

For reprint orders, please contact:
reprints@future-drugs.com



Current status of liver tumor ablation devices

Ann P O'Rourke, Dieter Haemmerich, Punit Prakash, Mark C Converse, David M Mahvi and John G Webster[†]

The liver is a common site of disease for both primary and metastatic cancer. Since most patients have a disease that is not amenable to surgical resection, tumor ablation modalities are increasingly being used for treatment of liver cancer. This review describes the current status of ablative technologies used as alternatives for resection, clinical experience with these technologies, currently available devices and design rules for the development of new devices and the improvement of existing ones. It focuses on probe design for radiofrequency ablation, microwave ablation and cryoablation, and compares the advantages and disadvantages of each ablation modality.

Expert Rev. Med. Devices 4(4), 523–537 (2007)

The liver is a common site of disease for both primary hepatic malignancies (hepatocellular cancer) and metastatic disease from gastrointestinal malignancies. Primary hepatocellular carcinoma (HCC) is a significant worldwide public health problem with an estimated 1 million deaths per year [1]. In the USA, 17,000 new cases and 15,000 deaths occurred in 2005 but only 0.8% of patients underwent curative resection [2]. The incidence of primary HCC in the USA is increasing with an expectation of a corresponding increase in the death rate due to poor patient survival [3]. Persistent or recurrent liver disease is the major cause of both morbidity and mortality in patients with HCC. Although the ultimate control of this disease rests with the treatment of at-risk populations with vaccines for both hepatitis B and C, extirpation of tumor is the only potentially curative therapy for established cancers.

Secondary liver metastases from the spread of colorectal cancer are the most common indication for liver-directed therapies in the USA. Almost 150,000 new cases of colorectal cancer are diagnosed in the USA each year, which is associated with 57,000 deaths [2]. Among men aged between 40 and 79 years, colorectal cancer is the second leading cause of cancer mortality. Metastatic disease of the liver is the major impediment to long-term survival in patients with colon cancer. Improved chemotherapy has

had a major impact on the treatment of stage 3 (nonmetastatic) disease but has not improved survival in patients with metastatic disease. Surgical resection is the gold standard for the treatment of patients with resectable isolated hepatic metastases, with a 40% 5-year and a 26% 10-year survival. Although initial guidelines suggested that patients with more than four metastases should not undergo resection, recent literature has demonstrated a 10-year actuarial survival of 29% among patients with more than four tumors, almost equal to that of patients with solitary tumors [4]. Therefore, it is now recommended that all patients with liver-only disease should undergo surgical resection if feasible, regardless of the number of lesions. Even patients with recurrent liver metastases may be eligible for repeat resection, with a 5-year survival equivalent to that of the initial treatment [5,6].

As advances have been made in surgical techniques, anesthesia and perioperative care, surgical resection for primary and metastatic liver tumors has become the standard of care for possible cure [7,8]. Unfortunately, most patients (~80%) have a disease that is not amenable to surgical resection, even if confined to the liver [9]. This may be due to anatomic considerations, such as bilobar disease, limited hepatic reserve in cirrhotic patients with HCC, high surgical risk or comorbid disease [10]. Therefore, a number of

CONTENTS

- Clinical experience
- Desirable characteristics for ablative technologies
- Principles of thermal tissue injury
- Comparison of existing ablative technologies
- Image guidance for ablation procedures
- Conclusions
- Expert commentary
- Five-year view
- Key issues
- Information resources
- References
- Affiliations

[†] Author for correspondence
Department of Biomedical
Engineering, University of
Wisconsin, Madison,
WI 53706, USA
Tél.: +1 608 263 1574
Fax: +1 608 265 9239
webster@engr.wisc.edu

KEYWORDS:
ablation, cancer, cryoablation,
electrodes, metastases, microwave
ablation, probe design,
radiofrequency ablation

technologies have been developed for local control of liver tumors through physical methods, that is, tumor ablation by freezing or heating. Clinically available ablative technology includes cryoablation, radiofrequency ablation (RFA) and microwave ablation (MWA). Regardless of the technique, the goal of ablative therapy is to destroy the tumor and a 1 cm margin of surrounding viable tissue [11]. Ablation may be used alone, in conjunction with surgical resection or as a therapy for recurrence following resection. Depending on the approach (open surgery, laparoscopy or percutaneously, i.e., minimally invasive through a small incision) either a surgeon or an interventional radiologist will perform the ablation procedure.

There is a need for more long-term survival data regarding ablative therapies; however, current data suggest that these therapies may improve survival in selected patients. In addition, these ablative techniques can provide palliation of symptoms from liver tumors that are causing pain or secreting active hormones.

This review will discuss the current status of thermal-based technologies for the treatment of liver cancer focusing on treatment applicator design. This will include a discussion of a surgeon's clinical experience with resection and alternative treatments, design goals, existing types of treatments and associated applicators and a basic comparison of treatment modalities.

Clinical experience

Many patients with solid tumors have been treated with ablative techniques. The majority of clinical studies have focused on ablation of malignant liver tumors, although ablation is used increasingly in other organs, such as lung, kidney, bone, prostate and adrenal gland. There have been no randomized trials comparing any ablative therapy to resection in patients who would be candidates for either therapy or comparing different ablation technology. The technology is, however, used routinely in the clinical practice of surgical oncology. The targeting of this technology to specific patients requires a multidisciplinary decision making team consisting of surgical oncologists, interventional radiologists, radiologists, medical oncologists and transplant surgeons.

Over the last 10 years, a body of literature has been developed describing the indications, techniques, efficacy, imaging characteristics and expected outcomes of this technology in liver cancer patients. Ablative technology is indicated in the patient with a liver tumor who is not amenable to resection and

who may gain some survival or palliative benefit. The literature is not mature at this point; thus, the most critical end point, long-term survival, is not known. The lack of comparative studies also suggests that selection bias may impact the clinical results. Local recurrence and short-term survival data do exist and allow for some comparison of the clinically available devices. TABLE 1 presents data on the recurrence and survival for both primary and metastatic liver cancer.

Radiofrequency ablation

Currently, RFA is the most commonly used ablation modality and can be used via open, laparoscopic or percutaneous approach on both HCC and metastatic disease. RFA kills tumors by converting radiofrequency energy into heat, which causes protein denaturation, a loss of cell structure and coagulative necrosis [5]. For tumors greater than 3–5 cm, multiple overlapping sequential ablations may be necessary to ensure adequate margins [12]. Placement of probes is guided by ultrasound or CT scan. The ablation is monitored in real time with ultrasound or contrast-enhanced ultrasound, following an expanding hyperechogenic zone. RFA is safe, with overall complication rates similar to that of cryoablation but with lower reported mortality rates [5,9,10,13]. Reported local recurrence following RFA varies from 2 to 39% depending on technique and patient selection [1,14]. Most series report local recurrence rates of 10–20%, roughly comparable to cryoablation but significantly worse than hepatic resection [15,16]. After recurrence, a patient may be retreated by RFA, while retreatment is typically not performed after resection. In general, percutaneous RFA has higher rates of local recurrence than open RFA [17]. There are few studies with long-term results following RFA. One report demonstrated a 3-year survival rate of 46% among 230 patients with colorectal metastases and 77% among 241 patients with HCC [18]. Two other recent studies found 5-year survival rates of 40% in 65 patients with HCC [19] and 30.5% in 100 patients with colorectal metastases [20]. Another study examined factors predicting survival after RFA and concluded that it positively impacts patient survival in patients with liver-predominant disease, particularly for patients with tumors smaller than 5 cm in diameter [21]. Early complications are more frequent after RFA during open surgery (8.6%) compared with percutaneous RFA (4.4%), while the rate of late complications is similar (2.4%) for both approaches [22]. While

Table 1. Comparison of local recurrence rates and survival by different ablative technologies. Results vary based on technique or patient selection.

Method	Local recurrence: HCC (%)	Local recurrence: metastatic (%)	3-year survival: HCC (%)	3-year survival: metastatic (%)	5-year survival: HCC (%)	5-year survival: metastatic (%)
Cryoablation	9–22	9–22	46–86		31–74	22–78
RFA	2–38		38–98	46–58	24–74	24–30
MWA	12–17		47	14–51	57–74	32

HCC: Hepatocellular carcinoma; MWA: Microwave ablation; RFA: Radiofrequency ablation.

liver abscess is the most frequent complication, other complications include colon perforation, portal vein thrombosis, pleural effusion, skin burns, hypoxemias and pneumothorax.

Microwave ablation

MWA is another hyperthermic technique for tissue destruction. Volumetric heating is accomplished by friction as microwaves propagate through the tissue and cause water molecules to rotate rapidly. While not as common as RFA, there is growing commercial and clinical interest in this technology owing to higher tissue temperatures, shorter treatment times and reduced effects by vascular-mediated cooling. In the treatment of HCC, MWA has been demonstrated to be as efficacious as RFA [23]. Small studies evaluating MWA for metastatic disease have also been performed, again with similar results to RFA [24]. As with the other ablative technologies, MWA can be applied via an open, laparoscopic or percutaneous technique.

Cryoablation

The first widely available ablative therapy was cryoablation. Performed via open surgical, laparoscopic or a percutaneous approach, cryoablation is performed by placing one or more cryoprobes within a tumor, which is then frozen by the closed circulation of liquid argon or nitrogen. Cell death is due to rapid freezing of intracellular water and subsequent cell lysis [25]. Freezing is followed in real time with ultrasound, as the pathologic size of the region of liver necrosis is approximated by the ice ball. Reported local recurrence rates following cryoablation range from 9 to 22% [26–32]. Mortality is low, from 1.5 to 5%, with a morbidity of 7–25% [29,33,34]. Complications include hypothermia and cryoshock syndrome. Cryoshock is a syndrome of disseminated intravascular coagulation and multiple system organ failure. This is thought to be mediated by cytokine release [5,35]. This complication has limited the utilization of cryoablation, although it is still considered to be an acceptable treatment modality and continues to see use at our institution.

