Radiology

REVIEWS AND COMMENTARY • EDITORIAL

Can the Injection of Adjuvant Gels Accelerate Heating for More Robust Thermal Ablation of Tumors?

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Conflicts of interest are listed at the end of this article.

See also the article by Maxwell et al in this issue.

Radiology 2019; 00:1–2 • https://doi.org/10.1148/radiol.2019190074 • Content code: IR •

Image-guided thermal ablation has now come into widespread use for the treatment of focal tumors in the liver, lung, kidney, bone, and other organ sites (1,2). This method relies on the delivery of high-energy radiofrequency (RF) waves and, more recently, microwaves that are delivered to a target via needle-like applicators placed by the interventional oncologist using US, CT, or MRI (3). This energy is largely converted to heat that in turn can be used to achieve controlled volumes of tissue coagulation. The extent of clinical use of these techniques and their adoption into multidisciplinary clinical guidelines and staging systems (4) had led many to advocate that interventional oncology should be considered the fourth pillar of cancer care—on a standing equal to conventional surgical treatment, radiation, and chemotherapy. Yet, numerous studies point out the hard reality that thermal ablation is best reserved for tumors smaller than 3 cm. It is generally acknowledged that the primary reason for this limitation is the technically demanding need to ablate not only the entire tumor, but in most cases at least a 5–10-mm margin of apparently "normal tissue" (ie, the "periablational margin") to maximize the chances for complete eradication of the target tumor (5).

The challenges in achieving large-volume heating are well known (3). During an ablation, large reservoirs of heat surround microwave antennae and RF electrodes, with temperatures reaching in excess of 110°C for many microwave devices. Yet, tissue thermal conductivity is sufficiently poor that very steep temperature gradients are seen radiating from most ablation applicators. Thus, the necessary thermal dose to achieve thermal coagulation (approximately 1 minute at 60°C and 4–6 minutes at 50°C–55°C, depending on tissue type) typically does not radiate more than a centimeter or two into the tissue. Accordingly, were one to enable more efficient heat transfer (eg, by accelerating heat transfer through the tissue to create a less steep gradient), a larger zone of ablation could in theory be achieved.

To overcome this barrier, over the past 2 decades a host of studies have attempted to elucidate the underlying principles that govern thermal ablation to provide rational adjuvant therapeutic strategies that can increase the effective zone of ablation (3). Two key intrinsic mechanisms that retard tissue heating are poor thermal conductivity and perfusion-mediated tissue cooling. Whereas multiple strategies for reducing tumoral blood flow have been proven successful, prior attempts to modify local tissue conductivity in a reproducible and effective manner have proven elusive.

In this issue of *Radiology*, Maxwell et al (6) report their preliminary experimental in vivo animal studies of microwave ablation in the porcine lung. They demonstrate that a proprietary thermal accelerant significantly increases the short-axis diameter and volume of a single set of microwave ablation parameters compared with control ablations by at least 35% and 200%, respectively. Volumetrically, this was even greater than their prior reports in normal liver and muscle (7). When taken in context with the aforementioned discussion, the lung is a most logical place to observe such gains given its high air content, which leads to poor thermal conductivity.

Maxwell et al took their study further to tackle another equally practical and relevant question when administering an adjuvant therapy: determining whether there is an optimal way to ensure appropriate distribution of the injectate. The difficulty in achieving predictable distribution of chemical sclerosants such as ethanol and hypertonic saline as an electrical conductor for RF ablation was a primary motivation for the field at large to largely abandon direct injection methods of chemical ablation in favor of the more readily controlled thermal ablation methods (3). Thus, the investigators delivered the thermal accelerant gel endobronchially (ie, from the outside in), rather than injecting it in the center of the ablation zone. Although the group did not find this approach produced as large an increase in the zone of ablation, they did find that endobronchial administration of thermal accelerant gel improved ablation precision in terms of well-defined, homogeneous margins relative to percutaneous injection. Plausible explanations include that the injected gel may have had better or greater distribution or longer dwell time when directly filling the alveolar sacks rather than interstitial tissue.

