Microwave ablation and irreversible electroporation

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Approximately 1 million hepatic malignancies (primary and secondary) are diagnosed annually worldwide. The most common tumor remains hepatocellular carcinoma (HCC), which is the third most common cause of cancer death (Rahib et al, 2014) (see Chapter 91). Secondary or metastatic tumors, which have metastasized from a primary tumors, include colorectal liver metastasis (CRLM; see Chapter 92), neuroendocrine tumor (Met NET; Chapter 93), and other metastases (Chapter 94) and are rapidly increasing in incidence. Current local treatment strategies for early-stage primary tumors or liver-only/dominant hepatic disease include resection, liver transplantation (primarily for early-stage HCC and unique patients with intrahepatic cholangiocarcinoma [ICC; see Chapter 50]) or MetNET, and ablation, both thermal- and nonthermal-based methods. Resection remains the gold standard of therapy; however, it remains available only in a small percentage of patients because of the extent of liver involvement, presence of extrahepatic disease, health of the underlying non–tumor-bearing liver, medical comorbidities, or a combination of factors (Groeschl et al, 2013). Liver ablative techniques have expanded the patient population who can be effectively treated because of its ability to overcome some of the contraindications to resection. Advancements in technology and a better understanding of patient selection, success, and recurrence have transformed ablation into an effective locoregional adjunctive therapy to resection, with an improved perioperative profile in relation to morbidity and mortality (North et al, 2014; Philips et al, 2013).

The most common thermoablative technologies used clinically are radiofrequency ablation (RFA; see Chapter 98B) and microwave ablation (MWA). Both modalities produce local tissue destruction that does not require organ resection, but the physical properties of the energy sources are different. These local tissue destruction properties (frequency, time, power/wattage) lead to significant potential advantages of MWA versus RFA. Benefits of MWA include larger ablation zone, no “heat-sink” phenomenon, a higher intratumoral temperature, faster ablation times, and multiple tumor treatments at once (Martin et al, 2010).

MICROWAVE ABLATION

Physics of Microwave Energy

Microwave ablation achieves heat destruction of tissue through both active and passive heating. The active heating process of microwave energy requires the presence of dipolar molecules, such as water, to function. MWA reaches a much higher operating frequency (2450 Mhz) than RFA, which makes it potentially more efficient (rapid temperature) for thermal ablation of solid organs. As a dipole molecule, water is affected by the applied electromagnetic field broadcasted by the microwave antenna during the procedure; this is called dielectric permittivity. This property allows for dielectric hysteresis, which induces rotation of the dipole molecules and accounts for the efficient amount of heat generated during MWA. One or more molecules are dipoles with unequal electric charge distribution, and they attempt to reorient continuously at the same rate in the microwave’s oscillating electric field. As a result of the microwave transmission, the water molecules flip back and forth at 1 billion times a second, leading to this vigorous movement to produce friction and heat, which leads to cellular death through coagulation necrosis. An additional mechanism responsible for heat generation in MWA is ionic polarization, which occurs when ions move in response to the applied electric field of the microwave. The displaced ions cause collisions with other ions, converting this kinetic energy into heat. However, this is the lesser of the two mechanisms that generate the efficient heat from MWA. Microwaves emit nonionizing radiation for heating, and this produces homogeneous heating within the field regardless of the tissue types; this distinguishes MWA from monopolar RFA in terms of mechanism of heating and makes it a clinically superior method for ablation (Martin et al, 2010). The passive phase of microwave heating is by conduction of heat beyond the active heating zone and is susceptible to local tissue factors such as heat sinking and current sinking.

The current frequencies of the commercially available microwave ablation devices are at 915 megahertz (MHz) or 2450 MHz (Fig. 98C.1). The reported potential benefit of the 915 MHz microwave is that it could penetrate deeper than the 2450 MHz microwave, which may theoretically yield larger ablation zones. However, the energy deposition is influenced by the dielectric properties of the antenna design (Martin et al, 2010). Microwave energy can be generated through a magnetron or solid-state amplifier (Brace et al, 2009), and the antenna broadcasts the electromagnetic energy to the target tissue. The coaxial cable consists of an inner and outer conductor, and the dielectric material is placed between the two layers. At its tip, the outer conductor is stopped to expose the inner conductor for broadcasting the microwave energy. This inner conductor is covered in a ceramic pointed tip for insertion into the tissue, and microwave energy can pass freely through the ceramic. Large ablative volumes through the 2450 MHz system can be created by increasing the power (wattage) and duration of the microwave energy. The ablative size can be manipulated to tailor the procedure to a specific patient. Physical factors that influence the ablative size include the water content of tissue
**Local Tissue Factors That Affect Thermoablation**

Local tissue factors play an important role in the final ablation volume and shape. Tissue factors such as electric conductivity and dielectric permittivity influence the deposition of energy for radiofrequency and microwave, respectively, which explains why MWA is more effective than RFA in depositing energy across vessels and liver parenchyma (see Chapter 98A, Table 98A.1).

Local tissue factors such as blood flow and tissue temperature affect energy deposition. Heat sinking is an adverse event that occurs when the electric current is too close to blood vessels. It relates to the cooling effect of blood flow in major vessels close to the tumor, which can result in incomplete tumor ablation. This proximity to blood vessels also causes a diversion of the current and decreases the amount of energy generated from the current; this is called current sinking. RFA causes both heat sinking and current sinking, which is why microwave technology is better for the patient in most of these cases. Microwave technology also encounters such limitations, but to a much lesser extent (Martin et al, 2010), because the propagation of microwave energy relies on the dielectric permittivity of the tissue, which stays fairly constant along the broadcasted electromagnetic field. This can overcome the effect of current and heat sinking within its field, resulting in deeper heat penetration and more uniform ablative size. However, awareness of these factors when performing MWA is essential, because the uniformity of an ablation cannot be assumed and must be followed throughout the ablation process.