Desirable characteristics for ablative technologies

Current technology, although effective, has several problems that have limited utilization in patients with unresectable disease. The generation of an appropriately sized ablation zone, long treatment times, insufficient interoperative imaging modalities and performance in the vicinity of vascular structures are limitations of current devices. Safety and efficacy are most important in the design of any ablative technology. An ideal ablative technology would ensure complete destruction of all malignant cells with no significant side effects or complications. Tumor sizes treatable with ablation range from 0.4 to 13.5 cm [22,36] and are generally spherical; therefore, the treatment applicator must create a spherical ablation region the size of the tumor plus a small rim (~1 cm) of normal tissue. The technology should be safe for both the patient and the practitioner applying it, regardless of the number of times it is applied. To work in all regions of the liver and other organs that

have large vasculature, it should not be affected by the thermal heat sink phenomenon adjacent to large vessels. The blood flow in large vessels can remove significant amounts of heat from the region, preventing temperatures in the neighborhood of the vessel walls from reaching levels required to achieve cell death. It is preferable if the blood inflow occlusion is not required for efficacy, as cirrhotic livers (often coexistent in patients with HCC) do not tolerate this ischemic insult well. The deposition of energy must be controllable; adjacent liver and other organs must be protected while the tumor and 1-cm margin are destroyed. Interpatient variability in the perfusion, thermal and electrical properties of the liver tissue and tumor should not impair the technology's effectiveness.

Ideally, the tumor, regardless of size, should be treatable with a single application of a single instrument. If overlapping ablations are required, simultaneous application of energy with multiple probes would be preferable, rather than multiple sequential applications of energy. The ablation time should be measured in a span of seconds or minutes. A faster ablation time is theoretically less likely to be affected by thermal heat sinks. In addition, shorter operative times are less expensive.

The instrument should be ergonomic and controllable by the practitioner, while maintaining a sterile technique. It should be visible with a currently available imaging modality to aid in accurate placement. In addition, the ablated tissue should have imaging characteristics that differentiate it from tumor or normal tissue.

While treatment would ideally be completely noninvasive, it is beyond current capabilities. As such, the choice of treatment technique tries to balance noninvasiveness with ablation effectiveness. The choice of technique depends on the location of the tumor and adjacent organs, as well as the condition of the patient. There are advantages and disadvantages to each of the three application techniques. A percutaneous application is particularly desirable in that it is a minimally invasive technique and has the lowest morbidity rates. Most patients do not require a general anesthetic and recovery time is usually quick, with patients typically leaving the hospital the same or the next day. However, current external imaging techniques are not as sensitive, often missing smaller lesions that would be discovered with intraoperative ultrasound [16,32]. Additionally, a percutaneous approach holds the theoretical risk of seeding the tract with malignant cells. A laparoscopic or open approach may be necessary for access to certain locations in the liver. Additionally, larger lesions are treated more easily with an open approach [37]. An open or laparoscopic technique is necessary when ablation is used in combination with resection, such as when disease is in both lobes of the liver. Laparoscopic and open cases share the same intraoperative imaging and placement advantages; however, laparoscopic cases are less invasive than open cases. Often, patients who have undergone laparoscopic treatment have shorter hospital stays and recovery times. The instrument should be easily applied percutaneously, laparoscopically or via an open surgical technique. BOX 1 summarizes the above described ideal parameters.

Principles of thermal tissue injury

Tissue injury from heating

Most thermal ablation devices cause tissue necrosis via heating (RFA, MWA, laser and high-intensity focused ultrasound). Tissue necrosis can occur from temperatures as low as 43°C after several hours. Hyperthermia studies have confirmed, in a large number of different tissues, that above 43°C, the time required to cause cell death is cut in half with each degree centigrade of temperature rise [38]. However, note that the exact time–temperature relationship depends on the tissue type and the thermal–dose relationship observed at lower temperatures (<45°C) may not hold true at ablative temperatures [39]. In the time scales relevant for ablation therapies (~5–30 min), tissue necrosis occurs above approximately 50°C, that is, the ablation zone extends from the probe to the 50°C isothermal surface (FIGURE 1). The most prevalent mechanism of necrosis during tumor ablation is due to protein coagulation (coagulation necrosis).

Box 1. Ideal characteristics of a technology used as an alternative to resection.

- Complete destruction of malignant cells
- No significant side effects or complications
- Application percutaneously, laproscopically, or via open surgical approach
- Efficacious adjacent to vascular structures (not effected by thermal sink)
- Fast
- Can be used on the same individual more than once (retreatment)
- Probe visible with imaging
- Ablative changes visible with imaging in real time and post ablation
- Images of ablative change distinguishable from tumor and normal parenchyma
- Single probe for any tumor size
- Ergonomic
- Can be controlled by surgeon while maintaining sterile technique (hand or foot pedal)
- Safe for practitioners applying the technology
- Inexpensive
- Placement tract ablated to prevent tumor seeding with withdrawal
- Short recovery time for patient
- Energy controllable to prevent damage to adjacent liver or organs
- Robust to inter-patient differences in tissue properties

Tissue injury from freezing

An alternative to heating tissue to cause necrosis is freezing tissue. For a discussion of the response of tissue to low temperatures refer to [40]. In addition to absolute temperature, the rate of freezing and thawing affects cell death, with a rapid freeze rate and a slow thaw rate improving tissue destruction. With regard to the threshold temperature, consensus is yet to be reached, although temperatures in the range of -40 to -50°C are generally considered lethal to cells [40]. Susceptibility to low temperatures varies between tissue type and studies have shown survival of tumors at temperatures of less than -50°C. However, results from cellular studies may not correctly predict damage at the tissue level. *In vivo* studies in porcine liver have shown that the zone of tissue necrosis extends close to the ice ball (~0°C) boundary [41] and a comprehensive study of cryodamage in the porcine kidney showed the region of complete cell death extending up to the -20°C isotherm [42]. Repeated freeze–thaw cycles produce more extensive tissue destruction and increase the likelihood of adequate ablation in the target region. The ice ball size after a second freeze cycle is large than after a single freeze [40] – possibly owing to change in thermal tissue properties after thawing [43].

Comparison of existing ablative technologies

Below we present descriptions of current alternative cancer treatment technologies and a summary of their status. TABLE 2 summarizes the relevant characteristics of current cryoablation, RFA and MWA devices. Current cryoablation devices, with diameters of 1.2–8 mm, produce ablation zones of 4–5 cm in diameter, in approximately 15–25 min. Radiofrequency devices, with diameters measuring 1.2–1.6 mm, produce ablation zones of 1.5–7 cm in diameter, in approximately 12–25 min. Microwave devices, with diameters of 1.2–5.7 mm, produce ablation zones of 1.5–6 cm in diameter, in approximately 1–12 min.

Radiofrequency ablation

During RFA, radiofrequency current is injected into the treatment region via a RFA electrode placed at the target location. A dispersive pad (ground pad) is typically placed on the patient's thigh or back to serve as a return electrode for completing the electric circuit. Within the tissue, the electric current is carried by ions (Na⁺, K⁺ and Cl⁻). Rapid ion oscillations due to radiofrequency current (typically in the frequency range of 450–500 kHz) result in resistive heating preferentially around the RFA electrode, where radiofrequency current density is highest. More detailed descriptions of radiofrequency tumor ablation and devices can be found in the literature [44].

RFA devices for tumor ablation were introduced in the early 1990s. Initial devices created ablation zone diameters of approximately 1.5 cm and ablation zone diameters increased with each new device generation. Current devices can create ablation zones of approximately 1.5–7 cm in diameter and up to 5 cm in length (FIGURES 2 & 3) [45–49]. Since the goal is to ablate the tumor plus a 1 cm margin of normal tissue, for tumors

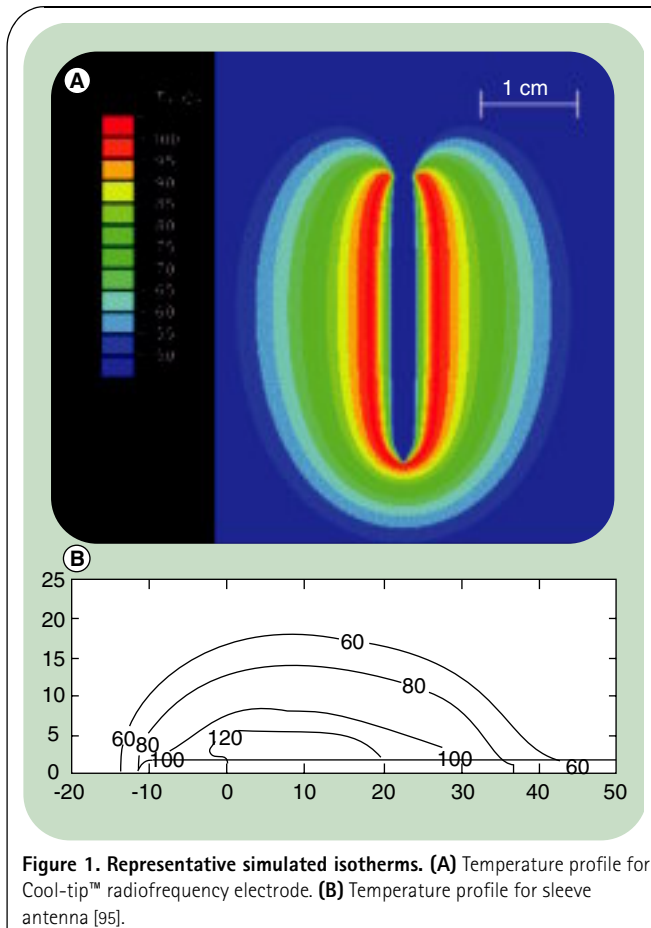


Figure 1. Representative simulated isotherms. (A) Temperature profile for Cool-tip™ radiofrequency electrode. **(B)** Temperature profile for sleeve antenna [95].

larger than 3–5 cm more than one ablation is typically required, depending on the device type. In most radiofrequency systems, this requires multiple sequential placements and ablations with a single electrode to create overlapping ablation zones [12,50].

