Safety and Efficacy of Radiofrequency Thermal Ablation in Advanced Liver Tumors

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Hypothesis: Radiofrequency thermal ablation (RFA) can be performed safely and effectively to control local disease in patients with advanced, unresectable liver tumors.

Design, Setting, and Patients: Prospective study of 76 patients with unresectable liver tumors who underwent RFA at a private tertiary referral hospital.

Interventions: Ninety-nine RFA operations were performed to ablate 328 tumors.

Main Outcome Measures: Complications and local recurrence.

Results: There was 1 death (1%), major complications occurred in 7 operations (7%), and minor complications occurred in 10 operations (10%). Local recurrence was identified in 30 tumors (9%) at a mean follow-up of 15 months. Size ($P<.001$), vascular invasion ($P<.001$), and total volume ablated ($P<.001$) were associated with recurrence but the number of tumors was not ($P = .39$).

Conclusion: Radiofrequency thermal ablation provides local control of advanced liver tumors with low recurrence and acceptable morbidity.

Arch Surg. 2001;136:864-869

Surgery is the primary curative treatment for tumors of the liver. Resection offers the potential for cure in primary hepatic malignancies and in some hepatic metastases such as colorectal carcinoma. Owing to constraints of size, location, or extent, however, only 10% to 20% of patients with hepatic malignancies are candidates for potentially curative surgical resection. Despite improvements in surgical and anesthetic techniques and postoperative care, major hepatectomy still incurs significant morbidity (5%-15%) and mortality (<5%). Major hepatic resection, then, is reserved for potentially curative intent.

Other modalities have been used to achieve local control in unresectable tumors. Chemical ablation (ethanol injection), cryoablation, and thermal ablation have been investigated as palliative—and occasionally curative—modalities to treat liver tumors. Investigation and use of thermal ablation, in particular, has increased with advances in radiofrequency thermal ablation (RFA) technology. Early reports have shown RFA to have fewer complications while achieving excellent local control. Initial studies of RFA applied this technique to smaller tumors in patients with less extensive disease. As experience with this modality has increased, so have the potential applications. The purpose of this study was to evaluate the safety and efficacy of ultrasound-guided RFA in unresectable liver tumors in patients with more advanced disease.

RESULTS

During the study period, 76 patients (43 men, 33 women) underwent a total of 99 RFA procedures. Age at the time of the first RFA procedure was 64.4±10.5 years (age range, 40-87 years). Hepatocellular carcinoma was diagnosed in 25 patients, CRM in 39 patients, and other metastases (carcinoid [3], breast [2], cholangiocarcinoma [2], and 1 each of gastric, ovarian, adrenal, leiomyosarcoma, and gastrinoma) in 12 patients. Clinical evidence of hepatic dysfunction (using the Child-Pugh classification A, B, and C) was evident in 20 (16, B and 4, C) of 25 patients with HCC preoperatively.

Ninety-nine RFA procedures were performed to ablate 328 tumors. Table 1 presents the number, average size, and total volume of tumors ablated per operation and length of hospitalization by the procedure type. Sixty patients had a single procedure while 16 patients underwent
PATIENTS AND METHODS

PATIENTS

A prospective evaluation of all patients undergoing RFA of unresectable liver tumors from August 1997 to October 2000 was performed. Patients with 15 or more liver tumors, greater than 50% involvement of the liver, or extensive extrahepatic metastases were not considered for RFA. Invasion or proximity to major vessels or bile ducts was not determined to be a contraindication to RFA treatment. Patients with cirrhosis or hepatic dysfunction (Child-Pugh classes B and C) were not excluded. None of the patients were candidates for liver transplantation.

PREOPERATIVE EVALUATION

All patients had preoperative laboratory tests that included hepatic enzyme profiles and tumor markers such as α-fetoprotein or carcinoembryonic antigen. All patients underwent helical computed tomography (CT) scanning with intravenous contrast, and were also evaluated by one of the authors (J.M.) using percutaneous ultrasound. Considerations in planning the surgical approach included number, size, and location of liver tumors, visualization on percutaneous ultrasound, need for concurrent operations (ie, synchronous colorectal or other organ resection), and patient condition in terms of surgical risk. The presence of vascular invasion, defined as tumor adjacent to the portal vein, hepatic artery or vein, or a primary branch of these vascular structures, was documented preoperatively. Tumor volume was estimated, assuming each tumor to be spherical with a radius = maximum diameter / 2, and the total volume to be ablated (sum of the volumes of all tumors to be ablated in a procedure) was calculated.