Tissue desiccation and scarring are other adverse events that can occur from the heated applicator during the radiofrequency treatment process. This significantly decreases final ablation volume in RFA because these factors block a complete electric circuit from forming, which leads to a decrease in heat production. On the other hand, if the target temperature of 100° C is reached too quickly, the intracellular content vaporizes and carbonizes. The gas formation acts as an insulator that increases the impedance and hinders the heat diffusion. Both the gas formation and the incomplete electric circuit result in a less uniform ablative zone. Microwave does not have such adverse effects because microwave energy is broadcast throughout the electromagnetic field and can achieve high power density uniformly, which results in the deeper heat penetration and a more consistent ablative size (Box 98C.1).

The currently available MWA systems in clinical use are highly variable. Some require a single probe, whereas others are multiprobe (Table 98C.1). Some are gas cooled, and others are saline cooled. Currently, there is minimal direct comparison...
## TABLE 98C.1 Currently Available Microwave Ablation (MWA) Systems

<table>
<thead>
<tr>
<th>System</th>
<th>Device Manufacturer</th>
<th>Generator and Antenna</th>
<th>Maximum Generator Power (W)</th>
<th>Maximum Antenna Power (W)</th>
<th>Maximum Selectable Ablation Time (min)</th>
<th>Proposed Maximum Ablation Time (min)</th>
<th>Frequency (Hz)</th>
<th>Water Cooled?</th>
<th>No. of Antennas</th>
</tr>
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<tbody>
<tr>
<td>A</td>
<td>Microsulis Medical Limited</td>
<td>Acculis Sulis VpMTA and Accu2i</td>
<td>180</td>
<td>Not specified</td>
<td>6</td>
<td>6</td>
<td>$2.45 \times 10^3$</td>
<td>Yes</td>
<td>1</td>
</tr>
<tr>
<td>B</td>
<td>HS Hospital Service</td>
<td>HS Amica-Gen and APK14150T19V4</td>
<td>140</td>
<td>100</td>
<td>25</td>
<td>10</td>
<td>$2.45 \times 10^3$</td>
<td>Yes</td>
<td>1</td>
</tr>
<tr>
<td>C</td>
<td>Covidien</td>
<td>Evident MWA Generator and VT1720</td>
<td>60 per device</td>
<td>45 per antenna</td>
<td>10</td>
<td>10</td>
<td>$915 \times 10^6$</td>
<td>Yes</td>
<td>1-3</td>
</tr>
<tr>
<td>D</td>
<td>Medwaves</td>
<td>AVECure Microwave Generator and 14-15-LH-35</td>
<td>40</td>
<td>32 (modulated)</td>
<td>15</td>
<td>15</td>
<td>$(902-928) \times 10^6$ (modulated)</td>
<td>No</td>
<td>1</td>
</tr>
<tr>
<td>E</td>
<td>BSD Medical</td>
<td>MicroThermX and SynchroWave Antenna</td>
<td>180</td>
<td>60 per antenna</td>
<td>—</td>
<td>—</td>
<td>$915 \times 10^6$</td>
<td>Yes</td>
<td>1-3</td>
</tr>
<tr>
<td>F</td>
<td>Neuwave</td>
<td>—</td>
<td>140</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>$2.45 \times 10^3$</td>
<td>No</td>
<td>1-3</td>
</tr>
<tr>
<td>G</td>
<td>Forsea</td>
<td>—</td>
<td>150</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>$2.45 \times 10^3$</td>
<td>Yes</td>
<td>1-2</td>
</tr>
<tr>
<td>H</td>
<td>Kang-you Medical</td>
<td>—</td>
<td>100</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>$915 \times 10^6$</td>
<td>Yes</td>
<td>—</td>
</tr>
<tr>
<td>I</td>
<td>Microtaze</td>
<td>—</td>
<td>70</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>$2.45 \times 10^3$</td>
<td>Yes</td>
<td>—</td>
</tr>
<tr>
<td>J</td>
<td>Covidien</td>
<td>Emprint Ablation System</td>
<td>100</td>
<td>—</td>
<td>10</td>
<td>—</td>
<td>$2.45 \times 10^3$</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>
of these systems based on the variability of tumor histology, size of tumors, and access of procedures. These ablation systems all have claims of being better, more efficient, or more uniform. In fact, one of the current limitations in all MWA systems is the lack of universally accepted quality standards, and nonclinically supported claims (i.e., by marketing divisions) lead to more confusion and less consistency in clinical use.

**Technical Considerations**

Three approaches can be used for MWA: open, laparoscopic, and percutaneous. The underlying principles of any microwave ablatively therapy stay the same, but the ability to accommodate and individualize each procedure in accordance to a patient’s unique needs is essential to MWA success. The approach chosen should reflect tumor biology and histology, size of the tumor, and segments involved; the skill level of the practitioner is also important, to tailor the choice to the patient’s needs. The goal of any MWA system should be complete ablation in greater than 95% of all tumors. The concepts of “cytoreduction,” “partial ablation,” and “debulking” are unproven in their benefit with respect to the tumors treated by ablative techniques and thus are not accepted treatment goals on oncology. Furthermore, therapeutic decision making in these patients is often complex and should be made in the context of multidisciplinary clinics or conferences. The technique used must always be in the patient’s best interest regardless of the MWA access.