The different manufacturers employed various strategies to obtain larger ablation zones [51]; there are currently three different manufacturers that offer commercial radiofrequency tumor ablation devices in the USA (Boston Scientific, Rita Medical and Valleylab) and an additional one in Europe (Celon). Two manufacturers (Boston Scientific and Rita Medical) employ multitined electrodes, to increase electrode surface area and volume of tissue heating (FIGURE 2B–E). For multitined electrodes typically an incremental deployment of the tines in stages is used, with ablation at each deployment stage for a certain amount of time or until the target temperature is achieved to ensure complete ablation of the target volume.

Two manufacturers use internal electrode cooling via circulation of water or saline to increase ablation zone size (Valleylab and Celon, FIGURE 2A & F). By cooling the electrode, the tissue surrounding the electrode is also cooled. The location of maximum temperature is ‘pushed’ further into the tissue, resulting in a larger ablation zone size [52]. A similar effect is obtained by infusing saline into the tissue via ports in the electrode [53] – this method is used by the Starburst Xli™ electrode (Rita Medical, FIGURE 2E) [45].

In addition, Valleylab recently introduced a system that allows the use of up to three electrodes simultaneously [54,55]. This system is based on rapid switching of radiofrequency energy between electrodes (i.e., time interleaving) to allow heating of all electrodes without electrical interactions that adversely affect the heating profile [56]. The advantages of the simultaneous use of multiple electrodes are a significant reduction in treatment time, simpler treatment planning compared with multiple sequential ablations and a synergistic thermal effect resulting in higher temperatures in between electrodes.

Another method that has been described in several studies is bipolar energy delivery between two electrodes or two separated conducting areas on a single electrode [57–60]. A second radiofrequency electrode replaces the dispersive electrode (ground pad) to close the electric circuit and the tissue is heated around both electrodes. An advantage of the bipolar method is that the region of direct heating extends further from the electrode resulting in more uniform tissue temperatures [59]. The bipolar method is used in the Celon device (FIGURE 2F), where up to three electrodes – each with two conducting regions – are used and radiofrequency energy is applied in a round-robin fashion between all possible combinations.

Control of applied power

During RFA, tissue temperatures are limited to a maximum of approximately 100–110°C. At higher temperatures, tissue vaporization and charring can occur; the latter should be avoided especially since charred tissue presents an electrically isolating layer that prevents further power deposition into tissue (for RFA but not for MWA). The manufacturers use two different approaches to control the applied radiofrequency energy. One manufacturer (Rita Medical) uses temperature control; the electrode has temperature sensors embedded in the tips of the tines (FIGURE 2C–E), and applied power is controlled such that tip temperature is kept between 100 and 105°C. All other manufacturers use impedance control; applied power is slowly ramped up (to prevent charring) until tissue impedance exceeds a threshold level as a result of tissue vaporization. Subsequently, power is turned off to allow vapor to settle and power is either reapplied at a lower level or ablation is terminated (Boston Scientific). The time required for a single ablation depends on device type and the desired size of the ablation zone; typically between 12 and 25 min are required for a single ablation. For multitined devices (FIGURE 2B–E) a step-wise expansion of times is recommended to ensure confluent ablation zones, that is, ablate at 2 cm expansion for 5 min, extend to 3 cm and ablate for 5 min, and so on.

Vascular-mediated cooling (heat sink effect)

One shortcoming of RFA devices is reduced performance close to large vasculature (i.e., vessels >3 mm in diameter) [48,60–62]. Reduced tissue temperatures due to convective cooling by blood flow results in a rim of viable tissue surrounding large vessels (FIGURE 4). Several case series have shown that local tumor recurrence occurs preferentially in tumors that are in close proximity to large vessels [17]. To counteract the heat sink effect of large

Table 2. Comparison of radiofrequency, microwave and cryoablation technologies.

	Radiofrequency	Microwave	Cryoablation
Heating mechanism	Resistive heating by RF current	Absorption of microwave power due to rapid rotation of polar molecules	Tissue freezing (Joule–Thomson effect)
Size of ablation zone	1.5–7 cm in diameter	1.5–6 cm in diameter	4–5 cm in diameter
Probe diameter	1.2–1.6 mm (17–14 gauge)	1.2–5.7 mm	1.2–8 mm
Ablation time	12–25 min	1–12 min	15–25 min
Frequency range	460–480 kHz	915 MHz, 2.45 GHz	N/A
Power control methods	Temperature, impedance feedback	No feedback currently used (constant power)	Flow rate control
Multiple probe devices	Available from one manufacturer (time interleaving)	Available (amplitude, phase, time interleaving)	Available
Effect of large-vessel heat sinks	Yes	Not affected (preliminary studies)	Somewhat affected
Advantages	Small diameter probes	Short ablation time, no ground pads	Ice ball visible under IOUS, no pain, no ground pads
Availability	Commercially available (WW)	Limited (Asia)	Commercially available (WW)
Companies	Boston Scientific (WW), Rita Medical (WW), Valleylab (WW), Celon (EU)	Azwell (Asia)	Endocare (WW), Galil Medical (WW)

IOUS: Intraoperative ultrasound; N/A: Not applicable; RF: Radiofrequency; WW: Worldwide.

vessels when RFA is used during laparoscopy or open surgery, blood inflow occlusion to the liver may be applied [63]. During minimally invasive application of RFA, pharmacologic agents can be employed to reduce blood flow temporarily, which decrease the heat sink effect [64].

Microwave ablation

MWA is another thermal ablation technology in which tissue is heated using microwaves. This approach exploits the phenomenon of volumetric tissue heating by microwaves, and preliminary investigations show that this phenomenon may be responsible for improved performance near blood vessels compared with RFA (FIGURE 4). Using an antenna, microwaves can be radiated through tissue creating a microwave energy field within a finite volume of that tissue. Within the microwave energy field, water molecules in the tissue rotate with the varying electric fields, causing frictional heating. This heating leads to temperatures capable of causing coagulation necrosis in the tissue. Current technologies for interstitial MWA of the liver utilize powers of 20–100 W, applied for 1–12 min at frequencies of either 915 MHz or 2.45 GHz.

Probes for microwave ablation

As with other thermal ablative procedures, the goal of MWA is to completely destroy tumors, as well as a small rim (~1 cm) of healthy tissue. Since most tumors are (near-)spherical in shape, MWA probes are designed to create large spherical ablation zones [65]. A variety of probes have been proposed for use in

MWA, with the majority being based on a coaxial structure due to the deep-seated location of many tumors (resulting in a need for interstitial applicators) and the angular symmetry of the tumor [66].

Initial antennas based upon a coaxial waveguide structure include designs, such as the monopole, dipole and slot antennas (FIGURE 5A–C), often encased in a polytetrafluoroethylene (PTFE) catheter to minimize adhesion of the probe to desiccated (charred) ablated tissue. An extensive review of these antenna designs, along with others, can be found in [66].

A number of challenges, characteristics and trade-offs have been identified in the design of MWA probes. Challenges include the reduction of backward heating, minimization of probe diameter and impedance matching of the antenna to the surrounding liver. Trade-offs in design involve probe diameter versus maximum application of power and ablation power versus ablation time.

Early coaxial antennas developed for MWA yielded ablation zones resembling a 'tear drop', as opposed to the desired spherical shape [66]. The tear drop is oriented along the axis of the antenna along the feedline, indicating undesirable heating along the feedline. There are three potential causes of detrimental heating along the coaxial feedline. First, any impedance mismatch between the antenna and the surrounding medium will create reflections that set up standing waves within the coaxial feedline. Under such conditions, the local currents on the inside of the outer conductor can become large enough to cause local heating. If the wall of the outer conductor is thin, the heat may transfer to