ABLATION METHODS

Ultrasound-guided RFA was performed using percutaneous, laparoscopic, and open surgical approaches. The selection of the RFA approach was individualized after full explanation to each patient of benefits and risks of each approach and informed consent was obtained. In general, percutaneous RFA was indicated for palliation, such as pain control, to prolong life (to prevent liver failure caused by tumor growth), for recurrent tumors, and for patients at too high a risk for laparoscopic or open surgery. Laparoscopic or open RFA was indicated more likely for potentially curative intent. Laparoscopic RFA was selected for smaller, superficially located, or easily accessible tumors with laparoscopic ultrasound. Open surgical RFA was indicated for larger or deeply located tumors. Open surgical RFA was also indicated in conjunction with other abdominal organ resections. Most patients received general inhalational anesthesia. Six percutaneous procedures were performed under local anesthesia in high-risk patients with small tumors. During laparoscopic or open operations, high-frequency laparoscopic or open intraoperative ultrasound was performed to screen the entire liver for occult tumors. Ablations were performed using a system (RITA Medical Systems, Mountain View, Calif) providing 460 kHz in alternating currents. Initially, a generator with a maximum power of 50 W and a 15-gauge cannula with 4-pronged and then 7-pronged retractable electrode needles were used. This allowed the ablation of 3 to 4 cm in diameter. From December 1999, a generator with a power up to 150 W and a 14-gauge cannula with 9-pronged needles were used. This new device allowed the ablation of lesions that were 5 cm in diameter. Thermocouples incorporated into the electrode monitored the heating process. After achieving a target temperature of 100°C to 110°C, ablation continued for 5 to 30 minutes depending on the size of the ablation. Multiple overlapping ablations were required for large tumors to achieve 1-cm ablation margins. The zone of ablation confirmed by intraoperative ultrasound monitoring of outgassing of dissolved nitrogen.

FOLLOW-UP

Postoperatively, systemic chemotherapy was usually used for patients with liver metastases, whereas regional chemotherapy was selectively provided to patients with hepatocellular carcinoma (HCC). Computed tomographic scans were obtained from all patients 1 week postoperatively to document ablation. Follow-up CT scans were obtained every 3 months for 1 year and every 6 months thereafter. Serum tumor markers were also followed up postoperatively. Occasionally, if CT scans failed to localize suspected tumor recurrence, gallium scans (for HCC) or positron emission tomography (for colorectal metastases [CRM]) were used. An increase in size or change in the CT contrast-enhanced appearance of the original tumors or positive nuclear scans diagnosed local recurrence. Surgical recurrence was defined as local recurrence of any of the tumors ablated in a given surgical procedure.

STATISTICS

Analyses were performed using SPSS 10.0.7 for Windows (SPSS Inc, Chicago, Ill) statistical software. The level of significance (α) was set at .05 for all tests. Continuous variables were expressed as mean ± SD. Continuous variables were tested using the t test or Mann-Whitney U test, categorical variables were tested using the χ² or Fisher exact test, and logistic regression was used for multivariate analyses. Survival rates were calculated using the Kaplan-Meier method and compared using the log rank test.

Of the 99 RFA procedures, 1 patient (1%) died 5 weeks postoperatively from progressive liver failure secondary to lack of hepatic reserve after a large ablation (1 HCC; size, 180 mm). Seven major complications occurred in 7 operations (7%) and 17 minor complications occurred in 10 operations (10%). Eighty-one procedures (82%) proceeded without complications. Individual complications and their frequency are pre-
The overall complication rates as well as the major and minor complication rates were similar when comparing A, B, and C patients \( (P = .57) \).