Surgical resection remains the optimal management in a majority of patients based on histology. A surgical MWA approach is primarily used when tumor morphology requires multiple ablation therapies, tumors are located near the dome of the liver (for which percutaneous ablation might cause pneumothorax or damage to the diaphragm), or the tumor is located near the visceral organs, such as the gallbladder, colon, or stomach (Itoh et al., 2011). If MWA alone is the sole therapy in a patient’s care, a laparoscopic approach should be performed in most cases. The use of MWA has significant advantages in regard to quality of life and minimizing the time off chemotherapy in certain liver histologies, while reducing complications and length of stay (Martin et al., 2007; Mbah et al., 2012). Lesions located anteriorly and not adjacent to a major pedicle can be ablated percutaneously using ultrasound (US) guidance and computed tomography (CT) confirmation. If the lesion is located deep in the liver at the dome, next to a major pedicle, or adjacent to other structures (e.g., diaphragm, colon), ablation of these lesions should be performed surgically with either a laparoscopic or an open approach, based on the patient’s past surgical history and body habitus and level of the surgeon’s laparoscopic ultrasound skill. If an open approach is used, it is best done through a subcostal or midline laparotomy.

Regardless of the approach, the patient is usually positioned supine or in a lateral position on the table. The key to a successful ablation session is adequate exposure of the liver to allow methodic evaluation of the liver by intraoperative US. All eight segments of the liver must be evaluated to ensure no lesions are overlooked. After all lesions have been identified, the plane of the needle track should be evaluated to ensure that it does not cross a portal or major hepatic vein pedicle. The type of antenna(s) that needs to be deployed should be decided before the operation. All the 915 MHz systems require at least two or three probes placed in parallel to obtain ablation similar to that achieved with a single antenna of the 2450 MHz systems when treating a lesion greater than 2.5 to 3.9 cm in size. It is important to ensure that there are no vital structures within 1.0 to 1.5 cm of the microwave field (Fig. 98C.2). MWA times can vary from 5 to 45 minutes. The deepest lesion is usually treated first; in a staged procedure, the most difficult lesion is treated first.

The need to perform overlapping ablations should be decided before the first ablation. However, artifact and distortion occur during the first ablation, which can distort the US image and lead to inaccurate placement of second and third needles to complete overlapping ablation. The three-dimensional (3D) ablation zone is conceptually difficult to grasp for practitioners because intraoperative US provides only a two-dimensional view.

Defining the success of the MWA is paramount. Well-established quality parameters were recently published and agreed on in a multiinstitutional review (North et al., 2014), as follows:

- **Ablation success:** Complete eradication of the tumor by using high-quality cross-sectional contrast-enhanced imaging (CT or MRI) within 4 weeks of ablation, specifically, disappearance of any intratumoral contrast enhancement as described in modified Response Evaluation Criteria in Solid Tumors (RECIST) criteria (see Chapters 18 and 19).
- **Local recurrence after ablation:** After confirmation of ablation success (>4 weeks), local recurrence is defined as evidence for viable tumor at or within 1 cm of a prior ablation site for which ablation success was documented (confirmed by multislice, multiphase dynamic imaging).
- **Nonlocal hepatic recurrence:** Evidence for viable intrahepatic tumor more than 1 cm from any prior ablation site at any time interval after ablation.

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**FIGURE 98C.2.** Proposed algorithm for use of the different techniques of image-guided ablation in the treatment of malignant liver tumors. The algorithm assumes a successful completion of the described clinical validation process and takes into account tumor size and location as the main drivers for the choice of the ablation technique. Radiofrequency ablation (RFA) is supposed to remain an accepted option for small (≤3 cm) tumors in nonperivascular location. Microwave ablation (MWA) is expected to become the preferred modality for ablation of tumors of intermediate size (3-5 cm) or in perivascular location. Tumors in proximity to vital structures (including vessels) are directed toward nonthermal techniques such as irreversible electroporation (IRE) or percutaneous ethanol injection (PEI). The use of PEI is only recommended for small, hepatocellular carcinoma tumors.
Indications for ablations and morbidity: The number of patients and the number of tumors with the segments involved should be reported with at least 90 day morbidity follow-up on all ablation cases regardless of access. Morbidity should be reported per established surgical morbidity definitions (Clavien et al, 2009).

Rate of complete ablation of liver tumors, ablation recurrence (defined as recurrent disease within 1 cm of ablation site), hepatic recurrence at nonablated sites, and associated morbidity and mortality should be reported in all clinical MWA studies regardless of access (Martin et al, 2010). It is also important to be able to define success shortly after the procedure so that any potential corrections can be made. Success can be defined on immediate or 24 hour CT scan that demonstrates a zone of ablation encompassing both the tumor and a rim of normal liver tissue approximately 1 cm beyond a tumor in each dimension (Groeschl et al, 2014).

Clinical Results

Hepatocellular Carcinoma (see Chapter 91)
The first open microwave application for tumor destruction was reported in the early 1990s in Japan. Seki and colleagues (1994) reported a series of 24 patients with HCC with a 92% survival at 3 years. The application of microwave technology has since expanded to treat colorectal liver metastases and metastases from other primary tumors, as discussed later.

Clinical trials, recent single institutional, and multiinstitutional studies have evaluated the efficacy of MWA for treating HCC, metastatic colorectal, metastatic NET, and other primary and secondary malignancies of the liver (Table 98C.2). In a trial that evaluated the safety of MWA, 100 patients underwent ablation treatment. The average tumor size was 3.0 cm (±0.6 cm), with a 98% success rate and 2% local recurrence after 36 months (Martin et al, 2010). In another study, 875 tumors were ablated with 98% success rate. The local recurrence rate was 6%, with tumors ranging from 0.5 to 11.0 cm (Poggi et al, 2013).

