a bit of discussion with respect to hepatic arterial inflow occlusion to prevent a washout cooling of the heat generated with the use of RFA. I would like to know whether you employ hepatic arterial inflow occlusion during the RFA?

Dr Bilchik: Dr Eckhauser, thank you for reviewing the manuscript and for your insightful comments. Although this paper represents a heterogeneous group of patients, we have previously reported our experience with individual malignancies (hepatoma, colorectal metastasis, and neuroendocrine tumors); in each case, patients undergoing ablation had similar local recurrence rates but better survival than matched, untreated controls. Survival was largely dictated by the biology of the disease, whereas local recurrence was related to the size of the lesion and the adequacy of its ablation.

Because the majority of patients with primary liver tumors or liver metastases die of liver failure, the goal of resection or ablation is to prevent hepatic failure and delay disease progression. Resection remains the gold standard, but we now have the technology to safely destroy unresectable tumors in patients with limited hepatic reserve. Clearly, however, it is not the technology but the judgment of the surgeon that should determine a patient’s management.

At the recent meeting of the American Society for Clinical Oncology, Dr Nancy Kemeny from Memorial Sloan-Kettering Cancer Center reported results of the first prospective randomized trial evaluating hepatic artery chemotherapy. Hepatic artery chemotherapy after hepatic resection significantly improved survival. There was no crossover between the groups, and toxicity was minimal. At the same meeting, we presented our experience in 153 patients with unresectable colorectal metastases who underwent CSA with fluorouridine or CSA with irinotecan. Although this was a nonrandomized trial, survival was significantly better for patients in the fluorouridine group. I believe that all patients undergoing resection or ablation of colorectal metastases should be considered for hepatic artery therapy.

Dr Stain, I did not include survival data because of the heterogeneity of our population and because our purpose was to evaluate efficacy, safety, and local recurrence rates. However, survival was comparable with that following resection. The overall median survival for colorectal metastases was 26 months, and the longest survivor is alive 77 months after surgery. The median survival for hepatoma and neuroendocrine tumors was 28 months and 35 months, respectively. The median follow-up was only 16 months because we included recent patients.

At the World Congress of Surgery in Vienna, Austria, we presented our data on prognostic factors. Carcinoembryonic antigen (CEA) levels and adjuvant treatment, but not size or number of lesions, were significant prognostic factors by multivariate analysis. I, therefore, believe that patients whose tumors are greater than 5 cm in diameter or more than 3 in number should be considered for ablation if they have no extrahepatic disease. However, all disease detected byIOUS must be treated, and postoperative CEA levels should be normalized.

Dr Schneider asked about ultrasound and imaging. We use color duplex ultrasound to monitor blood flow during ablation. The typical hypoechogenic zone confirms the adequacy of the
ablation. We do not have any experience with open MRI. In response to Dr Schneider's skepticism concerning RFA for multiple lesions, we have found that patients undergoing RFA of more than 5 lesions live significantly longer than untreated patients. However, as stated above, the patient must be free of extrhepatic disease, all lesions must be treated, and postoperative CEA must be normalized.

Dr O'Connell is correct—ours was not a randomized study. However, the selection of RFA vs CSA was not based on lesion size. In fact, 20% of patients underwent RFA of lesions larger than 3 cm in diameter. Our policy is to resect patients whenever possible, even those with borderline hepatic reserve.

I agree with Dr Latimer that positron emission tomographic scanning is an evolving, exciting technology. We have only performed this technique in a few patients after ablation; no uptake of FDG [fluodeoxyglucose F 18] correlates with a successful ablation.

Dr Chapman, it is well known that the heat-sink effect provided by large vessels may increase recurrences after both RFA and CSA. However, separate studies by Drs Gage and Weaver demonstrate that tumors close to blood vessels can be adequately ablated. In fact, the wall of the vessel can be frozen without any danger of hemorrhage, because the heat sink protects the vessel from cracking. In our study, surgical resection was considered whenever possible; many patients underwent resection plus CSA and RFA, and approximately 150 underwent resection alone.

Dr Abcarian, as I mentioned earlier, our recent data support placement of a hepatic artery pump in patients with metastatic colorectal disease. At a lower dose of floxuridine (0.18 mg/kg) and dexamethasone, there is less toxicity and better tolerance.

Dr Morris, we have performed both RFA and CSA on lesions adjacent to the vena cava. I suspect that the heat-sink effect applies to both methods. With the current technology, I would favor CSA of lesions larger than 3 cm in diameter.

My answer to Dr Smith is yes. Radiofrequency ablation is clearly safer and cheaper than CSA, and the advent of more versatile RFA probes that allow a larger volume of ablation should further increase use of this modality.

Dr Donovan, as you know, hepatic artery inflow occlusion is routinely applied by Dr Steve Curly at M. D. Anderson Cancer Center and probably explains why his recurrence rates are only 1.9%. I am not aware of any comparable study. At the John Wayne Cancer Institute, we are presently determining whether the ablation zone changes with inflow occlusion.

ARCHIVES OF INTERNAL MEDICINE

Systematic Lung Scans Reveal a High Frequency of Silent Pulmonary Embolism in Patients With Proximal Deep Venous Thrombosis

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Background: A high frequency of asymptomatic pulmonary embolism (PE) has been reported in patients with deep venous thrombosis (DVT) in studies of a limited number of patients using varying criteria for lung scan assessment.

Objectives: To estimate the frequency of PE using systematic lung scans in a large group of outpatients with DVT and to compare the results using varying lung scan assessment criteria.

Methods: An international multicenter study comparing 2 different regimens of low-molecular-weight heparin nadroparin in DVT: perfusion lung scans were performed in 622 outpatients with no clinical indication of PE and with proximal DVT confirmed by venography. Three hundred seventy-nine of these patients underwent ventilation lung scans. High-probability (HP) scans for PE were assessed separately using either ventilation scans or chest radiographs to define mismatched perfusion defects.

Results: Perfusion scans showed abnormalities in 82% of the patients; 59% had segmental defects and 30% had normal scans or scans with a very low probability of PE. Depending on the criteria used, 32% to 45% had HP scans for PE; these percentages were higher in young patients. No relationship was found between extent of thrombosis and HP scans. The estimated frequency of silent PE was 39.5% to 49.5%. During a 3-month follow-up period during which the patients received therapy, the rate of PE recurrence was low (1.3%) and did not differ between patients with baseline HP scans and those with normal scans.

Conclusions: Regardless of what interpretative criteria are used for assessing lung scans in PE, the frequency of silent PE is 40% to 50% in patients with DVT. A baseline lung scan may easily detect PE in these patients but is not useful for predicting early thromboembolic recurrences that may occur during therapy. (2000;160:159-164)

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