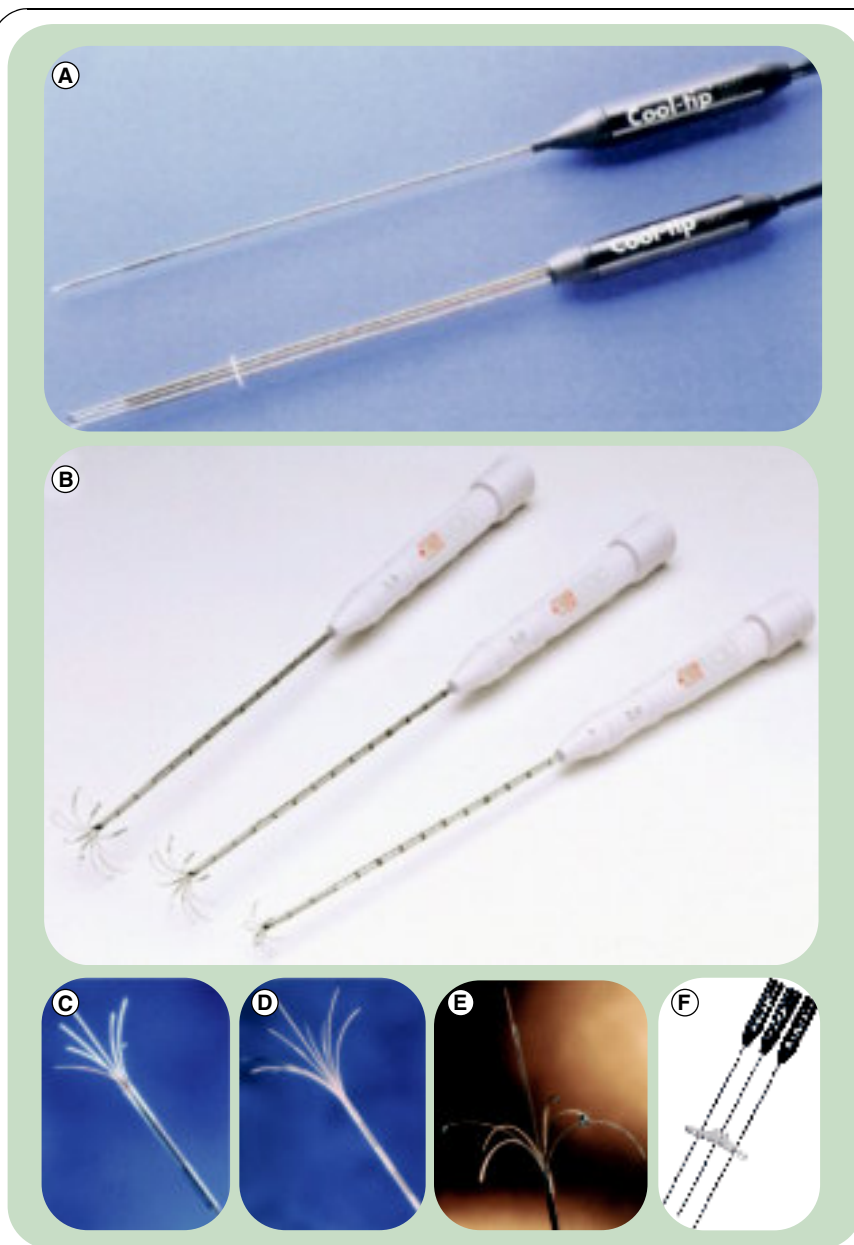


Figure 2. Radiofrequency electrodes from the three most widely used manufacturers. (A) Cool-tip™ single (top) and cluster electrode (bottom) from Valleylab. **(B)** LeVein electrode in 2-, 3- and 3.5-cm size from Boston Scientific (available up to 5 cm). **(C)** Starburst. **(D)** Starburst XL. **(E)** Starburst Xli from Rita Medical. **(F)** ProSurge electrode from Celon Medical. **(A–E)** have been reproduced with permission from [48], **(F)** has been reproduced with permission from Celon Medical.

the surrounding tissue. Second, an impedance mismatch between the antenna and surrounding medium may also result in unbalanced currents on the inner and outer conductors of the coaxial feed. In this case, a remainder current flows along the outside of the outer conductor of the coaxial feedline. The ‘tail’ seen in many of the specific absorption rate (SAR) patterns computed from simulations of MWA antennas is attributed to this current flow. Finally, most antenna designs are based upon copper coaxial cables. Since copper is a good thermal conductor, heat generated near the distal tip may be conducted along the feedline.

Impedance mismatches, while leading to additional heating along the feedline (due to power reflected from the antenna), also affect the efficiency of the antenna. Power reflected from the antenna is lost and reduces the efficiency of the treatment applicator. This mismatch between the antenna and the surrounding medium cannot be mitigated by the use of an external matching network as the amplitude of standing waves in the coaxial feedline would be increased leading to additional detrimental heating of the feedline.

A final challenge is to minimize the probe diameter. This has the effect of minimizing the invasiveness of the treatment applicator, as well as allowing the possibility of percutaneous application. Typically, probes under approximately 2 mm in diameter are considered amenable for percutaneous use. This minimization of the probe diameter leads to a trade-off in the design rules. More power applied to the applicator tends to lead to short treatment times or larger ablation zones. However, for a given size coaxial line there is a maximum power-handling capability beyond which heating of the coaxial line becomes a limiting factor, which, in this case, is expected to lead to detrimental heating along the coaxial feedline, thus damaging the tissue. Therefore, a balance must be found between power handling capability and probe size.

For a given desired ablation zone size more power radiating from the antenna leads to a shorter treatment time. Owing to higher tissue temperatures than during RFA, the microwave applicator requires shorter treatment times, which make MWA less dependent on thermal conduction and perfusion.

More recent MWA probes were designed to minimize probe size, maximize ablation zone size, minimize detrimental heating of the feedline and yield more spherical lesions, by minimizing impedance mismatch [65,67,68]. Geometries of some of these improved antenna designs are shown in FIGURES 5D–G.

Yang and colleagues proposed a 3.5-mm diameter floating sleeve antenna consisting of a coaxial dipole antenna with a conductive third copper cylinder approximately half a wavelength long, separated from the coaxial cable by PTFE insulation [65–68]. The sleeve constrains the fields to the proximal end of the sleeve, probably due to phase cancellation

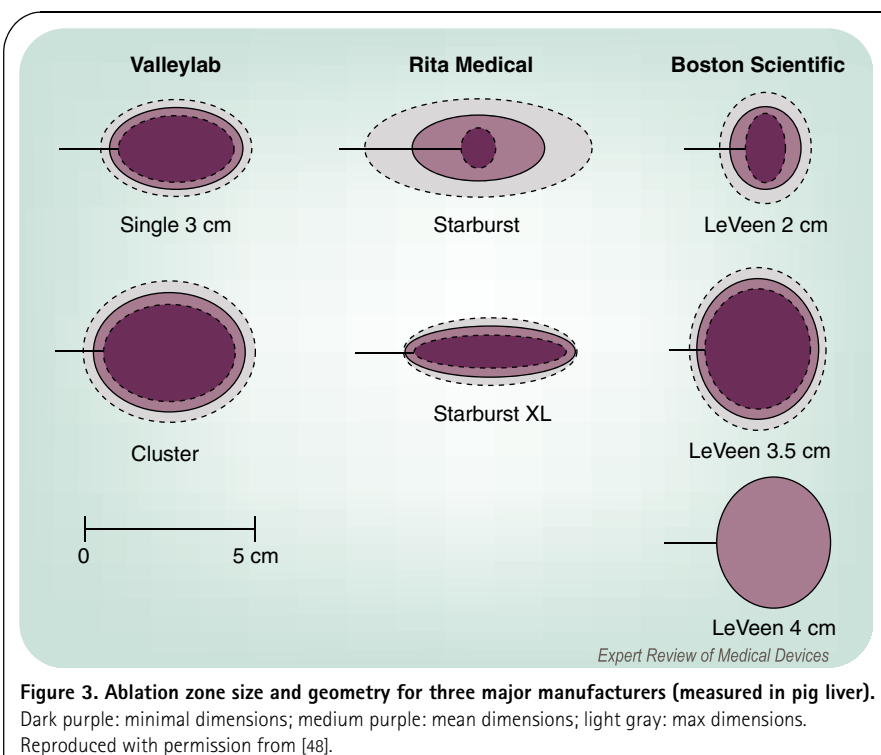


Figure 3. Ablation zone size and geometry for three major manufacturers (measured in pig liver).

Dark purple: minimal dimensions; medium purple: mean dimensions; light gray: max dimensions.

Reproduced with permission from [48].

of the fields above and below the sleeve. Brace and colleagues designed a triaxial antenna consisting of a coaxial monopole antenna inserted through a 17-gauge biopsy needle, positioned a quarter of a wavelength from the antenna tip [67,69,70]. This length may be readily adjusted so as to minimize reflected power during MWA. Another antenna is the minimally invasive choke antenna designed by Longo and colleagues [68]. This consists of a coaxial monopole antenna inserted through a 14-gauge biopsy needle. A conductive copper collar is soldered to the coaxial cable to electrically connect it to the biopsy needle. The distance between the connection point to the distal end of the biopsy needle is set to approximately a quarter of a wavelength (adjustable to minimize reflected power). Strickland and colleagues have developed a dielectric resonator antenna with a 5.7 mm diameter for large volume MWA [71]. While the large diameter allows the use of powers up to 150 W, the antenna is not suitable for percutaneous applications [72].

TABLE 3 summarizes performance characteristics of these antennas. It shows that the maximal ablation zone diameter varies with power levels and treatment durations, which are, to some extent, limited by probe diameter. Results shown are for *in vivo* animal experiments; the choke antenna was excluded since data from animal models have not been presented in the literature [68].

Cryoablation

Cryoablation systems consist of a cryogen, cryoprobe(s) and tools for imaging/monitoring the treatment. The structure of the cryoprobe depends on the type of cryogen used. In addition, most cryoprobes have an embedded thermocouple

that is used to both determine whether or not the probe is functioning and provide feedback for control during the ablation procedure.

Most modern cryoablation systems employ liquid nitrogen (LN_2) or argon as cryogens due to their extremely low boiling temperatures of -196 and -186°C , respectively. Argon-based probes make use of the Joule–Thomson (J–T) principle, which states that the temperature of a gas at a given pressure will decrease or increase (depending on ambient temperature) when allowed to expand freely at constant enthalpy. Cryoprobes take advantage of this effect for achieving low temperatures during freezing and for raising probe temperature to induce thawing. Active thawing may be performed with gases, such as helium, whereas passive thawing is used in LN_2 -based systems by shutting off the supply of the cryogen. Argon-based systems can respond to control adjustments in less than 1 s compared

with LN_2 -based systems, which may take up to 30 s to respond to a change [73]. Thus, argon-based systems are more amenable to repeat freeze–thaw cycles and allow surgeons to complete ablation of a single target in a shorter time. For smaller ablation zones and those that do not require a high degree of accuracy, single probe cryoablation suffices. For more precise coverage of the target region and uniform freezing, multiple cryoprobes are preferred [74].

A typical LN_2 cryoprobe funnels the cryogen down to a thermally uninsulated tip of a metallic probe, which is in direct contact with the target tissue. Vacuum insulation is used along the length of the cryoprobe above the tip to prevent freezing of healthy liver tissue. At the warm tip (due to contact with tissue at body temperature), LN_2 undergoes a phase change and expands. The cold gas cools the probe tip where an ice ball forms. The expanding gas, which exits the cryoprobe around the supply tube, sets up a back pressure (a phenomenon known as ‘vapor locking’), which, together with Liedenfrost boiling, limits the minimum temperature at the probe tip to approximately -160°C . Gas bubbles, formed due to Liedenfrost boiling, act as a thermal insulator and, thus, lesion diameter is wider at the probe tip where there are fewer bubbles [73]. The CMS Accuprobe[®] is an example of a LN_2 -based cryoprobe.

Endocare’s CryoCARE[®] probe is an example of a probe that uses the J–T principle with argon as the cryogen [101]. Argon gas, at a pressure of 3000 psi (21 MPa), is supplied to the probe and flows through the heat exchanger and out via the J–T nozzle. It then expands in the expansion chamber and is cooled to cryogenic temperatures. After expansion, the gas is at a lower pressure and exhausts flowing out over the heat exchanger. The gas flowing out cools the incoming gas thereby making the

probe more efficient. The surgeon can control the ablation zone size by adjusting the flow rate and pressure and lesion shape by adjusting positioning of the outer sheath.