Colorectal Liver Metastases (see Chapter 92)
Microwave ablation has had promising results in treating colorectal cancer (CRC). In one study, 38 CRC tumors with a median size of 2.5 cm (range, 1.5-4.0 cm) were ablated with 100% success (Martin et al, 2007). The local recurrence after a median of 19 months was 2.63%. The availability of MWA for patients with metastatic CRC and improvements in chemotherapy may improve overall survival. A recent prospective cohort study evaluated the outcomes of MWA of a variety of liver neoplasms, most of which were CRLM (Martin et al, 2010). The ablation-site recurrence in this subgroup was 6%. Furthermore, a matched comparison was made of 40 patients undergoing MWA and 40 receiving RFA. Matching criteria were gender, age, histology, number and size of tumors, operative exposure, and simultaneous liver or extrahepatic resection. MWA was superior to RFA in each outcome measure. In this matched analysis, local recurrence was 2% for MWA versus 17% for RFA. A multiinstitutional Phase II study enrolled 87 patients with unresectable liver tumors (38% CRLM) to undergo MWA. At a mean follow-up of 19 months, these patients exhibited a local recurrence rate of 3%, and 47% were alive with no evidence of disease (Iannitti et al, 2007).

Neuroendocrine Tumors and Metastasis From Other Primary Tumors (See Chapters 93 and 94)
Lesions from neuroendocrine or other primary tumors should be evaluated for resection when deemed appropriate by a physician. It is estimated that a large majority of these patients will not be candidates for resection (Frilling et al, 2014), and MWA has contributed to treating this specific type of cancer. Optimal resection and control of the liver tumor burden have been shown to improve the 5-year survival from 40% to 60%, with the vast majority of patients remaining symptom free for 2 years (Cho et al, 2008; Frilling et al, 2014; Musunuru et al, 2006). Groeschl and colleagues (2014) treated 61 neuroendocrine liver metastases with an overall median survival of 91.9 months. Other studies have showed that an average of 35% of patients survive up to 10 years after treatment (Lewis & Hubbard, 2011).

Specific Microwave Complications and Future Applications
Microwave ablation heats the entire electromagnetic field, and several potential complications may arise from this modality. Technical advances have made ablation near large vessels possible, which increases the potential for thrombus in the hepatic vein.

Skin burn at the needle track during laparoscopic or percutaneous application is a MWA-specific injury reported in the literature (Poggi et al, 2013). All structures within the microwave field are heated, so it is essential to be aware of critical structures within the field, such as the diaphragm and heart. Further research is ongoing for development of a microwave shield to decrease risks to vital organs. Other complications include hepatic abscess, which required drainage; chest infections (Lloyd et al, 2011); and liver failure (Ding et al) allows ablation of larger lesions in the liver. Many studies report that IRE can be evaluated for resection when deemed appropriate by a physician. It is estimated that a large majority of these patients will not be candidates for resection (Frilling et al, 2014), and MWA has contributed to treating this specific type of cancer. Optimal resection and control of the liver tumor burden have been shown to improve the 5-year survival from 40% to 60%, with the vast majority of patients remaining symptom free for 2 years (Cho et al, 2008; Frilling et al, 2014; Musunuru et al, 2006). Groeschl and colleagues (2014) treated 61 neuroendocrine liver metastases with an overall median survival of 91.9 months. Other studies have showed that an average of 35% of patients survive up to 10 years after treatment (Lewis & Hubbard, 2011).

IRREVERSIBLE ELECTROPORATION
Irreversible electroporation (IRE) is a novel, non–thermal injury, ablative technology that uses multiple short pulses (pulse length, 70-90 μsec) at high voltage (2250-3000 volts) of electrical energy to induce permanent electroporation of the tissue (Charpentier et al, 2011). The U.S. Food and Drug Administration (FDA) has approved IRE for soft tissue ablation (first 510(k) indications in 2006) (Rubinsky et al, 2007). This ablation technique takes advantage of the electrical potential gradient that exists across cell membranes. IRE was reported as early as the 1750s but has been used for medical purposes only in the last 30 years (Lee et al, 2010), first developed in conjunction with chemotherapy.

