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Expanded Treatment of Hepatic Tumors With Radiofrequency Ablation and Cryoablation

ABSTRACT

Three definitive treatment options are available for patients with hepatic tumors: hepatic resection, tumor ablation, and hepatic transplantation. Ablative techniques—including radiofrequency ablation (RFA) and cryoablation—have greatly improved physicians' ability to definitively treat patients with primary and secondary hepatic tumors. Both RFA and cryoablation are safe and well-tolerated, but the effectiveness for local tumor eradication depends on many factors, including tumor size, location, number, and type. The choice of ablation modality is based on user and institutional biases. Assessing outcome after ablation is difficult because few studies with good long-term follow-up have evaluated local recurrence, disease-free survival, and overall survival after ablation. This and other limitations make it difficult to draw meaningful conclusions.

Ablative techniques have greatly improved physicians' ability to definitively treat patients with primary and secondary hepatic tumors. These techniques include radiofrequency ablation (RFA) and cryoablation, as well as the newer microwave and laser ablation methods. Ablation devices, used either alone or combined with hepatic resection, have made it feasible to treat patients with bilobar lesions and those who would not tolerate liver resection due to underlying comorbidities.

Patient Selection

Patient selection for ablative techniques depends partially on whether the patient has primary or metastatic liver tumors. Liver resection remains the treatment of choice, when possible, for patients with isolated hepatic colorectal metastases. Most patients with metastatic disease are not amenable to resection, however, because of the number, size, or location of metastases, comorbidities, or limited hepatic reserve. Patients with limited hepatic metastatic disease who cannot, should not, or refuse to undergo resection are candidates for laparoscopic or percutaneous ablation techniques. In this population, patients with fewer than five tumors less than 3 cm in diameter tend to have better local control postablation, resulting in greater long-term survival. Preliminary 5-year survival data for this population are just becoming available. One recent series reported 3-year survival of 46% with a median survival of 33 months,[1] which approaches the survival rate following hepatic resection.[2]

Several other types of patients with metastatic colorectal tumors are increasingly being referred for tumor ablation. The first group comprises patients with treatable hepatic metastatic disease and limited extrahepatic disease. An example is a patient with a solitary retroperitoneal lymph node and treatable hepatic metastases. This patient is not likely to be a hepatic resection candidate, but ablation in addition to chemotherapy (and/or radiotherapy) may have a survival advantage vs chemotherapy alone. The results of trials to determine the efficacy of this strategy are not yet available.

A second group of patients who are increasingly being referred for ablation are those with hepatic tumors larger than 5 cm in size. Development of improved ablation technology and strategies, such as higher power generators, multiple probe devices, infusion of adjuvant materials and drugs, and protective techniques to limit collateral damage, will eliminate many of the barriers to treating these patients.

While prolonged survival is possible for patients with hepatic colorectal metastases adequately treated with ablation techniques, the utility of therapy for other types of metastatic tumors to the liver is unclear. For this reason, it is essential that patients are evaluated by multidisciplinary teams that may include a medical oncologist, hepatobiliary and/or transplant surgeon, radiologist, interventional radiologist, radiation oncologist, and anesthesiologist. In our practice, pa-