The CryoHit® system developed by Galil Medical supports up to 25 cryoprobes allowing for simultaneous ablation of multiple tumors or large lesions in a single procedure. The system uses MR-compatible 17-gauge cryoprobes based on the J–T principle, employing argon as the cryogen and helium for thawing. A thermocouple is embedded in each probe for temperature monitoring of the ablation process.

Littrup and colleagues have recently developed a system to mitigate vapor locking by raising the pressure of the cryogen above a critical value ensuring that it is supplied at a molar volume that prevents vapor lock [102]. This elevated pressure is maintained over the length of the cryoprobe by introducing an object in thermal contact with the cryogen to raise its temperature. By maintaining the inflowing cryogen at an elevated temperature and pressure, the vapor lock phenomenon is avoided.

Image guidance for ablation procedures

Imaging of radiofrequency & microwave ablation

Ultrasound imaging is the most commonly used modality for interventional device placement and ablation zone monitoring during RFA [75,76]. Advantages of ultrasound imaging for device placement and treatment are real-time visualization, low cost and portability for easy access. Monitoring ablation zone size during RFA has had limited success due to low contrast between normal and ablated tissue, as well as gas bubble formation during ablation. These issues lead to inaccuracy in determining the ablation zone boundary during ultrasound monitoring of ablation zone size. In an attempt to overcome these problems, some investigators have focused on monitoring changes in the ultrasound properties that occur with changes in temperature during ablation [77]. Ultrasound strain imaging, or elastography, is also being explored as a method for monitoring ablation zone size by taking advantage of

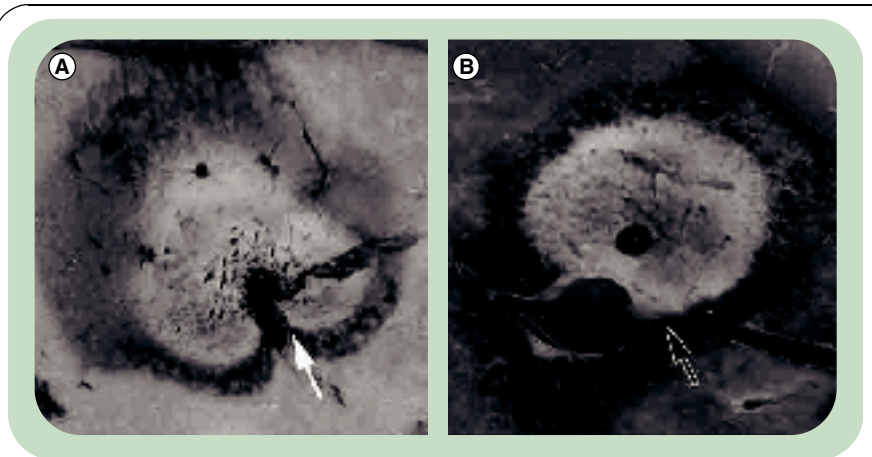


Figure 4. Gross image comparison of heat sink effect of local blood vessels at (A) radiofrequency ablation and (B) microwave ablation. Note deflection of the coagulation zone at radiofrequency ablation (arrow) and the absence of deflection after MW ablation (arrow). Reproduced with permission from [96].

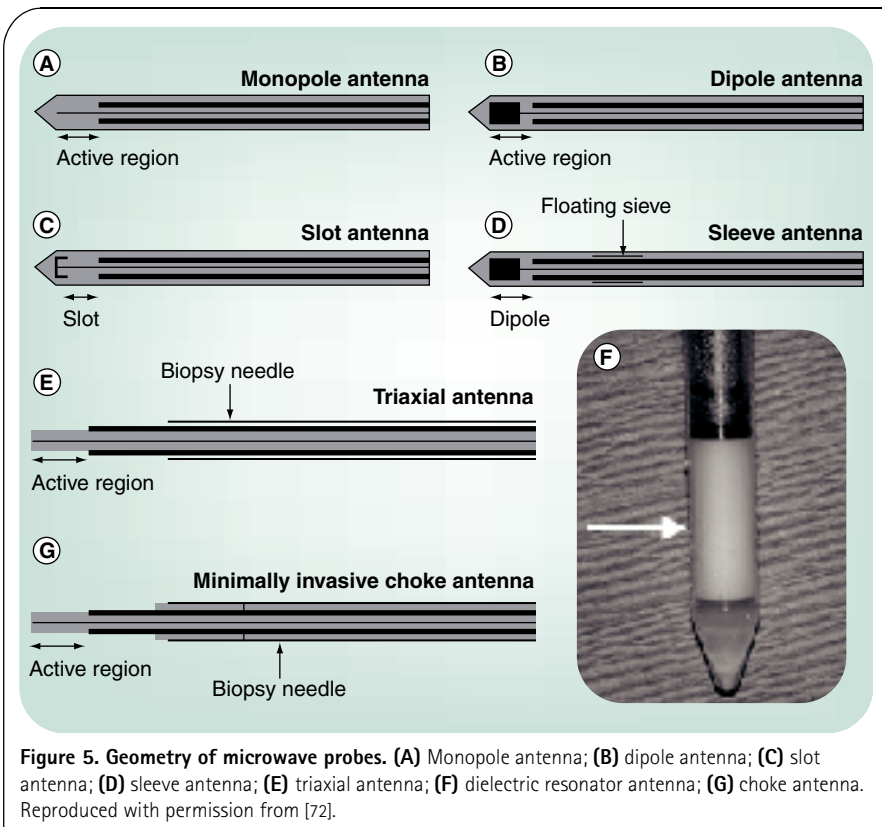
changes in tissue stiffness during the course of ablation [78]. In Europe, microbubble contrast agents are available currently for imaging of RFA that show vascular regions and allow depiction of residual tumor after ablation [79]; these contrast agents are currently under review by the US FDA and may be available in the USA in the near future.

In addition to ultrasound imaging, CT is frequently used to guide placement of the probes to the target location, especially during minimally invasive procedures. CT is also the most commonly used modality to confirm treatment results since it gives a much more reliable depiction of ablated/nonablated interfaces than ultrasound imaging with a better correlation between measured and actual ablation zone size (based on pathology) [80]. Disadvantages of CT include longer times for probe placement and the exposure of the patient and physician to ionizing radiation. However, to deal with these disadvantages, combining ultrasound imaging for probe placement and CT for ablation monitoring may be used.

Recently, there has been considerable research into using MRI to image ablation probe placement and temperature profile imaging [81–83]. Sequeiros and colleagues have reviewed the current status of MRI as a monitoring tool in interventional procedures [82]. Advantages of using MRI for device placement and temperature monitoring include high resolution,

Table 3. Comparison of performance of various microwave ablation probes.

Antenna type	Metric			
	Ablation zone diameter (cm)	Probe diameter (mm)	Treatment duration	Power levels (W)
Sleeve	5.87	3.5	150 s	120
Triaxial	1.7–2.9	1.2	2–12 min	68
Dielectric resonator	2.8–6.0	5.7	4–20 min	50–150
Dipole	2.1	1.8	10 min	40



MRI has been explored as a method for visualizing lesion growth during cryosurgery. Owing to the short T2 of frozen tissues the cryolesion appears as a dark region in conventional MRI scans [90]. As with ultrasound imaging, MRI scans can only be used to visualize the 0°C isotherm and not lower temperatures of -20 to -40°C, which are usually associated with necrosis. MRI can also be used in conjunction with mathematical models to estimate temperature within the ice ball [90]. Such techniques may be useful in defining regions of the ice ball assumed sufficient for ablation. As stated above, major disadvantages of MRI include high cost, an open-magnet configuration and the necessity of MR-compatible probes.

Conclusions

This review discusses the current status of ablative technologies used as alternatives for resection, clinical experience with these technologies, and design rules for the development of new devices and the improvement of existing devices.

multiplane imaging and the possibility of monitoring perfusion effects during the course of ablation. Significant disadvantages are high cost, limited access to the patient due to the magnet structure, slower refresh rate than ultrasound imaging, the need for all surgical tools and implements to be MRI compatible, and patient populations that cannot have MRI due to implants or body habitus. Other possible candidates under investigation to monitor antenna placement and ablation zone size during ablation are optical monitoring [84], remote sensing via microwave imaging [85–88] and electrical impedance tomography [89].

Imaging of cryoablation

Ultrasound imaging is also the most widely used imaging modality for cryoablation of liver tumors. The ultrasound transducer is usually placed on the surface of the liver for real-time visualization of the growing ice ball. The mismatch in acoustic impedance at the frozen–unfrozen tissue interface results in close to 99% reflection of the incident acoustic wave and ensures the ice ball boundary appears distinctly on the ultrasound image. However, owing to reflection of almost all of the acoustic energy at the ice ball boundary, ultrasound imaging cannot be used to image regions of tissue behind the ice ball. Moreover, the position of the tumor relative to the ice ball boundary is not clear [41]. Surgeons typically combine information from thermocouples, either embedded in the cryoprobe or inserted into the target tissue, and position of the ice ball boundary to determine the extent of the cryolesion.

Expert commentary

RFA has become an acceptable alternative treatment modality for unresectable liver tumors, has been shown to improve patient survival in certain populations and is currently the most widely used tumor ablation modality. The rapid growth of RFA procedures in recent years has been due to several advantages compared with alternative treatments for patients not amenable to surgery. While RFA devices have seen considerable improvement within the last decade, there are still several areas where there is need for improvement. One major problem with RFA is that thermal conduction from a thin rim around the probe to the margin of the tumor takes a considerable amount of time (~12–35 min). During this time the large vessels in the liver carry heat away as fast as it is generated. Thus, temperature of cancer cells next to the large vessels may never increase to lethal temperature. In addition, treatment of large tumors is still problematic due to the limited size of the ablation zone of current devices, typically requiring multiple sequential overlapping ablations. There is a need for more sophisticated, computer-supported treatment planning to help the physician and make outcomes less dependent on the experience of the treating physician. One problem common to most ablation therapies is insufficient intraprocedural imaging. This will be partially addressed by upcoming ultrasound contrast agents but further progress in this area will benefit treatment outcome.