Patient follow-up after ablation has been 15.0±10.3 months (range, 1-39 months). Of the 328 tumors ablated, local recurrence was identified in 30 tumors in 26 operations on 22 patients (local tumor recurrence rate, 9% [30/328], surgical recurrence rate, 26.3% [26/99]). Large tumors and tumors with vascular invasion exhibited significantly higher local recurrence rates (Table 3). The total volume ablated was a significant predictor of surgical recurrence but the number of tumors ablated per operation was not (Table 4). In addition to tumor size and vascular invasion, more advanced hepatic dysfunction (by the Child-Pugh classification) was found to be associated with local tumor recurrence \( (P < .001) \) using a forward stepwise logistic regression model. Age, sex, and tumor type did not enter into the model. There was no statistically significant difference in local recurrence or surgical recurrence when operative approaches were compared \( (P = .62) \).

The surgical recurrence rate was higher in patients with metastatic disease (CRM, 30.8%; other metastases, 46.2%) than in those with HCC (14.7%) and this association approximated statistical significance \( (P = .06) \) on univariate analysis. Using a logistic regression model, volume and tumor type entered the equation, with larger volumes and metastatic tumors associated with surgical recurrence \( (P < .001) \). Age, sex, Child-Pugh classification, number of tumors, and the occurrence of any complications were not associated with surgical recurrence in this model.

In 75 of 99 operations, tumor markers were elevated preoperatively. The tumor marker levels decreased after RFA in 71 operations (95%). The level did not decrease in 4 operations for patients with extrahepatic metastases or with early postoperative recurrence. Four patients had abdominal or back pain attributable to liver tumors. After RFA, the pain remarkably improved in 3 patients and did not change in 1 patient despite appropriate RFA treatment. Twenty-five patients (33%) were alive without recurrence after the first RFA and 5 (7%) were alive without recurrence after repeated RFA. Of the 5 patients with no evidence of disease after repeated RFA, 2 patients underwent 2 procedures each, 2 patients underwent 3 procedures each, and 1 patient underwent 4 procedures. Nineteen (25%) were alive with recurrence. Twenty-three (30%) died of cancer and 4 (5%) died of other causes without evidence of recurrent disease. Survival rates (Figure) were similar \( (P = .38) \) in patients with HCC and metastatic diseases, averaging 24±3 months in patients with HCC and 25±2 months in patients with hepatic metastases.
Historically, patients with metastatic disease were not considered to be candidates for surgical treatment. Changing concepts in cancer surgery suggest that surgery might play a more important role in some advanced or metastatic diseases. This has been demonstrated in colorectal carcinoma with metastases to the liver. Because of its metachronous pattern of dissemination, aggressive metastasectomy has been shown to prolong life in patients who can be rendered clinically disease-free and to cure up to 30% of those treated. The prognosis of patients with colorectal metastases to the liver without treatment is poor, with median survival varying from 5 to 13 months. Even with current chemotherapy regimens, response rates range from 18% to 31%, with median survival of 8 to 14.2 months. For this reason, aggressive surgical treatment has been advocated, including repeated liver resections for hepatic metastases, despite a 40% morbidity rate and an average hospital stay longer than 3 weeks. The prognosis of gastric, pancreatic, and biliary metastases to the liver is even worse, with a median survival of less than 2 months when untreated. Left untreated, HCC also has a dismal prognosis, with fewer than 10% of patients alive at 1 year. Even with “curative” resection in HCC, recurrence is common—as high as 80% at 5 years following resection. Obviously, newer and better treatment modalities are needed to have a significant effect on a disease with such a poor prognosis.

Rossi et al reported the first large clinical study of RFA in 1996. Since then, several investigators have reported results of RFA in resectable and unresectable HCC and CRM. Collectively, favorable results were reported with no mortalities and complication rates ranged from 0% to 17% in a combined total of 357 procedures in 10 studies. Most of these studies consisted of patients with smaller, less extensive diseases, and the number of tumors ablated per procedure ranged from 1 to 3, averaging fewer than 2 tumors. In our series of 99 operations on patients with more extensive disease (3.3 tumors per procedure; average size, 30.3 mm), the complication rate was similar to the higher end of the spectrum previously reported. Not surprisingly, as RFA was applied to more extensive tumors, the potential for complication increased. Two complications not previously observed in RFA of less extensive disease, thrombocytopenia and myoglobinuria, were identified in 4 and 5 RFA procedures, respectively. These complications are well recognized after extensive cryosurgery, suggesting that they may be related to the amount of hepatic destruction rather than to the ablative modality.