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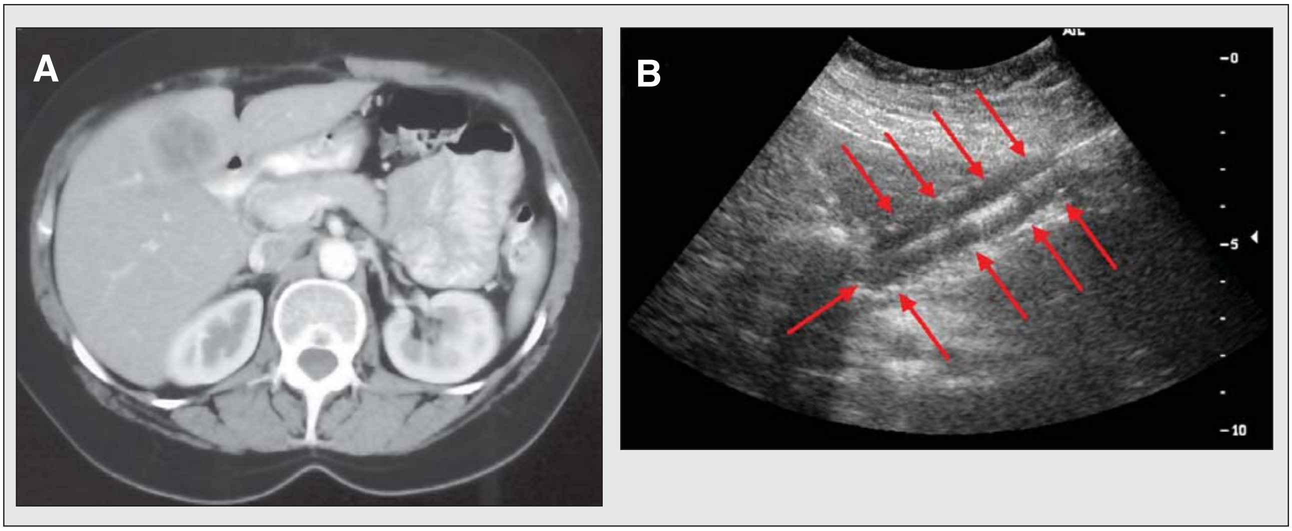

Figure 1: Percutaneous Cryoablation—(A) CT scan shows liver metastases immediately adjacent to duodenum. (B) Balloon (arrows) placed percutaneously using ultrasound guidance allowed separation of liver from duodenum with resultant safe percutaneous cryoablation of liver metastasis.

Table 1

Comparison of Ablation Procedures

	Percutaneous	Laparoscopic	Open
Usually requires general anesthesia	x	x	x
Requires laparotomy incision			x
Allows evaluation of intra-abdominal cavity and intraoperative ultrasound of liver	x	x	
Additional surgical procedures can be performed		+/-	x
Optimal imaging with ultrasound for monitoring zone of ablation			x
CT/MR guidance for monitoring zone of ablation	x		
Multiple probes can be used	x	+/-	x
Able to treat recurrent tumor with minimal morbidity	x		

CT = computed tomography; MR = magnetic resonance; +/- = in some cases.

tients with noncolorectal hepatic metastatic tumors are triaged on a case-by-case basis, taking into account the presence of extrahepatic tumor, other treatment options, the patient's age and medical condition, and the natural history of the tumor.

Three definitive treatment options are available for patients with hepatocellular carcinoma: hepatic transplantation, hepatic resection, and ablation.

Transplantation is the favored modality for cirrhosis due to hepatitis, because it offers the ability to cure both the background disease and the accompanying tumor. However, a shortage of organs, a long waiting list, and age or medical comorbidities remove transplantation as an option for many patients.

Hepatic resection generally cures the targeted tumor, but is associated with high morbidity and mortality in patients with Child's B and C cirrhosis, does not cure the underlying cirrhosis, and removes functioning liver along with tumor. Increasingly, patients who are not transplant candidates or who are on a potentially long waiting list for a transplant are being treated with percutaneous ablation. The technical success rate is very high, depending on tumor size, due to the encapsulated nature of hepatocellular carcinoma in cirrhotics, which selectively retains heat (RF, microwave, laser) or injected materials (ethanol, acetic acid, hot saline) and limits damage to the background liver. Survival advantage vs untreated hepatocellular carcinoma has been demonstrated for ablation at a rate similar to hepatic resection, but recurrence of tumor elsewhere in the liver is common (up to 85% at 5 years).[3]

The decision to perform percutaneous, open, or laparoscopic ablation is based on known advantages of each technique (Table 1). Although percutaneous interventions do not require a laparotomy incision, most procedures require general anesthesia. Radiofrequency ablation causes severe pain during current application, but cryoablation is virtually painless after the probes have been introduced. There are anecdotal reports of only minimal pain associated with microwave ablation, but to our knowledge a clinical trial quantifying this effect has not yet been published.