MWA has seen a considerable amount of research performed in the last few years with most of the work focused on interstitial probe design for control of shape and maximization of ablation

region size. The explanation for improved performance seen near large blood vessels, as compared with radiofrequency, is commonly ascribed to the volumetric heating effect due to the propagation of microwaves through the tissue and/or the higher temperatures, which can be achieved during MWA. The contributions of each of these effects on perivascular heating could be better understood, as well as a systematic approach to the study of microwave heating near large blood vessels exploring the limitations both in simulation and experiment. More work on the basic physiological response of the liver during MWA at high temperatures (>100°C) and its effect on probe performance is required. This includes an understanding (both qualitative and quantitative) of how the tissue structure changes (in this case) as temperatures increase above 100°C (i.e., loss of tissue water as seen in lower water content of tissue near the probe), how these structural changes will affect the tissue thermal and electromagnetic properties, and what affects the movement of the steam that is generated during MWA at high temperatures. While some of the work of understanding the response of tissue to heating has been done in other areas, this needs to be translated to the problem of interstitial microwave heating of tissue. This will aid in the design of new more effective treatment probes and help reduce undesired damage to healthy tissue.

Advancements in cryosurgical technology and intraoperative monitoring methods have led to the development of applicators for treatment of large liver tumors. Although traditionally performed under laparotomy, percutaneous treatment is now feasible. Reliable indicators for adequate ablation, such as size of the ice ball relative to target zone, are not widely agreed upon. Improved imaging technology may help alleviate this problem. As with other ablative technologies, comparison with surgical resection has not been performed. Although cryoablation has been challenged and, in many cases, replaced by RFA, it remains a viable technique for the treatment of selected patients with liver tumors.

Five-year view

In 5 years we will focus percutaneous liver ablation on patients with HCC either as a stand-alone therapy or as a bridge to transplant. Unless good prospective randomized data is generated, the standard of care for colorectal metastases will be either open or laparoscopic resection. Ablation will be reserved for unresectable patients and patients with bilobar disease.

Even though the use of tumor ablative therapies started more than 10 years ago, clinical trials establishing survival and other benefits in direct comparison to other treatment modalities are still missing, thus, making evidence-based conclusions intractable and making patient selection the object of discussion among experts [91]. This problem is further complicated by a 'moving target' owing to improved ablation devices becoming available at short intervals. We expect MWA will become more popular as the devices mature. There seems to be little need to increase the size of RFA zones. Cryosurgical ablation will continue to be used by some centers but will, we suspect, continue to decline in popularity. Much of this technology has at least implied conflicts of interest and these should continue to be disclosed in any clinical report on ablation. We hope that prospective randomized comparisons of different ablation techniques and ablation comparisons with resection will be reported.

Current shortcomings of ablation procedures are attacked from several different directions. Apart from research in advanced probe designs as described above, benefits of adjuvant therapies in reducing tumor recurrence, such as radiotherapy and the use of chemotherapeutic agents are under evaluation [92,93,201]. Improved imaging modalities may provide better feedback during and after the procedure. Ultrasound contrast agents, MR and ultrasound thermometry, as well as image coregistration, between different modalities, are examples of current research directions in this area [77–79,81,83].

The integration of probe tracking, image registration and thermal modeling may lead to advanced treatment planning systems that facilitate patient-specific tumor ablation [94].

Key issues

- A number of new technologies (cryoablation, radiofrequency ablation [RFA] and microwave ablation [MWA]) have been developed for local control of liver tumors – both hepatocellular carcinoma and metastatic – for patients whose disease is not amenable to surgical resection (the gold standard).
- The literature on patient survival is not mature at this point; thus, the most critical end point, long-term (>5 years) survival, is not known. However, local recurrence and short-term (1-, 3- and 5-year) data do exist and allow for some comparison of the clinically available devices.
- Ideal characteristics for ablative technologies include complete destruction of malignant cells, no significant side effects or complications, flexible application, efficacious adjacent to vascular structures, controllable to prevent damage to adjacent liver or organs, robust, fast, inexpensive and ergonomic.
- Cryoablation, RFA and MWA are discussed with an emphasis on probe design, current state of existing technologies and clinical results and future trends.
- Modalities currently used for probe placement and treatment monitoring are discussed, as well as indications of new technologies that may improve the effectiveness of treatment monitoring.

Information resources

Books & book chapters

- van Sonnenberg E, McMullen W, Solbiati L. *Principles and Practice*. Springer Verlag, Berlin, Germany (2005).
- Haemmerich D. Tissue ablation. In: *Wiley Encyclopedia of Medical Devices and Instrumentation (2nd Edition)*. Webster JG (Ed.). John Wiley & Sons, NY, USA (2006).
- Lencioni R, Cioni D, D'Angelica M, Zogatis TG, Bilchik AJ. Ablation of liver tumors. In: *Surgery of the Liver, Biliary Tract, and Pancreas (4th Edition)*. Blumgart LH (Ed.). Elsevier, Oxford, UK (2006).

Papers

- Poon RT, Fan ST, Tsang FH, Wong J. Locoregional therapies for hepatocellular carcinoma: a critical review from the surgeon's perspective. *Ann. Surg.* 235(4), 466–486 (2002).
- McGahan JP, Dodd GD. Radiofrequency ablation of the liver: current status. *Am. J. Roentgenol.* 176(1), 3–16 (2001).

Websites

- NIH radiofrequency ablation
www.cc.nih.gov/drd/rfa
- MWA
www.rf-ablation.engr.wisc.edu
- Tumor ablation
www.radiology.wisc.edu/research/TumorAblationLab/index.php
- Rita Medical System
www.ritamedical.com
- Boston Scientific
www.bostonscientific.com/med_specialty/deviceCategoryList.jsp?task=tskCategoryList.jsp§ionId=4&relId=4,178,2104
- Valley Lab
www.valleylab.com/product/ablation/index.html

References

Papers of special note have been highlighted as:

- of interest
- of considerable interest

- 1 Curley SA, Izzo F, Delrio P *et al.* Radiofrequency ablation of unresectable primary and metastatic hepatic malignancies: results in 123 patients. *Ann. Surg.* 230(1), 1–8 (1999).
- 2 Jemal A, Murray T, Ward E *et al.* Cancer statistics, 2005. *Cancer J. Clin.* 55(1), 10–30 (2005).
- 3 Kim WR, Gores GJ, Benson JT, Therneau TM, Melton LJ 3rd. Mortality and hospital utilization for hepatocellular carcinoma in the United States. *Gastroenterology* 129, 486–493 (2005).
- 4 Minagawa M, Makuuchi M, Torzilli G *et al.* Extension of the frontiers of surgical indications in the treatment of liver metastases from colorectal cancer: long-term results. *Ann. Surg.* 231(4), 487–499 (2000).
- 5 Nagakura S, Shirai Y, Suda T, Hatakeyama K. Multiple repeat resections of intra- and extrahepatic recurrences in patients undergoing initial hepatectomy for colorectal carcinoma metastases. *World J. Surg.* 26(2), 141–147 (2002).
- 6 Petrowsky H, Gonen M, Jarnagin W *et al.* Second liver resections are safe and effective treatment for recurrent hepatic metastases from colorectal cancer: a bi-institutional analysis. *Ann. Surg.* 235(6), 863–871 (2002).
- 7 Cha C, DeMatteo RP, Blumgart LH. Surgery and ablative therapy for hepatocellular carcinoma. *J. Clin. Gastroenterol.* 35(5 Suppl. 2), S130–S137 (2002).
- 8 Fong Y, Fortner J, Sun RL, Brennan MF, Blumgart LH. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. *Ann. Surg.* 230(3), 309–321 (1999).
- 9 Jamison RL, Donohue JH, Nagorney DM *et al.* Hepatic resection for metastatic colorectal cancer results in cure for some patients. *Arch. Surg.* 132(5), 505–511 (1997).
- 10 Cha C, Lee FT Jr, Rikkers LF *et al.* Rationale for the combination of cryoablation with surgical resection of hepatic tumors. *J. Gastrointest. Surg.* 5(2), 206–213 (2001).
- 11 Goldberg SN, Gazelle GS, Mueller PR. Thermal ablation therapy for focal malignancy: a unified approach to underlying principles, techniques, and diagnostic imaging guidance. *Am. J. Roentgenol.* 174(2), 323–331 (2000).
- 12 Chen MH, Yang W, Yan K *et al.* Large liver tumors: protocol for radiofrequency ablation and its clinical application in 110 patients – mathematic model, overlapping mode, and electrode placement process. *Radiology* 232(1), 260–271 (2004).
- 13 Amin Z, Bown SG, Lees WR. Local treatment of colorectal liver metastases: a comparison of interstitial laser photocoagulation (ILP) and percutaneous alcohol injection (PAI). *Clin. Radiol.* 48(3), 166–171 (1993).
- 14 Solbiati L, Livraghi T, Goldberg SN *et al.* Percutaneous radio-frequency ablation of hepatic metastases from colorectal cancer: long-term results in 117 patients. *Radiology* 221(1), 159–166 (2001).
- 15 Wood TF, Rose DM, Chung M *et al.* Radiofrequency ablation of 231 unresectable hepatic tumors: indications, limitations, and complications. *Ann. Surg. Oncol.* 7(8), 593–600 (2000).
- 16 Siperstein A, Garland A, Engle K *et al.* Local recurrence after laparoscopic radiofrequency thermal ablation of hepatic tumors. *Ann. Surg. Oncol.* 7(2), 106–113 (2000).
- 17 Mulier S, Ni Y, Jamart J *et al.* Local recurrence after hepatic radiofrequency coagulation: multivariate meta-analysis and review of contributing factors. *Ann. Surg.* 242(2), 158–171 (2005).
- **Analysis of factors contributing to local tumor recurrence.**
- 18 Solbiati L. Percutaneous ultrasound-guided radio frequency ablation of HCC and liver metastases: results and long-term 7-year follow-up. *Ultrasound Med. Biol.* 29(5 Suppl.), S48 (2003).
- 19 Machi J, Bueno RS, Wong LL. Long-term follow-up outcome of patients undergoing radiofrequency ablation for unresectable hepatocellular carcinoma. *World J. Surg.* 29(11), 1364–1373 (2005).
- 20 Machi J, Oishi AJ, Sumida K *et al.* Long-term outcome of radiofrequency ablation for unresectable liver metastases from colorectal cancer: evaluation of prognostic factors and effectiveness in first- and second-line management. *Cancer J.* 12(4), 318–326 (2006).
- 21 Berber E, Pelley R, Siperstein AE. Predictors of survival after radiofrequency thermal ablation of colorectal cancer metastases to the liver: a prospective study. *J. Clin. Oncol.* 23(7), 1358–1364 (2005).