Major bleeding occurred in only 1 patient; a delayed hepatic rupture caused by hematoma formation a few hours after RFA required reoperation. None of the other patients in this study required blood transfusion. Blood products were often required preoperatively, however, to correct coagulopathy or thrombocytopenia for patients with Child-Pugh class B or C. Bile duct injury was the most frequent major complication, occurring in 5 patients. Three bile leaks occurred early and were attributed to cannula injury of large ducts. Two strictures, observed late, were the result of treating tumors near the confluence of the hepatic ducts and likely resulted from thermal injury.

While mortalities were not previously reported, 1 death (1%) occurred in a patient with a very large HCC with extrahepatic metastases. While the patient had no evidence of hepatic insufficiency preoperatively (Child-Pugh class A) and was felt to have adequate hepatic reserve, the patient progressed to liver failure and death 5 weeks after the percutaneous RFA. Death was a result of more extensive tumor involvement of the liver, which was confirmed by autopsy but not appreciated on CT scan or percutaneous ultrasound preoperatively. Percutaneous RFA relies on CT scans and percutaneous ultrasound to identify and localize tumors. One of the advantages of laparoscopic and open RFA is the improved sensitivity of intraoperative ultrasound in detecting occult disease.

We found RFA to be efficacious in ablating advanced, unresectable liver tumors, with a local recurrence rate of only 9%. However, this study did not intend to investigate how this local control affected the long-term survival of patients treated by RFA. To our knowledge, the only previously reported prospective, randomized trial of RFA compared it with ethanol ablation in the treatment of small HCC but did not evaluate long-term survival. While a trial randomizing patients to receive RFA or no treatment for hepatic metastases or HCC would clearly define the potential survival benefit of treatment, such a study would not be performed, given the known dismal prognosis of untreated hepatic tumors. A more acceptable alternative might be a randomization of patients with unresectable liver tumors to receive chemotherapy with or without RFA, or a randomization of patients with resectable tumors to undergo either surgical resection or RFA. Until such studies are performed, the only insight into the potential survival benefit offered to patients undergoing RFA can be found in comparing our results with historical controls. With a mean survival of 25±2 months in metastatic disease and 24±3 months in HCC, our patients seemed to do consid-
erably better than those left untreated, among whom survival averaged 5 to 13 months.\textsuperscript{21} While surgery remains the standard of care for resectable lesions in both HCC and CRM, it is interesting to note that the survival curve in our study of patients with unresectable tumors (Figure) at 3 years is comparable with curves generated in patients with resectable tumors undergoing surgical resection of both HCC\textsuperscript{24} and CRM.\textsuperscript{28} A large percentage of our patients had or developed extrahepatic metastases during follow-up observation. That our survival curve approximates those in patients with resectable tumors supports the conclusion of Jaffe et al.\textsuperscript{4} that when metastases to the liver occur, they seem to be the dominant influence on survival. With further study, we may find that a more aggressive attempt to control hepatic disease will prolong survival.

The results of our study suggest that RFA is a safe, effective, and repeatable method of local control of advanced hepatic tumors. Predictors of local tumor recurrence include large tumor size and the presence of major vascular invasion. Large ablation volume, but not number of tumors treated, is predictive of surgical recurrence. Local control of hepatic disease using current or future RFA technology may prolong survival of patients with unresectable or advanced liver tumors. The utility of RFA in this setting warrants further study.

Presented at the 72nd Annual Meeting of the Pacific Coast Surgical Association Banff, Canada, February 18, 2001.

Richard Severino, MS was the validating statistician.