The advantage of IRE over conventional thermal ablation techniques is its non–thermal injury delivery mechanism. When properly applied, theoretically, IRE only affects the target tissue; proteins, extracellular matrix, and critical structures are unaffected (Davalos et al, 2005). This expands the scope of treatment of lesions near major vascular and biliary structures compared to conventional thermal injury ablative techniques. The major disadvantage is the need for general anesthesia (deep paralysis) for its energy delivery (Cannon et al, 2013). IRE can
<table>
<thead>
<tr>
<th>Study</th>
<th>No. Patients</th>
<th>Histology</th>
<th>Was Ablation Success Reported and Defined?</th>
<th>Overall Survival (Y/N) Median</th>
<th>Local Recurrence (Within 1 cm of Ablation)</th>
<th>Liver Recurrence</th>
<th>Mortality</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Livraghi et al, 2012</td>
<td>736</td>
<td>522 HCC</td>
<td>Defined only</td>
<td>None reported</td>
<td>None reported</td>
<td>None reported</td>
<td>0%</td>
<td>Major: 2.7%, Minor 7.3%</td>
</tr>
<tr>
<td>Bhardwaj et al, 2010</td>
<td>31</td>
<td>Mixed histologies</td>
<td>No</td>
<td>29 mo, 3 yr: 40%</td>
<td>3.2% (1/31)</td>
<td>22.6% (7/31)</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Itoh et al, 2011</td>
<td>60</td>
<td>HCC</td>
<td>Yes, 95% (57/60)</td>
<td>1 yr: 93.9%</td>
<td>11.6% (7/60)</td>
<td>53.4% (32/60)</td>
<td>0%</td>
<td>18.30%</td>
</tr>
<tr>
<td>Lee et al, 2012</td>
<td>26</td>
<td>HCC</td>
<td>Yes, 96% (25/26)</td>
<td>25 mo</td>
<td>19% (5/26)</td>
<td>23% (6/26)</td>
<td>0%</td>
<td>19%</td>
</tr>
<tr>
<td>Poggi et al, 2013</td>
<td>144</td>
<td>HCC</td>
<td>94.3% (183/194)</td>
<td>Not available</td>
<td>6.9% (10/144)</td>
<td>27.7% (40/144)</td>
<td>0%</td>
<td>Major: 0% Minor: 5.1%</td>
</tr>
<tr>
<td>Lloyd et al, 2011</td>
<td>140</td>
<td>38 HCC</td>
<td>97% (66/68)</td>
<td>30 day: 61.4%</td>
<td>Indeterminate</td>
<td>35.3% (24/68)</td>
<td>0%</td>
<td>Major morbidity: 8.3%</td>
</tr>
<tr>
<td>Liang et al, 2009</td>
<td>1136</td>
<td>Mixed Histologies</td>
<td>Defined only</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>0.20%</td>
<td>Major: 2.6% Minor: almost all</td>
</tr>
<tr>
<td>Swan et al, 2013</td>
<td>54</td>
<td>HCC</td>
<td>Yes, 94.1%</td>
<td>1- and 2-year survival: 72.8% and 58.8%, respectively</td>
<td>2.9% (2/68 tumor sites)</td>
<td>27.50%</td>
<td>90 day: 5.6%</td>
<td>30-day morbidity: 28.9% Delayed complications: 7.8%</td>
</tr>
<tr>
<td>Liu FY et al, 2010</td>
<td>40</td>
<td>HCC 915 MHz vs. 2450 MHz</td>
<td>Yes, 80% (32/40)</td>
<td>—</td>
<td>20% (8/40): no distinction between local and liver recurrence</td>
<td>—</td>
<td>0%</td>
<td>46.15%</td>
</tr>
<tr>
<td>Takami et al, 2013</td>
<td>719</td>
<td>HCC</td>
<td>Yes, 100%</td>
<td>Overall survival: 97.7%, 79.8%, 62.1%, 45.3%, and 34.1% at 1, 3, 5, 7, and 10 years, respectively</td>
<td>Yes; local recurrence rates at 1, 3, and 5 years: 1.9%, 4.8%, and 5.9%, respectively</td>
<td>—</td>
<td>Overall survival: 7.00%</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>No. Patients</td>
<td>Histology</td>
<td>Was Ablation Success Reported and Defined?</td>
<td>Overall Survival (Y/N) Median</td>
<td>Local Recurrence (Within 1 cm of Ablation)</td>
<td>Liver Recurrence</td>
<td>Mortality</td>
<td>Complications</td>
</tr>
<tr>
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</tr>
<tr>
<td>Liu Y et al, 2013</td>
<td>80</td>
<td>HCC</td>
<td>Yes, 87.5% (70/80)</td>
<td>Yes; 56 months (median)</td>
<td>Yes, 22.2% (16/72)</td>
<td>43.75% (35/80)</td>
<td>0%</td>
<td>Major: 7.5%</td>
</tr>
<tr>
<td>Jiao et al, 2012</td>
<td>60</td>
<td>HCC</td>
<td>Yes, 92.7% (89/96 tumors)</td>
<td>—</td>
<td>5.21%</td>
<td></td>
<td>NR</td>
<td>0%</td>
</tr>
<tr>
<td>Jagad et al, 2008</td>
<td>57</td>
<td>11 HCC 46 liver Met</td>
<td>Yes, 100%</td>
<td>22.6 months (mean)</td>
<td>Yes, 17.7% (29/164 lesions)</td>
<td>26.3% (15/57)</td>
<td>NR</td>
<td>Major: 0%</td>
</tr>
<tr>
<td>Groeschl et al, 2013</td>
<td>72</td>
<td>10 HCC 39 CRLM 20 Met carcinoid 14 other</td>
<td>Yes, 95% (149/157)</td>
<td>36.1 months (median)</td>
<td>Yes, 12% (10/83)</td>
<td>20% (17/83) plus 7% (6/83) intra- and extrahepatic recurrence</td>
<td>1%</td>
<td>16%</td>
</tr>
<tr>
<td>Groeschl et al, 2014</td>
<td>450</td>
<td>139 HCC 198 CRLM 61 NET liver Met 75 other</td>
<td>Yes, 97% (839/865) tumors</td>
<td>18 months</td>
<td>6%</td>
<td></td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Ding et al, 2013</td>
<td>198</td>
<td>HCC</td>
<td>Yes, 99.1% (1080/1090 ablations)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Martin et al, 2007</td>
<td>20</td>
<td>5 HCC 9 CRLM 2 Met carcinoid 1 other</td>
<td>Yes, 100%</td>
<td>NR</td>
<td>1/40 (2.5%)</td>
<td>8/20 (40%)</td>
<td>0%</td>
<td>25%</td>
</tr>
<tr>
<td>Martin et al, 2010</td>
<td>100</td>
<td>270 ablations 17% HCC 50% CRLM 11% Met carcinoid 22% other</td>
<td>Yes, 98%</td>
<td>Met CRC: 36 HCC: 41 Met carcinoid: 18 Other Met disease: 12</td>
<td>5/100 (5%)</td>
<td>37/100 (37%)</td>
<td>90 day: 0%</td>
<td>Morbidity: 29%</td>
</tr>
<tr>
<td>Zhou et al, 2009</td>
<td>53</td>
<td>Mixed histologies</td>
<td>Yes, 91%</td>
<td>NR</td>
<td>NR</td>
<td>8.94% (local tumor progression)</td>
<td>NR</td>
<td>0%</td>
</tr>
<tr>
<td>Ierardi et al, 2014</td>
<td>25</td>
<td>21 CRC 10 non-CRC</td>
<td>Yes, not defined</td>
<td>20.5 months</td>
<td>12.9%</td>
<td></td>
<td>0% at 30 days</td>
<td>44.8%</td>
</tr>
</tbody>
</table>

CRC, Colorectal cancer; CRLM, colorectal liver metastasis; HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma; Met, metastasis; NET, neuroendocrine tumor; NR, not reported.
be performed with an open, laparoscopic, or percutaneous approach. Repeated reports have demonstrated the advantages of IRE over other thermal ablation techniques, including no heat-sink effect, tumor-specific immunologic reactions, minimal impact on the collagen network within treated tissues, and the potential to ablate tumor tissues near large vessels (Guo et al, 2011).