- 22 Curley SA, Marra P, Beaty K *et al.* Early and late complications after radiofrequency ablation of malignant liver tumors in 608 patients. *Ann. Surg.* 239(4), 450–458 (2004).
- 23 Shibata T, Imuro Y, Yamamoto Y *et al.* Small hepatocellular carcinoma: comparison of radio-frequency ablation and percutaneous microwave coagulation therapy. *Radiology* 223(2), 331–337 (2002).
- 24 Abe H, Kurumi Y, Naka S *et al.* Open-configuration MR-guided microwave thermocoagulation therapy for metastatic liver tumors from breast cancer. *Breast Cancer* 12(1), 26–31 (2005).
- 25 Weber SM, Lee FT Jr, Chinn DO *et al.* Perivascular and intralesional tissue necrosis after hepatic cryoablation: results in a porcine model. *Surgery* 122(4), 742–747 (1997).
- 26 Ruers TJ, Joosten J, Jager GJ, Wobbes T. Long-term results of treating hepatic colorectal metastases with cryosurgery. *Br. J. Surg.* 88(6), 844–849 (2001).
- 27 Kane R. Five year survival in US-guided hepatic cryosurgery. *Radiology* 205, 201 (1997).
- 28 Seifert JK, Morris DL. Indicators of recurrence following cryotherapy for hepatic metastases from colorectal cancer. *Br. J. Surg.* 86(2), 234–240 (1999).
- 29 Seifert JK, Morris DL. World survey on the complications of hepatic and prostate cryotherapy. *World J. Surg.* 23(2), 109–113 (1999).
- 30 Bageacu S, Kaczmarek D, Lacroix M *et al.* Cryosurgery for resectable and unresectable hepatic metastases from colorectal cancer. *Eur. J. Surg. Oncol.* 33(5), 590–596 (2007).
- 31 Pearson AS, Izzo F, Fleming RY *et al.* Intraoperative radiofrequency ablation or cryoablation for hepatic malignancies. *Am. J. Surg.* 178(6), 592–599 (1999).
- 32 Bilchik AJ, Wood TF, Allegra D *et al.* Cryosurgical ablation and radiofrequency ablation for unresectable hepatic malignant neoplasms: a proposed algorithm. *Arch. Surg.* 135(6), 657–662 (2000).
- 33 Sheen AJ, Poston GJ, Sherlock DJ. Cryotherapeutic ablation of liver tumours. *Br. J. Surg.* 89(11), 1396–1401 (2002).
- 34 Chapman WC, Debelak JP, Blackwell TS *et al.* Hepatic cryoablation-induced acute lung injury: pulmonary hemodynamic and permeability effects in a sheep model. *Arch. Surg.* 135(6), 667–672 (2000).
- 35 Washington K, Debelak JP, Gobbell C *et al.* Hepatic cryoablation-induced acute lung injury: histopathologic findings. *J. Surg. Res.* 95(1), 1–7 (2001).
- 36 Bleicher RJ, Allegra DP, Nora DT *et al.* Radiofrequency ablation in 447 complex unresectable liver tumors: lessons learned. *Ann. Surg. Oncol.* 10(1), 52–58 (2003).
- 37 Siperstein A, Garland A, Engle K *et al.* Laparoscopic radiofrequency ablation of primary and metastatic liver tumors. Technical considerations. *Surg. Endosc.* 14(4), 400–405 (2000).
- 38 Dewhurst MW, Viglianti BL, Lora-Michiels M, Hanson M, Hoopes PJ. Basic principles of thermal dosimetry and thermal thresholds for tissue damage from hyperthermia. *Int. J. Hyperthermia* 19(3), 267–294 (2003).
- 39 Mertyna P, Hines-Peralta A, Liu ZJ *et al.* Radiofrequency ablation: variability in heat sensitivity in tumors and tissues. *J. Vasc. Interv. Radiol.* 18(5), 647–654 (2007).
- 40 Mala T, Edwin B, Tillung T *et al.* Percutaneous cryoablation of colorectal liver metastases: potentiated by two consecutive freeze-thaw cycles. *Cryobiology* 46(1), 99–102 (2003).
- 41 Weber SM, Lee FT Jr, Warner TF, Chosy SG, Mahvi DM. Hepatic cryoablation: US monitoring of extent of necrosis in normal pig liver. *Radiology* 207(1), 73–77 (1998).
- 42 Rupp CC, Hoffmann NE, Schmidlin FR *et al.* Cryosurgical changes in the porcine kidney: histologic analysis with thermal history correlation. *Cryobiology* 45(2), 167–182 (2002).
- 43 Poppendiek HF, Randall R, Breeden JA, Chambers JE, Murphy JR. Thermal conductivity measurements and predictions for biological fluids and tissues. *Cryobiology* 3(4), 318–327 (1967).
- 44 McGahan JP, Dodd GD. Radiofrequency ablation of the liver: current status. *Am. J. Roentgenol.* 176(1), 3–16 (2001).
- 45 Lobik L, Leveillee RJ, Hoey MF. Geometry and temperature distribution during radiofrequency tissue ablation: an experimental *ex vivo* model. *J. Endourol.* 19(2), 242–247 (2005).
- 46 Stippel DL, Brochhagen HG, Arenja M *et al.* Variability of size and shape of necrosis induced by radiofrequency ablation in human livers: a volumetric evaluation. *Ann. Surg. Oncol.* 11(4), 420–425 (2004).
- 47 Denys AL, De Baere T, Kuoch V *et al.* Radio-frequency tissue ablation of the liver: *in vivo* and *ex vivo* experiments with four different systems. *Eur. Radiol.* 13(10), 2346–2352 (2003).
- 48 Mulier S, Ni Y, Miao Y *et al.* Size and geometry of hepatic radiofrequency lesions. *Eur. J. Surg. Oncol.* 29(10), 867–878 (2003).
- 49 Pereira PL, Trubenbach J, Schenk M *et al.* Radiofrequency ablation: *in vivo* comparison of four commercially available devices in pig livers. *Radiology* 232(2), 482–490 (2004).
- 50 Dodd GD 3rd, Frank MS, Aribandi M, Chopra S, Chintapalli KN. Radiofrequency thermal ablation: computer analysis of the size of the thermal injury created by overlapping ablations. *Am. J. Roentgenol.* 177(4), 777–782 (2001).
- 51 Goldberg SN, Gazelle GS. Radiofrequency tissue ablation: physical principles and techniques for increasing coagulation necrosis. *Hepatology* 48(3), 359–367 (2001).
- 52 Haemmerich D, Chachati L, Wright AS *et al.* Hepatic radiofrequency ablation with internally cooled probes: effect of coolant temperature on lesion size. *IEEE Trans. Biomed. Eng.* 50(4), 493–500 (2003).
- 53 Goldberg SN, Ahmed M, Gazelle GS *et al.* Radio-frequency thermal ablation with NaCl solution injection: effect of electrical conductivity on tissue heating and coagulation-phantom and porcine liver study. *Radiology* 219(1), 157–165 (2001).
- 54 Laeseke PF, Sampson LA, Haemmerich D *et al.* Multiple-electrode radiofrequency ablation: simultaneous production of separate zones of coagulation in an *in vivo* porcine liver model. *J. Vasc. Interv. Radiol.* 16(12), 1727–1735 (2005).
- 55 Laeseke PF, Sampson LA, Haemmerich D *et al.* Multiple-electrode radiofrequency ablation creates confluent areas of necrosis: *in vivo* porcine liver results. *Radiology* 241(1), 116–124 (2006).
- 56 Haemmerich D, Lee FT Jr, Schutt DJ *et al.* Large-volume radiofrequency ablation of *ex vivo* bovine liver with multiple cooled cluster electrodes. *Radiology* 234(2), 563–568 (2005).
- 57 Berjano EJ, Burdío F, Navarro AC *et al.* Improved perfusion system for bipolar radiofrequency ablation of liver: preliminary findings from a computer modeling study. *Physiol. Meas.* 27(10), N55–N66 (2006).
- 58 Clasen S, Schmidt D, Boss A *et al.* Multipolar radiofrequency ablation with internally cooled electrodes: experimental study in *ex vivo* bovine liver with mathematic modeling. *Radiology* 238(3), 881–890 (2006).
- 59 Haemmerich D, Staelin ST, Tungjitkusolmun S *et al.* Hepatic bipolar radio-frequency ablation between separated multiprong electrodes. *IEEE Trans. Biomed. Eng.* 48(10), 1145–1152 (2001).