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REFERENCES


Clifford W. Deveney, MD, Portland, Ore: The authors have presented a series of 77 patients who underwent 99 radiofrequency ablations of metastatic or primary tumors of the liver. There was 1 operative death in a patient with a large hepatic primary liver tumor who subsequently died of liver failure, and there were 7 major complications, including 3 bile leaks and 1 bile duct stricture.

At 15 months' follow-up (and by the way the patients were followed with helical CT and gallium or positron emission tomography [PET] scans where necessary) the recurrence rate for CRM was 30% and for HCC was 14.7%. Tumor survival in this group of patients who were not operative candidates was 25 months—quite good considering that survival in nonoperative patients with these diseases is probably less than a year. In summary, the authors have treated a group of patients who were not operative candidates with liver tumors with radiofrequency ablation. To date they were able to successfully ablate the tumors in 40% of their patients. Mortality and morbidity were minimal. These results compare favorably with those of others who employed a radiofrequency ablation to treat liver tumors. These data strongly support the use of radiofrequency ablation in the treatment of liver tumors in those patients who are not operative candidates.

I have several questions for the authors. Have you had any problems assessing at the operation the completeness of your ablation? That is, particularly in the large tumors that require several ablations within the tumor, how are you sure that you have gotten to the edges? I note that your recurrence rate is higher in these larger volume tumors. Can you comment on the complications of the bile leaks, how they were handled, and was there any indication or prediction that you might have a bile leak, ie, the tumor was in proximity to a large bile duct? In the follow-up of these patients, did you find the helical CT for the most part accurate and helpful, or did you have to rely on PET and gallium scan?

How many of the patients in your group developed other metastatic lesions in the liver during the follow-up, that is, distinct lesions from the ones you treated? And finally, with these results, which compare favorably with resection in terms of recurrence, is it time to do a randomized prospective trial comparing radiofrequency ablation of selected tumors in patients who are candidates for cure?
Theodore X. O'Connell, MD, Los Angeles, Calif: The first question I have is regarding the CT scan you showed of the patient who had 2 lesions of the right lobe. That patient seemed to be resectable. Why was that patient not resected and treated with RFA instead? The second question is that it is well known that lesions over 3 cm do not do well with RFA and certainly if over 5 cm is probably a contraindication to RFA. Why were the large lesions treated with RFA and not with cryoablation, which you can do better with the larger lesions?

The third question is, is there vascular invasion? I don’t think that the authors can really say that the patients had vascular invasion. That is only a pathological diagnosis at the time of biopsy or resection, and what they really mean, I think, is vascular proximity in that there is a large vessel very close to the tumor. It is well known both with cryoablation and with RFA that having large vessels close to the tumor abrogate the effects of both the freezing and the heating because of the radiator effect of the close, large vessels.

Charles H. Scudamore, MD, Vancouver, British Columbia: How do you select your patients for open, laparoscopic, and percutaneous treatment? It appears that you have quite a large number of patients who are at high risk for an open operation undergoing open ablations. Did you separate for primary and secondary tumors, how did you stratify your complication between cirrhotic patients who had HCC by Child-Pugh score, and was the poor liver function the reason for nonresectability?

Lastly, I am very concerned about the myoglobinuria. This is a very high rate of myoglobinuria in this series. Was this clinically significant? What was the reason for such a high incidence?

Diana Farmer, MD, San Francisco, Calif: I am particularly interested in your experience with the collateral damage, notably the bile duct injuries that you saw. We have some experience using radiofrequency ablation in hydroropic fetuses from sacrococcygeal teratoma and while we have been successful in saving some of these moribund fetuses, we have 2 patients in whom we have seen moderate collateral damage. I am wondering if you have any recommendations on how to control the collateral damage that you can see with RFA.

Robert C. Lim, MD, San Francisco: You divided your series into 3 groups, namely, percutaneous, laparoscopic, and open. I was wondering if you can elaborate as to the time of hospitalization in each of the groups. Also, would you further define vascular invasion?

Sherry M. Wren, MD, Stanford, Calif: As attractive as it is to surgeons to resect, I would be interested if the authors looked at a cohort of patients within the same time period comparing hepatoma patient survival with a standard program of chemoembolization; and for patients with unresectable colorectal metastases, compare to treatment with CPT-11 as adjuvant therapy. How does your overall survival, not tumor-free survival, compare?