Physics of Irreversible Electroporation

Electroporation is a dynamic phenomenon by which cell membrane integrity is compromised by inducing permanent nanopores using transmembrane electrical distortion (Martin et al, 2014). Reversible electroporation has been used as a technique for electrotransfection of genetic material or intracellular drug delivery. When the energy of the pulses is increased above a certain electric field threshold, the permeabilization becomes irreversible, resulting in electrolyte disturbances, predominantly calcium, and thus cell death through apoptosis (Bower et al, 2011). Immunohistochemistry studies confirm the induction of the apoptotic pathway by electroporation, which will ultimately lead to cell death and necrosis.

Using an electrical field of 2500 V/cm, it is postulated that IRE creates nano-sized pores (0.08-0.5 μm) in the cell membrane that are unable to reseal, because the electrical pulse strength and duration surpass the cell membrane threshold, permanently damaging the plasma membrane. The nanopores then allow micromolecules and macromolecules to be transported into and out of the cell. With high voltage, cells are unable to compensate for their altered transmembrane ionic concentration differences at which cell death occurs secondary to disruption of cellular homeostasis (Lee et al, 2010).

The area of tissue where the cells have been altered is the ablation zone. Thermal injury ablation techniques have varying degrees of damage because of their reliance on passive heat diffusion or degree of water molecule distribution across the ablation area, which can lead to uncertainty in the effectiveness of the procedure. IRE is advantageous because of the well-defined region of tissue ablation. The ablation zone in IRE shows where a cell is either destroyed or not destroyed with no uncertainty (Rubinsky et al, 2007). The complete electroporation zone and cell death occur over weeks, and 8 to 10 weeks is required for electroporation efficacy.

Local Tissue Factors

When delivered appropriately, IRE affects the target tissue that is bracketed by the probes and does not damage the surrounding structures, provided the IRE probes were placedatraumatically. Proteins, extracellular matrix, and critical structures such as blood vessels and nerves are not affected and are left intact by this treatment (Martin et al, 2014). Blood vessels and bile ducts are not permanently damaged by IRE (Charpentier et al, 2010, 2011; Martin et al, 2014), apparently because higher collagenous connective tissue and elastic fiber contents lack the normal cellular membrane that is affected by IRE. The electric currents of IRE that affect the cell membrane may travel through the gap junctions from one cell to the other without changing or disrupting the integrity of the smooth muscle cell membrane (Lee et al, 2010).

Preclinical studies have demonstrated the potential efficacy of IRE in ablation of HCC in an animal model (Guo et al, 2010). Additional preclinical work (Bower et al, 2011; Charpentier et al, 2010, 2011) has shown that the electric pulses do damage the cellular membrane of normal tissue (e.g., blood vessel endothelium, biliary epithelium), although the collagenous structures remain intact. Intact adventitia and laminae are visible at 2 days, with no smooth muscles cells present (Maor et al, 2007). The endothelium is largely repopulated at 2 days, with smooth muscle repopulation at 2 weeks. This slow method of repopulation has been demonstrated in preclinical studies on pancreatic tissue (Bower et al, 2011). It allows for vital structures to remain intact, patent, and viable for at least 1 month in both acute and chronic animal studies, as well as in human evaluation (Martin et al, 2012, 2013).

Technique in Liver for Tumors With Vascular Proximity

The clinical indication for IRE of liver tumors must be made based on (1) tumor biology, (2) tumor size less than 4 cm, (3) tumor location within 5 mm or less of a vital structure that needs to be spared, and (4) patient’s ability to undergo general endotracheal anesthesia. IRE is not a replacement for MWA or RFA. The current commercially available system consists of a computer-controlled pulse generator that delivers a maximum 3000 V between each probe pair based on the number and spacing configuration of the IRE probes. A minimum of 90 pulses must be delivered, lasting from 20 to 100 microseconds (μsec) each. The most common pulse length is 70 to 90 μsec, based on the degree of electrical resistance encountered.

Patient selection is crucial. A multidimensional thin-cut (0.7-1 mm) CT scan or contrast-enhanced dynamic magnetic resonance imaging (MRI) must be performed, preferably less than 1 month before treatment (Martin, 2013; Martin II, 2015; Martin et al, 2015). From these images, a 3D reconstruction can be used to plan number of IRE needles required, needle trajectory, and access (open, laparoscopic, or percutaneous). The tumor dimensions are input into the IRE pulse generator, which will recommend the number and possible spacing of probes needed to create the desired electroporation zone based on a mathematical algorithm. Optimal probe spacing is critical to the safety and efficacy of the device, with optimal spacing of 1.5 cm to 2.3 cm. Spacing less than 1.5 cm can lead to a small or ineffective electroporation (called reversible) or thermal damage (defined as >54°C for >10 sec) (Dunki-Jacobs et al, 2014). Probe spacing too far (>2.3 cm) will lead to ineffective electroporation. This precision of spacing places the burden on the physician to ensure high-quality US is used during needle placement and to document this spacing. The IRE probes are 19 gauge diameter and radiopaque to aid in intraprocedural identification of the probe tip (Cannon et al, 2013). Consideration of intraoperative navigation systems should also be considered for physicians who are not expert in liver US (Agle et al, 2015; Kingham et al, 2012). The pulses delivered from the NanoKnife system are synchronized with the patient’s electrocardiogram (ECG) to avoid cardiac arrhythmias (Martin et al, 2014).