Another disadvantage of percutaneous approaches to liver tumors is the lack of a thorough evaluation of the abdominal contents to assess for extrahepatic disease and the lack of intraoperative ultrasound, which detects additional sites of hepatic disease in 40% to 55% of patients.[4-6] Although percutaneous ablation has historically been limited in its ability to safely treat lesions near other structures, the use of ablation with displacement techniques such as infusions of saline or dextrose in water or air, or physical barriers such as balloons, has made it possible to perform an increasing number of these procedures safely (Figure 1).

Finally, open and laparoscopic ablation performed by an appropriately trained laparoscopic surgeon enables utilization of other operative interventions, including hepatic or colon resection and hepatic artery chemotherapy pump placement (Table 1). Unfortunately, laparoscopic ablation is technically difficult, due to the limited ability to image the liver in multiple planes, which severely limits accurate applicator placement. Open ablation is therefore preferred for patients who can tolerate laparotomy.

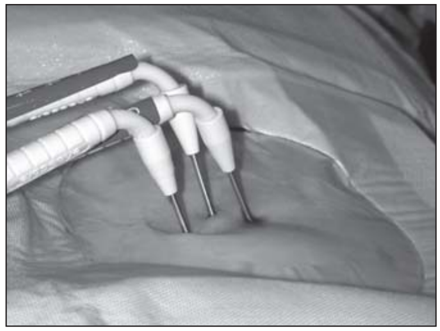

Figure 2: Cryoprobe Placement— Percutaneously placed cryoprobes for liver ablation.