- 60 Haemmerich D, Wright AW, Mahvi DM, Lee FT Jr, Webster JG. Hepatic bipolar radiofrequency ablation creates coagulation zones close to blood vessels: a finite element study. *Med. Biol. Eng. Comput.* 41(3), 317–323 (2003).
- 61 de Baere T, Denys A, Johns WB *et al.* Radiofrequency liver ablation: experimental comparative study of water-cooled versus expandable systems. *Am. J. Roentgenol.* 176(1), 187–192 (2001).
- 62 Lu DS, Raman SS, Vodopich DJ *et al.* Effect of vessel size on creation of hepatic radiofrequency lesions in pigs: assessment of the “heat sink” effect. *Am. J. Roentgenol.* 178(1), 47–51 (2002).
- 63 de Baere T, Bessoud B, Dromain C *et al.* Percutaneous radiofrequency ablation of hepatic tumors during temporary venous occlusion. *Am. J. Roentgenol.* 178(1), 53–59 (2002).
- 64 Goldberg SN, Hahn PF, Halpern EF, Fogle RM, Gazelle GS. Radio-frequency tissue ablation: effect of pharmacologic modulation of blood flow on coagulation diameter. *Radiology* 209(3), 761–767 (1998).
- 65 Yang D, Bertram JM, Converse MC *et al.* A floating sleeve antenna yields localized hepatic microwave ablation. *IEEE Trans. Biomed. Eng.* 53(3), 533–537 (2006).
- 66 Bertram JM, Yang D, Converse MC, Webster JG, Mahvi DM. A review of coaxial-based interstitial antennas for hepatic microwave ablation. *Crit. Rev. Biomed. Eng.* 34(3), 187–213 (2006).
- **Reviews probes designed for hepatic microwave ablation.**
- 67 Brace CL, Laeseke PF, van der Weide DW, Lee FT Jr. Microwave ablation with a triaxial antenna: results in *ex vivo* bovine liver. *IEEE Trans. Microw. Theory* 53(1), 215–220 (2005).
- 68 Longo I, Gentili GB, Cerretelli M, Tosoratti N. A coaxial antenna with miniaturized choke for minimally invasive interstitial heating. *IEEE Trans. Biomed. Eng.* 50(1), 82–88 (2003).
- 69 Brace CL, van der Weide DW, Lee FT, Laeseke PF, Sampson L. Analysis and experimental validation of a triaxial antenna for microwave tumor ablation. *Microwave Symposium Digest. IEEE MTT-S Intl* 3, 1437–1440 (2004).
- 70 Brace CL, Laeseke PF, Sampson LA *et al.* Microwave ablation with a single small-gauge triaxial antenna: *in vivo* porcine liver model. *Radiology* 242(2), 435–440 (2007).
- 71 Strickland AD, Clegg PJ, Cronin NJ *et al.* Experimental study of large-volume microwave ablation in the liver. *Br. J. Surg.* 89(8), 1003–1007 (2002).
- 72 Hines-Peralta AU, Pirani N, Clegg P *et al.* Microwave ablation: results with a 2.45-GHz applicator in *ex vivo* bovine and *in vivo* porcine liver. *Radiology* 239(1), 94–102 (2006).
- 73 Rewcastle JC, Sandison GA, Saliken JC, Donnelly BJ, McKinnon JG. Considerations during clinical operation of two commercially available cryomachines. *J. Surg. Oncol.* 71(2), 106–111 (1999).
- 74 Seifert JK, Junginger T, Morris DL. A collective review of the world literature on hepatic cryotherapy. *J. R. Coll. Surg. Edinb.* 43(3), 141–154 (1998).
- 75 Cui Y, Zhou LY, Dong MK *et al.* Ultrasonography guided percutaneous radiofrequency ablation for hepatic cavernous hemangioma. *World J. Gastroenterol.* 9(9), 2132–2134 (2003).
- 76 Curley SA, Izzo F, Ellis LM, Vauthey NJ, Vallone P. Radiofrequency ablation of hepatocellular cancer in 110 patients with cirrhosis. *Ann. Surg.* 232(3), 381–391 (2000).
- 77 Varghese T, Zagzebski JA, Chen Q *et al.* Ultrasound monitoring of temperature change during radiofrequency ablation: preliminary *in vivo* results. *Ultrasound Med. Biol.* 28(3), 321–329 (2002).
- 78 Bharat S, Techavipoo U, Kiss MZ, Liu W, Varghese T. Monitoring stiffness changes in lesions after radiofrequency ablation at different temperatures and durations of ablation. *Ultrasound Med. Biol.* 31(3), 415–422 (2005).
- 79 Solbiati L, Ierace T, Tonolini M, Cova L. Guidance and monitoring of radiofrequency liver tumor ablation with contrast-enhanced ultrasound. *Eur. J. Radiol.* 51(Suppl.), S19–S23 (2004).
- 80 Cha C, Lee FT, Gurney JM *et al.* CT versus sonography for monitoring radiofrequency ablation in a porcine liver. *Am. J. Roentgenol.* 175, 705–711 (2000).
- 81 Samset E. Temperature mapping of thermal ablation using MRI. *Min. Invasive Ther. Allied Technol.* 15(1), 36–41 (2006).
- 82 Sequeiros RB, Ojala R, Kariniemi J *et al.* MR-guided interventional procedures: a review. *Acta Radiol.* 46, 576–586 (2005).
- 83 Vigen KK, Jarrard J, Rieke V *et al.* *In vivo* porcine liver radiofrequency ablation with simultaneous MR temperature imaging. *J. Magn. Reson. Imaging* 23, 578–584 (2006).
- 84 Hsu CP, Razavi MD, So SK, Parachikov IH, Benaron DA. Liver tumor gross margin identification and ablation monitoring during liver radiofrequency treatment. *J. Vasc. Interv. Radiol.* 16, 1473–1478 (2005).
- 85 Reznik AN, Yurasova NV. Electrodynamics of microwave near-field probing: application to medical diagnostics. *J. App. Physics* 98, 114701–114709 (2005).
- 86 Meaney PM, Paulsen MW, Fanning DL, Fang Q. Image accuracy improvements in microwave tomographic thermometry: phantom experience. *Int. J. Hyperthermia* 19(5), 534–550 (2003).
- 87 Bertero M, Miyakawa M, Boccacci P *et al.* Image restoration in chirp-pulse microwave CT (CP-MCT). *IEEE Trans. Biomed. Eng.* 47(5), 690–699 (2000).
- 88 Jacobsen S, Stauffer PR. Multifrequency radiometric determination of temperature profiles in a lossy homogeneous phantom using a dual-mode antenna with integral water bolus. *IEEE Trans. Microw. Theory* 50(7), 1737–1746 (2002).
- 89 Paulsen KD, Moskowitz MJ, Ryan TP. Temperature-field estimation using electrical-impedance profiling methods 1. Reconstruction algorithm and simulated results. *Int. J. Hyperthermia* 10(2), 209–228 (1994).
- 90 Mala T. Cryoablation of liver tumours – a review of mechanisms, techniques and clinical outcome. *Min. Invasive Ther. Allied Technol.* 15(1), 9–17 (2006).
- **Reviews the role of cryoablation in the treatment of hepatic tumors.**
- 91 Tanabe KK, Curley SA, Dodd GD, Siperstein AE, Goldberg SN. Radiofrequency ablation: the experts weigh in. *Cancer* 100(3), 641–650 (2004).
- 92 Ahmed M, Liu Z, Lukyanov AN *et al.* Combination radiofrequency ablation with intratumoral liposomal doxorubicin: effect on drug accumulation and coagulation in multiple tissues and tumor types in animals. *Radiology* 235(2), 469–477 (2005).
- 93 Dupuy DE, DiPetrillo T, Gandhi S *et al.* Radiofrequency ablation followed by conventional radiotherapy for medically inoperable stage I non-small cell lung cancer. *Chest* 129(3), 738–745 (2006).
- 94 Wood BJ, Locklin JK, Viswanathan A *et al.* Technologies for guidance of radiofrequency ablation in the multimodality interventional suite of the future. *J. Vasc. Interv. Radiol.* 18(1 Pt 1), 9–24 (2007).

- 95 Yang D. Measurements, antenna design and advanced computer modeling for microwave tissue ablation. Ph.D. Thesis. University of Wisconsin, WI, USA. Dept Electrical and Computer Engineering (2006).
- 96 Wright A, Sampson LA, Warner TF, Mahvi DM, Lee FT. Radiofrequency versus microwave ablation in a hepatic porcine model. *Radiology* 236, 132–139 (2005).
- **Presents results from a preliminary study comparing radiofrequency ablation with microwave ablation in a hepatic porcine model.**

Patents

- 101 Milkus PW, Kelly GL, Brady RK. Cryoprobe. US5800487 (1998).
- 102 Littrup P, Babkin AV, Duncan R, Boldarev S. Methods and systems for cryogenic cooling. US2005261753 (2005).

Website

- 201 NIH, NCI. Phase I clinical trial: heat activated liposomal doxorubicin and radiofrequency ablation in treating patients with primary or metastatic liver tumors www.cancer.gov/clinicaltrials/NCI-04-C-0263

Affiliations

- *Ann P O'Rourke, MD MPH*
Resident, Department of Surgery, University of Wisconsin, Madison, WI 53792, USA
Tel.: +1 608 262 2122
Fax: +1 608 263 7652
orourke@surgery.wisc.edu
- *Dieter Haemmerich, PhD*
Assistant Professor,
Department of Pediatrics; Medical University of South Carolina, Charleston, SC 29425, USA;
and
Department of Bioengineering, Clemson University, Clemson, SC, USA
Tel.: +1 843 792 1396
Fax: +1 834 792 5878
haemmer@musc.edu

- *Punit Prakash, MS*
Graduate Student, Department of Biomedical Engineering, University of Wisconsin, Madison, WI 53706, USA
Tel.: +1 608 265 3953
Fax: +1 608 265 9239
pprakash@cae.wisc.edu
- *Mark C Converse, PhD*
Assistant Scientist, Department of Surgery, University of Wisconsin, Madison, WI 53792, USA
Tel.: +1 608 265 6145
Fax: +1 608 263 7652
converse@cae.wisc.edu
- *David M Mahvi, MD*
Professor of Surgery, Department of Surgery, University of Wisconsin, Madison, WI 53792, USA
Tel.: +1 608 263 1383
Fax: +1 608 263 7652
mahvi@surgery.wisc.edu
- *John G Webster, PhD*
Professor Emeritus, Department of Biomedical Engineering, University of Wisconsin, Madison, WI 53706, USA
Tel.: +1 608 263 1574
Fax: +1 608 265 9239
webster@engr.wisc.edu