There was a dichotomy: Direct percutaneous central injection of the gel resulted in bigger ablation zones, but more predictable zones of ablation were seen when injecting the adjuvant endobronchoscopically. This dichotomy brings to the fore another key issue: achieving a judicious clinical balance in defining the most critical end point for any interventional oncologic procedure. One can readily envision occasions where large volumes can be safely ablated by using a central direct-injection approach. Other times, particularly when there is a safety concern, including adjacent structures not to be ablated or a limited pulmonary reserve, a more predictable endobronchial injection will represent the more prudent or ideal approach. The

nature of these potentially more delicate cases may counter arguments against increasing the complexity of what ideally should be a straightforward, minimally invasive procedure by requiring a highly experienced anesthesiologist for more complex intubation and/or an interventional pulmonologist to perform endobronchoscopy.

Despite reason for substantial enthusiasm, two points of caution must be raised. First, it must be noted that the overall increase in short-axis diameter in these experiments was modest, only approximately 4 mm. However, it is more than likely that the experimental design and the resultant 1–2 cm diameters of coagulation represent proof-of-principle given model constraints rather than the maximum gain possible. Although the investigators have previously demonstrated that their thermal accelerant gel can increase temperatures deeper in a phantom agarose model, it must be pointed out that increased temperatures have not as of yet been demonstrated in the lung and many other relevant tissues (8). While the placement of multiple tissue sensors in the lung is not particularly practical as this would alter the very properties of the aerated lung tissue—especially given the high risk for pneumothorax—this does open the possibility for other causes for the increase in ablation. Increased heat retention from fluid-filled alveoli (ie, an oven effect) rather than an accelerated heat transfer could also account for the findings. Although the gel has been described as proprietary in nature, more information regarding the properties of the compound would be most welcome as this would enable others to help optimize its utility based on a rationale mechanistic foundation. Regardless, from a goal-oriented perspective, increased coagulation was noted and this would represent a clinical boon.

As noted in the study limitations, there is much further basic work to be done. Prior work with hypertonic saline and other compounds has demonstrated that injection volumes and concentrations will need to be optimized and most likely matched with different energy settings, possibly on a device-by-device basis. Although as noted, studying the effect of the thermal accelerant gel on ablation of lung parenchyma is a wise choice, it must be stated outright that different tissues have a wide range of physical properties. Hence, for any tumor ablation application, full evaluation will need to identify the interaction of the gel in terms of both its physical distribution as well as its thermal distribution for essentially two tissue compartments, which for intrapulmonary ablation would include the inner tumor and the outer surrounding lung. One can readily surmise that injection of a viscous gel is likely to be easier in aerated lung sacs than a potentially fibrotic cancer. By direct contrast, increased heat distribution may be easier to achieve in the more solid cancer. Thus, future translational study will likely need to occur on a tissue-by-tissue basis.

A final word of caution is mandated as this study reports short-term results in animals. By definition, the safety evaluation is somewhat limited and thus any potential long-term toxic effects are currently unknown. Ultimately, clinical trials and evaluation will be needed, acknowledging that local tumor control and possibly overall survival will be key study end points.

In conclusion, given the limitations of current ablation sizes, the development of thermal accelerant compounds that can be injected or delivered in a straightforward fashion during the procedure to successfully augment ablation outcomes has been somewhat of a "holy grail" in interventional oncology. Maxwell et al have brought us closer to this goal and will hopefully continue to do so until we successfully achieve our quest to identify adjuvant therapies to increase the size and completeness of tumor ablation, potentially expanding the number of patients who can benefit from our image-guided procedures.

Disclosures of Conflicts of Interest: Activities related to the present article: disclosed no relevant relationships. Activities not related to the present article: is a paid consultant for Cosman Company and Angiodynamics. Other relationships: disclosed no relevant relationships.

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