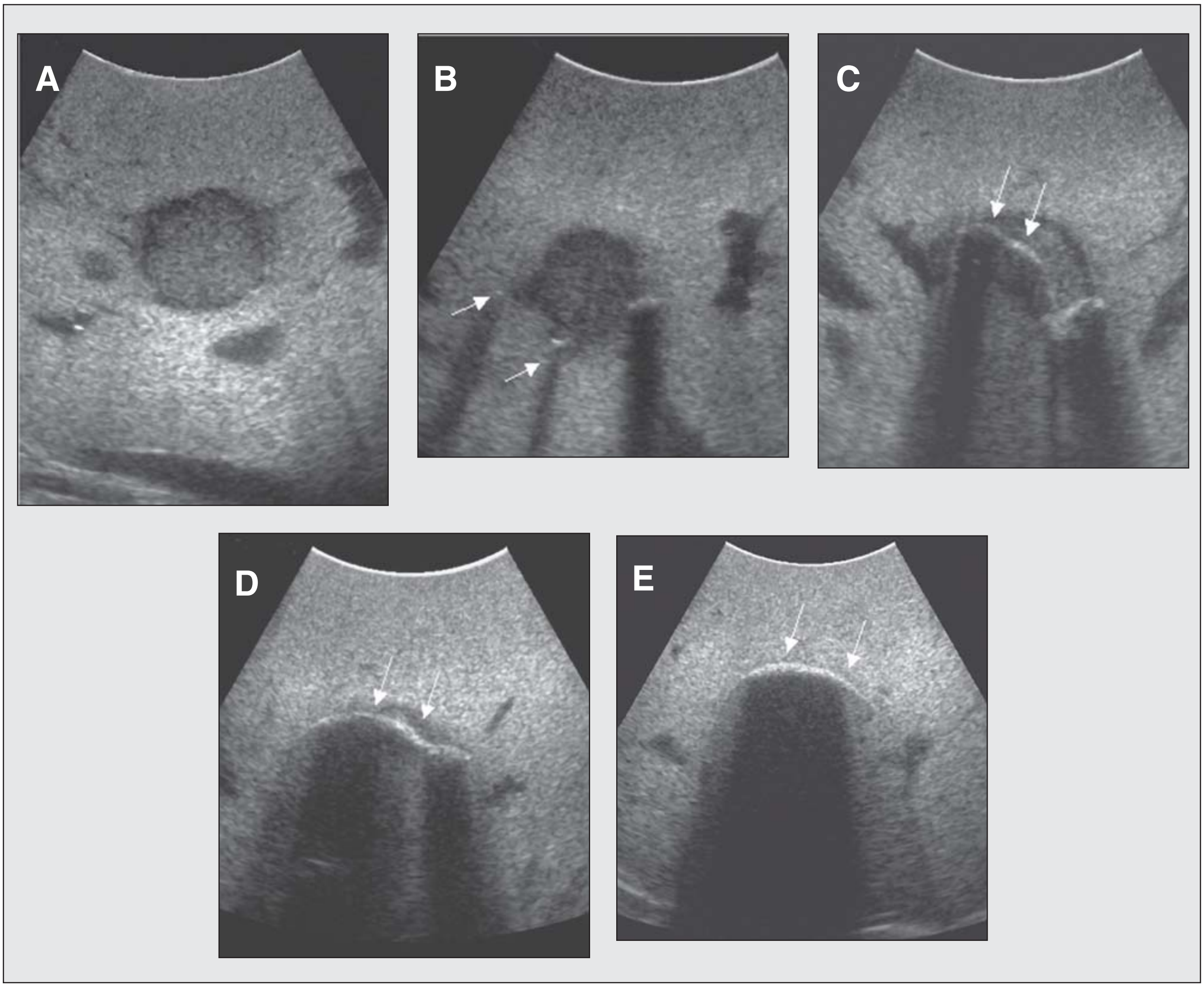

Figure 3: Tumor Visualization and Iceball Formation—(A) Small liver tumor is seen with intraoperative ultrasound. (B) After probe placement (arrows represent probes), two cryolesions growing from the two separate probes can be seen as hyperechoic foci (arrows in parts C, D, and E). When the iceballs fuse (E), a single conglomerate iceball completely obscures the tumor.

Choice of Ablation Technique

The choice of ablative technique depends on both the availability of the necessary equipment and the surgeon's or radiologist's familiarity with the technique. As many of the features of the various ablation modalities overlap, it is often unclear which is best for a given application. Although cryoablation was initially widely used for liver tumor ablation, RFA is currently the most commonly used modality in the United States. European and Asian practitioners have extensive experience with microwave and laser ablation, but for various reasons these technologies have not been widely used worldwide.

Radiofrequency ablation has been advocated as resulting in fewer complications and shorter procedure times; it is ideally suited for percutaneous use because the intrinsic cautery effect decreases bleeding complications. It is, therefore, probably the favored modality for coagulopathic patients and patients with severe morbidities who cannot tolerate even minor complications. The recent introduction of a multiple-probe RFA system (Cool-tip switching controller, Valleylab) enables simultaneous use of up to three RF electrodes. Clinical experience with this device is limited, however, and not all manufacturers support multiple probe use.

Cryoablation can be performed with multiple applicators, allowing the operator to sculpt a cryolesion for maximum tumor coverage with minimum collateral damage. Until recently, cryoablation was associated with large-diameter applicators (3 to 8 mm), but small-gauge devices (down to 17-gauge) are now available for percutaneous use (Figure 2). Regardless of the approach to the patient—open, laparoscopic, or percutaneous—one of the main advantages of cryoablation over the heat-based ablation methods is the ability to visualize the developing iceball with ultrasound, computed tomography, and magnetic resonance imaging (Figure 3), and the excellent correlation between the location of the iceball and the zone of cell death.[7-9] This is an important advantage of cryoablation, as the success of any ablation technique is dependent on the ability to visualize the complete destruction of the targeted tumor.

Thermal ablation techniques cause tissue destruction by creating ionic agitation (in the case of RFA and microwave ablation) and heat, which results in tissue boiling and the creation of water vapor. If lethal temperatures above 60°C are reached, protein denaturation, tissue coagulation, and vascular thrombosis will result in a zone of complete ablation. A zone of partial tissue destruction up to 8 mm in diameter can be seen surrounding the zone of coagulation. The mechanism of tissue destruction by heat is very different from that created by cryoablation. In cryoablation, the freezing and thawing process destroys cell membranes and organelles, due to the mechanical stresses associated with the phase change from ice formation. At gross pathology, this results in a well-defined zone of tissue destruction (Figure 4).