1. Benjamin Paz, MD, Duarte, Calif: I was puzzled by the fact that the authors did not perform the ablation only in patients with extensive extrahepatic metastases. I wonder why they would do it with any extrahepatic metastases, since there is no improvement in survival with resection or any other ablative treatment. What was the indication?

Ronald K. Tompkins, MD, Los Angeles: In light of the controversy regarding the appearance of metastases after operating on malignant tumors with laparoscopic surgery, I wonder if you have looked at your laparoscopic group vs the other groups to see if there is any difference in the recurrence rates.

Dr Wong: As some of you may have heard, there has been trouble with Dr Limm arriving from Hawaii, so I will do my best to address these questions. I think it is fair to say that we have substantial evidence that surgical resection of metastatic disease can achieve in some patients with hepatic metastases, durable disease-free survival, if not potentially cure some of these individuals. But not all of these individuals obviously are candidates for surgical resection, and for this reason alternatives have to be examined.

It was a natural extension of Dr Junji Machi’s interest in ultrasound to apply a new technology which requires ultrasound to utilize in hepatic tumors. Most of this patient experience, in fact, represents his personal experience with RFA. To address and try to put some of the multiple questions together, there were a number of questions regarding operative approaches in RFA. When is a laparoscopic vs open vs a percutaneous approach appropriate? The choice of approach by the authors was largely a philosophical approach in the management of these patients. They have not had a large experience with ultrasonic probe placement during laparoscopic interventions and for that reason there was a greater comfort level in using an open or a percutaneous approach. This allowed a better 3 dimensional reconstruction of the tumor and more accurate probe placement in their hands.

Was there a difference between the various techniques in terms of outcome? Although there was a slight increase in the recurrence rate when the open surgical techniques were utilized, this was not a statistically significant difference.

Dr Deveney asked the optimal method to follow these individuals. The authors have used CT scan as a follow-up procedure of choice. It is readily available and it is simple. We have 1 PET scanner in Hawaii. It is a state-of-the-art PET scanner, but it is available only at 1 facility and not readily available. Positron emission tomography was utilized to evaluate patients when it was difficult to assess the CT findings. In our growing experience with PET, it appears that PET is a much more sensitive imaging modality than CT but we are unsure of its role at this point in time in these patients, particularly when you are evaluating metastatic disease and the outcome of early diagnosis in metastatic disease remains unclear as far as we are concerned.

Dr O’Connell and others asked about vascular invasion and perhaps I should clarify that we can’t categorically say that these lesions invade. Instead the term that I think should more appropriately be utilized is vascular proximity. This is an ultrasound diagnosis that is made when the tumor abuts or is adjacent to a major vessel. We found as well that vascular proximity did portend a poor ability to local control of these patients.

There were several questions about myoglobinuria. Myoglobinuria was associated with the very large tumors that were ablated in this series. There was an attempt to ablate tumors up to 15 cm in size, and the myoglobinuria in those 3 patients, I believe, was associated with these very larger tumors and the very prolonged ablation times. One of the interesting findings of this report is the bile injuries, and there were a number of questions regarding this observation. The bile leaks the authors believe are technical in nature and can be avoided by carefully evaluating the liver by ultrasound and directing the probe around major bile ducts. Bile leaks all appear to be transsections of the bile duct by the probe at the time of the operation and can be avoided by avoiding placing the probe through the biliary radical.

The more interesting or perhaps problematic issue is the long-term bile strictures that occur in this series. This appears to occur when the lesion is in proximity to a major biliary radical. It may be that a lesion in proximity to a major bile radical may be a contraindication to this technique.

A number of individuals asked: Should we compare RFA with other modalities of therapy? We believe that that this is probably an appropriate trial to consider. Many of us have the bias that the only benign tumor is a tumor that is in formalin, but given the extraordinary potential for bias in this setting, it would be appropriate to stratify this modality against possibly a more morbid resection such as hepatic resection.

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