Every patient requires individualized care and service for a successful treatment, and the surgeon’s skills should be assessed before performing IRE. Factors to consider are size of ablation zone, number of probes needed for the procedure, distance between the probes, and length of the active electrode tip; a set plan minimizes the risk for complications or mistakes. After gaining access to the liver, the probes are inserted under continuous US guidance to ensure accurate placement, but also to
avoid mechanical damage to the hepatic inflow, bile ducts, or hepatic outflow based on the lesion location. Once the probes are in the correct positions, the electric pulses are delivered from the NanoKnife system (Dunki-Jacobs et al, 2014). This can last from 10 to 60 minutes (Philips et al, 2013). Once the electric pulses are finished, the patient is closed and is sent to recovery. Detailed procedural steps have been presented for hepatic tumors (Martin, 2013).

Irreversible electroporation of the liver has well-defined criteria. Ablation recurrence is defined as persistent viable tumor as determined by dynamic imaging in comparison to pre-IRE scan or tissue diagnosis. Ablation success is defined as the ability to deliver the planned therapy in the operating room and at 3 months to have no evidence of residual tumor on cross-sectional imaging (CT, MRI, or PET, if preoperative PET-avid scan) (Martin et al, 2014; Philips et al, 2013).

**Clinical Results for Hepatic Malignancies**

The initial IRE use for liver was reported in 44 patients undergoing 51 total IRE procedures (Table 98C.3) (Cannon et al, 2013). Lesions were in proximity to vital structures in 40 patients (88%). Initial success was achieved in 50 treatments (100%). Five patients had nine adverse events, with all complications resolving within 30 days. Local relapse-free survival at 3, 6, and 12 months was 97.4%, 94.6%, and 59.5%, respectively. There was a trend toward higher recurrence rates for tumors larger than 4 cm (hazard ratio [HR], 3.236; 95% confidence interval [CI], 0.585-17.891; \(P = .178\)). The authors were able to conclude that IRE was a safe treatment for hepatic tumors in proximity to vital structures. A significant inflection point occurred for all tumors greater than 3 cm, with higher local recurrence rates. Thus the initial recommendation for new users was to start with hepatic tumors that were less than 3 cm and in proximity to vital structures.

The true technical reports on which tumor locations were appropriate for IRE, especially within the hepatic hilum, were published by Martin (2013). Typically, a minimum of 90 pulses is delivered, lasting from 20 to 100 µsec each. The most common pulse length is 70 to 90 µsec, with the shorter durations used in cases in which high electrical resistance is encountered. The pulse voltages and duration are based on preclinical studies (Bower et al, 2011; Charpentier et al, 2010, 2011). Treatment planning is based on 3D preoperative CT in which the tumor dimensions and location of surrounding structures are measured. From the preoperative scan, the tumor dimensions are input into the pulse generator, with a set planned margin. Multiple monopolar probes are used (maximum of six), with greater numbers of probes needed for larger ablation zones. The maximum effective probe spacing can vary from only from 1.4 to 2.2 cm apart. If the probe spacing is less than 1.4 or greater than 2.2 cm, the effectiveness of the electroporation is reduced and will lead to an incomplete ablation. The maximum probe exposure used in liver IRE is 2 to 2.5 cm. Optimal technique requires the user to place the needle along the longest axis of the tumor, most often the caudal-to-cranial plane (coronal plan), and then perform sequential pullbacks to achieve both cranial and caudal margins. We recommend not to attempt to perform the “overlapping ablation” technique first popularized with RFA, because IRE therapy induces artifact, and human error to ensure precise spacing would lead to a greater incidence of ineffective therapy (i.e., reversible electroporation).

These results were further confirmed by an analysis of 150 consecutive patients treated in seven institutions from 2010 to 2012. Patients were divided into three groups, A (first 50 patients treated), B (second 50 patients), and C (third 50 patients), chronologically, and analyzed for outcomes (Philips et al, 2013). Key definitions for IRE success and IRE recurrence were defined and established. Follow-up imaging to confirm ablation success was performed at IRE therapy, then at 12 weeks and at 3 month intervals. An initial discharge scan was done to evaluate any complications from this new technique, not for treatment efficacy. Dedicated body-imaging radiologists at each center, who were not blinded to treatment, made radiologic interpretation of recurrence, as defined by the RECIST criteria (Therasse et al, 2000). In cases in which imaging was equivocal, biopsies were obtained at the discretion of the treating physician. A total of 167 IRE procedures were performed, with a majority being liver (39.5%) and pancreatic (35.5%) lesions. The three groups (A, B, and C) were similar with respect to comorbidities and demographics. Group C had larger lesions (3.9 vs. 3 cm; \(P = .001\)), more numerous lesions (3.2 vs. 2.2; \(P = .07\)), more vascular invasion (\(P = .001\)), more associated procedures (\(P = .001\)), and longer operative times (\(P < .001\)). Despite this, complication and high-grade complication rates were comparable among the three groups (\(P = .24\)). IRE-attributable morbidity rate was 13.3% (total, 29.3%), and high-grade complications were seen in 4.19% of patients (total, 12.6%). Pancreatic lesions (\(P = .001\)) and laparotomy (\(P = .001\)) were associated with complications. This represented the single largest review of IRE soft tissue ablation showing initial patient selection and safety. With time, complex treatments of larger lesions and those with greater vascular involvement were performed, without a significant increase in adverse effects or impact on local relapse-free survival. This evolution demonstrates the safety profile of IRE and ability of initial IRE users to treat more complex lesions, which was after more than five cases by institution. IRE is a safe and effective alternative to conventional ablation, with a demonstrable learning curve of at least five cases to become proficient.

