

Radiofrequency Ablation of Hepatic Malignancies: Is Heat Better Than Cold?

The article by Curley and colleagues¹ in this issue of *Annals of Surgery* is notable for several reasons: 1) it is the largest patient series to date using radiofrequency ablation (RFA) for destruction of malignant neoplasms of the liver; 2) it is the first large clinical trial of combined RFA and a Pringle maneuver for control of tissue cooling; and 3) it has the lowest reported local recurrence rate (1.8%) for any sizable clinical series of *any* focal ablative technology in the liver. This fact alone calls for careful scrutiny of this study.

Long-term survival for patients with primary and metastatic malignancies confined to the liver is primarily a function of the biology of the tumor and not the interventions used to eradicate it. A critical factor that can be influenced by surgical therapy, however, is local control of the treated tumor. Because the local recurrence rate reported in this study is extraordinarily low, we need to carefully examine the factors that may have played a role in this result. For comparative purposes the local recurrence rates of the four previously published clinical RFA series in which local recurrence was reported were 50%, 50%, 90%, and 100% respectively.^{2–5} In fact, four of four patients resected after RFA all had residual live tumor in the specimen.³ Some parameters that are different in this study when compared to other RFA studies include the large proportion of patients who had RFA performed intraoperatively with ultrasound guidance, rather than percutaneously, and the use of the Pringle maneuver.

What are the advantages of intraoperative RFA? Certainly the tumor can be better seen with intraoperative ultrasound (IOUS) when compared to percutaneous ultrasound due to higher frequency transducers and lack of an intervening body wall.⁶ This may result in more precise localization of tumors and increased sensitivity for lesion detection. While it is probably safe to conclude that the use of IOUS may be responsible for an incremental decrease in positive margins, it likely does not explain the large difference in results between this study and others.

An additional advantage of the intraoperative use of RFA is the ability to combine it with a Pringle maneuver. In animal models, a Pringle maneuver (clamping of the porta

hepatis during ablation, thus interrupting hepatic arterial and portal venous flow to the liver) decreases the amount of heat that is “stolen” from the RFA lesion, which allows a larger zone of tissue ablation. This is the largest study in humans of the Pringle maneuver used in conjunction with tumor ablation. If the very low local recurrence rates using this combined technique are confirmed in subsequent studies, it means that the RFA generators currently in use may not generate enough thermal energy to overcome the cooling effect of intrahepatic blood flow when used without a Pringle maneuver.

However, the intraoperative (*vs.* percutaneous) use of RFA negates many of the advantages of the technology. RFA has proven to be safe when applied percutaneously because it cauterizes tissue in the probe tract, and thus avoids bleeding after the probe is withdrawn. If RFA is to be used during an open surgical procedure, it needs to be compared to cryoablation, the current standard. Cryoablation of both primary and metastatic hepatic cancer has been extensively reported. An advantage of cryosurgical ablation with respect to other ablative modalities is the ability to visualize both the cryoprobes and the iceball by ultrasound, which allows precise probe placement and control of margins during treatment.^{7–9} Local recurrence has been a problem at some centers after cryoablation, with widely varied local recurrence rates (2–44%) attesting to operator variability (also a major issue with RFA).^{10,11} In general, centers that are inexperienced with IOUS are more likely to have higher recurrence rates. This likely is a result of the lack of coverage of the entire tumor by the iceball rather than survival of tumor within the treated area.

We disagree with the authors' assertion that it is particularly difficult to freeze tumors near major vascular structures. Modern cryoablation systems can overcome the heat sink effect of blood flow in adjacent major vessels without a Pringle maneuver.⁷ The treatment of central tumors in close proximity to major vascular structures does require the placement of more probes than are utilized for similar peripheral lesions, and the probes must be placed adjacent to larger vessels rather than at the center of the lesion. Blood vessels are remarkably resistant to damage from freezing, even when completely frozen,¹² and therefore the freezing process does not need to be modified to avoid vascular damage.

Another advantage of cryoablation over RFA is the abil-

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ity to freeze with up to eight probes simultaneously, which allows rapid creation of a large iceball of virtually any shape. With RFA, large tumors require multiple consecutive probe placements, which can be very time-consuming and confusing when attempting to determine areas within the tumor that have not yet been treated.

We believe that the authors have overstated the complications of cryoablation. A recent worldwide survey of 2173 cryoablation cases reported perioperative mortality of only 1.5%.¹³ This figure is not statistically different from the zero of 123 cases presented in this study ($p = 0.17$, chi-squared). It must also be kept in mind that the complications reported in the worldwide survey include the earliest experiences of *any* type of ablative technology in the liver where the potential risks and complications were not yet known. Because RFA has only recently been introduced, practitioners of RFA have had the benefit of learning from the complications of hepatic cryoablation. For instance, the exclusion in the current study of patients with Child's class C cirrhosis or tumor adjacent to major biliary structures is prudent, but also the result of lessons learned the hard way from cryoablation. Careful patient and lesion selection has decreased the risk of ablative procedures, and complications after hepatic cryosurgery for metastatic disease are now unusual.

Because the follow-up in this study, and indeed all RFA studies, is quite short, local recurrence—not mortality—is the most useful endpoint, and the method of detecting local recurrence is thus critical in defining it. Because CT findings of tumor recurrence can be quite subtle, readings can be easily underestimated in determining postablation tumor recurrence. Experience clearly plays a role in accurate CT evaluation, as does consistency of observation technique. To eliminate inter-reader variability, CT scans in postablation patients at our institution are almost always evaluated by a single radiologist; in several instances, an initial negative reading by a less-experienced radiologist has been changed to positive when reevaluated by the more experienced reader. The CT and MRI findings of postablation patients is a topic of considerable interest in the radiology community, and only now are studies becoming available that elucidate both the normal and abnormal findings after therapy.¹⁴

Given this variability in interpretation (and CT technique) of posttherapy scans, it would have been desirable for the authors to provide a more complete description of the postablation imaging findings. What were the criteria for calling a case negative? Did a single radiologist interpret the images? What CT technique was used? Were biopsies performed of equivocal cases? Relying on radiology reports that may have been generated by several different radiologists of varying experience levels may be a significant source of unreliability in this study.

In the patient with a resectable primary hepatocellular carcinoma and adequate hepatic reserve or metastatic colorectal carcinoma confined to a single lobe of the liver, resection with an intervening margin of uninvolved liver

tissue is the procedure of choice. Both morbidity and local recurrence after hepatic resection are low, and thus any ablative therapy is unlikely to be superior to resection. In patients treated with ablative therapy, a margin of treated liver beyond the lesion is necessary, and it is imperative that the entire targeted zone of tissue be destroyed. Previous studies of RFA have not consistently met these goals, as demonstrated by high local recurrence rates.^{3,15} It is possible that the combined Pringle-RFA procedure described in this study achieves better local control and thus represents a major therapeutic advance, but confirmation of these results is critical.

In summary, the authors of this article have provided provocative data with local recurrence rates after RFA that are far superior to previous studies. The reasons for the discrepancies between this and previous studies are likely multifactorial, but include the use of intraoperative rather than percutaneous probe placement and a Pringle maneuver combined with RFA. This study would have benefited from a careful examination of the CT images by a single experienced abdominal radiologist. It is increasingly clear that ablative techniques can play an important role in the treatment of patients with hepatic malignancies by increasing the number of patients able to undergo potentially curative procedures. However, until the results of randomized trials become available, the relative roles of different ablative technologies will remain unclear.

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