Heat-based ablation modalities cause profound vascular thrombosis. As a result, bleeding is an unusual complication of RF ablation. In contrast, cryoablation has no intrinsic hemostatic properties and has rarely been associated with substantial hemorrhage during large-volume freezes performed at open laparotomy.[10] With new technology resulting in smaller probes sizes (1.7 mm) for cryoablation, this is not a clinically significant problem, except when freezing results in cracking of the liver capsule during thawing. Percutaneous cryoablation does not, however, appear to result in a high bleeding rate, perhaps because in contrast to laparotomy, percutaneous ablation does not have the iceball-air interface, is not performed in a low-pressure environment, and has the benefit of surrounding tissues for tamponade.[11-13]

Outcome

Assessing outcome after ablation is difficult because few studies with good long-term follow-up have evaluated local recurrence, disease-free survival, and overall survival after ablation. In addition, a heterogenous patient group has been reported, including patients with both hepatic primary and metastatic tumors and those who have received open, laparoscopic, and percutaneous applications. The conclusions that can be drawn from these studies are thus limited. Finally, ablation has typically been used to treat unresectable patients, but the definition of unresectable depends on institutional and physician biases. Unfortunately, all these limitations make it difficult to draw meaningful conclusions from the available data.

Perioperative Morbidity

A recent, large, single-institution series evaluating periprocedural outcome after RFA found an overall morbidity of 10%, which was higher in patients treated with open RFA (13%) than in patients undergoing a percutaneous approach (8%).[14] In addition, patients with cirrhosis had a higher periprocedural complication rate.[14] In two other large studies, the overall morbidity rate for patients undergoing RFA was 7% to 9%, with a mortality rate of 0.3% to 0.5%.[15,16] Overall, it is clear that RFA is safe and well-tolerated.

Cryoablation has been associated with a systemic complication termed cryoshock, which can result in disseminated intravascular coagulopathy and multisystem organ failure. The rapid destruction of cell membranes and the relative lack of protein denaturation associated with freezing (compared with thermal ablation) may be responsible for this systemic response. The hypothesis is that intact cellular elements are more readily delivered into the bloodstream by freezing than with heat ablation, and this can result in thrombocytopenia, disseminated intravascular coagulation, and hepatic and renal failure in severe cases.[17] Furthermore, an increased quantity of systemic inflammatory mediators is present in the blood after cryoablation, compared with RFA.[18,19]

The actual incidence of cryoshock has probably been overestimated in many reports, as a recent review of the world literature on cryoablation found a 3% incidence of major complications and a 1% incidence of cryoshock after hepatic cryoablation.[20] Because it is now recognized that large-volume ablations involve an increased risk of cryoshock,[21] the occurrence of this complication can probably be decreased by limiting the volume of tissue destroyed by freezing.

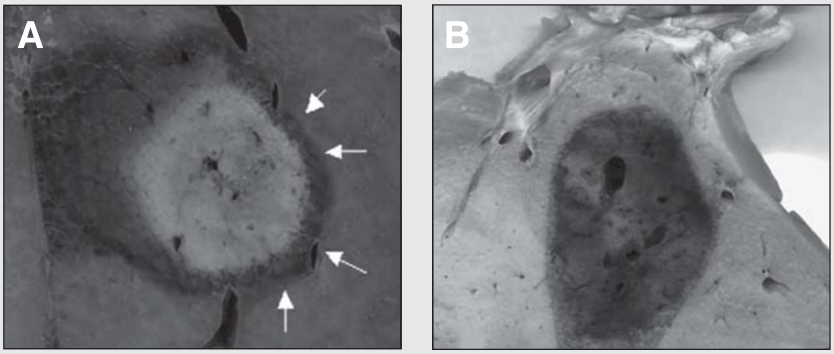

Figure 4: Pathology of RFA vs Cryoablation—(A) RFA lesion in normal pig liver demonstrates a central pale zone corresponding to the area of coagulation necrosis. Surrounding dark zone (arrows) represents area of liver injury with some remaining viable tissue seen on histology. (B) Cryoablation lesion in normal pig liver. Note abrupt transition between normal and necrotic liver, and the lack of a zone of partial necrosis.