Martin and colleagues (2015) performed a prospective evaluation of 107 consecutive patients from seven institutions who had tumors with vascular invasion and were treated with IRE from 2010 to 2012. Locally advanced tumors were defined as primary tumor with less than 5 mm from major vascular structure based on preoperative dynamic imaging or intraoperative criteria. IRE was used in locally advanced tumors in the liver (\(n = 42, 40\%\)) and in the pancreas (\(n = 37, 35\%\)), with a median of two lesions and mean target size of 3 cm. IRE-attributable morbidity rate was 13.3% (total, 29.3%), with high-grade complications seen in 4.19% (total, 12.6%). No significant vascular complications were seen, and of the high-grade complications, bleeding (two), biliary complications (three) and deep vein thrombosis or pulmonary embolism (DVT/PE, three) were the most common. Complications were more likely with pancreatic lesions (\(P = .0001\)) and open surgery (\(P = .001\)). Calculated local recurrence-free survival was 12.7 months, with median follow-up of 26 months censured at last follow-up. The tumor target size was inversely associated with recurrence-free survival (\(R = 0.81, 95\% CI, 1.6 \text{ to } 4.7, P = .02\)), but this did not have a significant overall survival impact. The authors were able to
TABLE 98C.3 Animal and Human Studies of Irreversible Electroporation (IRE) for Liver Tumors

<table>
<thead>
<tr>
<th>Study</th>
<th>No.</th>
<th>Patients</th>
<th>Histology</th>
<th>Was Ablation Success Reported and Defined</th>
<th>Overall Survival (Y/N) Median</th>
<th>Local Recurrence</th>
<th>Liver Recurrence</th>
<th>Mortality</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Animal Studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guo et al, 2011</td>
<td>44</td>
<td>HCC: animal model</td>
<td>Yes, 90%</td>
<td>Kept alive for 15 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6.67% from preoperative complications No postoperative complications observed</td>
</tr>
<tr>
<td>Lee et al, 2010 (power point)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Yes, 100%</td>
<td>Kept alive for 3 wk after IRE</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>None</td>
</tr>
<tr>
<td>Lee et al, 2007 (24 hour study)</td>
<td>4</td>
<td>—</td>
<td>—</td>
<td>Yes, 100%</td>
<td>Kept alive for 24 hr</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>None</td>
</tr>
<tr>
<td>Lee et al, 2010</td>
<td>16</td>
<td>—</td>
<td>Success, not defined</td>
<td>Kept alive for 24 hr to 14 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6/65 ablation zones had hypoa attenuation</td>
</tr>
<tr>
<td>Charpentier et al, 2011</td>
<td>8</td>
<td>—</td>
<td>Success, not defined</td>
<td>Kept alive for up to 14 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 animal acquired a descended stomach</td>
</tr>
<tr>
<td><strong>Human Studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thomson et al, 2011</td>
<td>38</td>
<td>25 liver</td>
<td>Liver: (15/18)</td>
<td>Monitored 1 and 3 mo after procedure</td>
<td>0% for patients who had successful procedures</td>
<td>—</td>
<td></td>
<td>0%</td>
<td>Brachial plexus injury, pneumothorax, urinary tract infection, pain after recovery (36%)</td>
</tr>
<tr>
<td>Yeung et al, 2014</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cardiac arrhythmia, pneumothorax, electrolyte disturbance</td>
</tr>
<tr>
<td>Ball et al, 2010</td>
<td>21</td>
<td>28 procedures: 8</td>
<td>—</td>
<td>—</td>
<td></td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Ventricular tachycardia (25%), pneumothorax (11%), postoperative pain (46%)</td>
</tr>
<tr>
<td>Martin et al, 2014</td>
<td>107</td>
<td>42 liver</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>5%</td>
<td>—</td>
<td>13.3%</td>
<td>Bleeding, biliary complications, DVT/PE (4.19%)</td>
</tr>
<tr>
<td>Ryan et al, 2013</td>
<td>23</td>
<td>29 lesions: 23 liver, 4</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>7%</td>
<td>—</td>
<td>—</td>
<td>Pneumothorax (9%)</td>
</tr>
<tr>
<td>Kingham et al, 2012</td>
<td>28</td>
<td>2 HCC</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>5.7%</td>
<td>1.9%</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Cannon et al, 2013</td>
<td>45</td>
<td>14 HCC</td>
<td>—</td>
<td>—</td>
<td>Study lasted 2 yr</td>
<td>3, 6, and 12 mo: 2.6%, 5.4%, and 40.5%, respectively</td>
<td>—</td>
<td>—</td>
<td>10% of patients had adverse events; 3/3 procedure related (neurogenic bladder, abdominal pain, flank pain)</td>
</tr>
<tr>
<td>Cheung et al, 2013</td>
<td>11</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Follow-up: 18 mo</td>
<td>0%</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
</tbody>
</table>

CRLM, Colorectal liver metastasis; DVT/PE, deep vein thrombosis/pulmonary embolism; HCC, hepatocellular carcinoma; NE, neuroendocrine.
conclude that IRE represents a novel therapeutic option in patients with locally advanced tumors involving vital structures that are not amenable to surgical resection. Acceptable to high local disease control and the long local relapse-free survival can be achieved with IRE in combination with other multidisciplinary therapies.

Irreversible electroporation has the potential to become an efficacious cancer treatment. More complex treatments of larger lesions and lesions with greater vascular involvement will become available with more research and clinical trials.

References are available at expertconsult.com.
REFERENCES