Overall and Disease-Free Survival

Comparing the relative effectiveness of tissue destruction by RFA and cryoablation is problematic due to the lack of well-controlled studies. Most authors conclude that cryoablation has a slight advantage in the ability to cause cell death when tissue has been appropriately targeted in the laboratory,[22] but controlled clinical studies have not been performed. To thoroughly assess oncologic outcomes, it is important to evaluate overall and disease-free survival, including evaluation of local recurrence. Unfortunately, the limitations in the literature make it difficult to define overall and disease-free survival for specific tumor types because of the short follow-up, mixed histologies of tumors that are reported, and lack of assessment of disease-free survival.

In general, published series evaluating liver ablation report local recurrence rates that appear lower after cryoablation. However, these studies were generally performed during open laparotomy, and most RFA studies were performed percutaneously or included a mixture of intraoperative and percutaneous cases. Thus, it is difficult to directly compare local recurrence rates for the two technologies.

The RFA trial with the lowest local recurrence rates (1.8%) included a large proportion of patients ablated intraoperatively, many with a concurrent Pringle maneuver.[23] Alternatively, a recent series has reported local recurrence of up to 33% after laparoscopic RFA.[24] Tumor recurrence at the site of a cryolesion occurred in 9% to 20% of patients.[25-28] For both technologies, there appears to be an increased incidence of local recurrence using percutaneous approaches compared with ablation performed at open laparotomy,[29] but percutaneous ablation offers the potential to retreat local failures with minimal morbidity.

Although flaws in the existing data limit evaluation of overall survival, a few studies have examined survival by specific tumor type, making it possible to compare outcomes with series appraising other types of treatment, including resection or chemotherapy. Overall survival for colorectal and hepatocellular cancer after ablation is listed in Tables 2 and 3, respectively.

Table 2

Overall Survival After Ablation of Colorectal Hepatic Metastases

Author	Ablation Type	Number of Patients	Median Follow-up	Median Survival	3-Year Survival
Berber 2005[24]	RF	135	Not given	29 mo	35%
Solbiati 2004[1]	RF	184	38 mo (mean)	33 mo	46%
Abdalla 2004[30]	RF	57	21 mo	Not given	37%
Yan 2003[31]	Cryoablation	172	23 mo	28 mo	41%
Ruers 2001[32]	Cryoablation	30	26 mo	32 mo	37%
Seifert 1998[33]	Cryoablation	116	21 mo	26 mo	32%
Weaver 1995[34]	Cryoablation	47	26 mo	26 mo	Not given

RF = radiofrequency.

Conclusion

Both RFA and cryoablation are safe and well-tolerated, but the effectiveness for local tumor eradication depends on many factors, including tumor size, location, number, and type. The choice of ablation modality is based on user and institutional biases. The choice of percutaneous, laparo-

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Table 3

Overall Survival After Ablation of Hepatocellular Carcinoma

Author	Ablation Type	Number of Patients	Median Follow-up	Median Survival	3-Year Survival
Lencioni 2005[35]	RF	187	Mean, 24 mo	57 mo	67%
Tateishi 2005[36]	RF	319	2.3 yr	Not given	78%
Lin 2004[1]	RF	52	25 mo	Not given	74%
Lam 2004[37]	RF	51	Not given	Not given	61% (at 18 mo)
Curley 2000[29]	RF	110	19 mo	Not given	Not given[a]

[a]Actual survival 59% at 19 mo follow-up.

RF = radiofrequency.

scopic, or open ablation should be evaluated on a case-by-case basis. The less invasive approaches are associated with faster recovery times and fewer complications but do not afford the ability to thoroughly explore the abdomen for other sites of disease, and probably are less efficacious for tumor control than ablation performed at laparotomy.

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