

TECHNIQUE SPOTLIGHT

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Radiofrequency Ablation: Current Status

RFA TECHNOLOGY

Radiofrequency ablation (RFA) is an ablative technology that uses thermal energy to induce cell death. The technology has been used for nearly three decades with an extensive body of evidence. RFA can be used percutaneously with imaging guidance, and by surgeons either laparoscopically or in the OR in an open setting. RFA is now used in the treatment, both curative and palliative, for the thermal coagulation necrosis of soft tissues throughout the body.¹

The RF ablation electrode acts as a cathode of an electrical circuit, which is closed by the application of dispersing pads on the patient's thighs or back.

After the position of the electrode is verified under CT guidance, the RF generator delivers pulses of high frequency alternating current, which causes rapid vibration of water molecules generating frictional heat. Temperature elevation in the range of 500C to 1050C leads to coagulative necrosis of cells and inevitable destruction of cancerous tissue with steep decline in heat generation at the periphery. RF pulse frequency should be gradually increased to avoid tissue charring and impedance of thermal propagation.

This tool is most commonly utilized in the interventional radiology suite under CT scan or ultrasound guidance.

General anesthesia or conscious sedation is used to minimize patient discomfort during the procedure. Procedure times are adjusted according to the size and type of tumor being treated.

Some contraindications to the procedure include excessive tumor burden, uncorrectable coagulopathy or active infection. The ablation area is replaced by fibrosis and scar tissue with gradual decrease in size noted on imaging in the following months.

COMMERCIALLY AVAILABLE RFA SYSTEMS

Commercially available RFA systems can be broadly classified as temperature-based or impedance-based systems. Impedance-based systems operate under the principle that heat conductivity decreases as impedance increases. As the tissue is ablated the ability to conduct heat decreases leading to an increase in impedance. This leads to "roll-off" when the tissue is completely ablated and the generator shuts off automatically.

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Boston Scientific (Natick, Massachusetts) has an impedance-based system that utilizes a 480-kHz generator with maximum power of 200W, which features an impedance-based feedback algorithm to achieve appropriate energy output. The electrode employs an umbrella like deployment configuration (LeVein™ Needle Electrodes; Boston Scientific) with diameters of 2-5cm in increments of 0.5 cm in various lengths. Delivery starts at 20-80W and increases 5-10W/min to maximum values of 55-200W. The ablation end-point is denoted by a dramatic increase in impedance, termed “roll-off”.

RFA ROLE IN HCC MANAGEMENT

Hepatocellular carcinoma is the fifth most common cancer, and the third leading cause of cancer death worldwide. In the United States, the overall incidence of HCC is 15,000 new cases a year. Although hepatic resection remains a first line treatment, approximately 80% of patients are not candidates as a result of inadequate hepatic reserve, tumor location, or tumor burden.² Orthotopic liver transplantation offers high rates of disease-free remission, but is limited by stringent selective criteria, cost and donor availability.³ Overall 5-year survival rates for HCC are below 10% in Europe and the United States.⁴ As such, percutaneous ablation utilizing radiofrequency, microwave, and cryoablation is the preferred mode of treatment for non-surgical candidates with one or several tumors up to 3cm, or up to 5cm in select situations.⁵

RF Ablation

Complete ablation rates for small to medium HCC exceed 80% in a single treatment session, and exceed 90% with two sessions; 5-year survival rates in the largest studies are 40%-58%.^{6,7} Local progression after complete ablation is uncommonly observed (1%-12%). Studies of RFA related complications range from 0.9%-5%.⁸ Peritoneal hemorrhage, bile duct injury, abscess, and intestinal perforation are the most notable adverse outcomes. RFA limitations are based on its method of delivery. Specifically, thermal conduction is impeded by tissue desiccation and scarring, when high temperatures are reached quickly. RFA is also susceptible to a heat sink effect from flowing blood, which results in sub-lethal temperatures adjacent to vessels larger than 3mm in size.⁹ Because of electromagnetic interference only one RF electrode can be activated at one time and may lengthen procedure time in medium and large lesions.

RFA versus Surgical Resection

Two randomized controlled trials to compare percutaneous thermal ablation versus surgical resection in small to medium-sized HCC demonstrated no difference in overall or disease-free survival at 3-4 years.¹⁰ It is worth noting that complication rates were higher in the operative groups (11%-56%, including 4% operative mortality rate) compared to RFA groups (1%-10%).¹¹

RFA for large HCC

Two studies examined RFA success in large HCC and reported complete ablation rates of 24% and 62% in tumors measuring 5-9.5cm and 5-7cm, respectively. Complication rates were between 2%-10%, but one death was reported.⁸ To overcome these limitations newer RFA technologies including perfusion electrodes and bipolar devices were introduced. When three bipolar electrodes were utilized, an 81% complete ablation rate in HCCs measuring 5-8.5cm was achieved, with local progression rate at 14% and 2 year survival rate at 56%.¹² However, only InCircle™ Bipolar Device (RFA Medical, Fremont, California) is currently FDA approved in the United States.

Combined Therapy: RFA after Transarterial Chemoembolization (TACE)

Microvascular invasion and propensity to produce microsatellites are risk factors for local HCC recurrence. Sasaki et al was the first to show that HCC tumors >25mm in greatest dimension with moderate to poor differentiation were likely to have microsatellites at a distance >5mm from main HCC tumor.¹³ Microsatellite distribution that depends on tumor size and blood vessels that reduce the effective heat zone of adjacent HCC lesions are limitations of successful RFA treatment.

To investigate a synergy between various HCC treatment models, Veltri et al. conducted a retrospective review of HCC lesions treated with RFA 24 hours after chemoembolization with epirubicin, PVA particles or microspheres. The aim of blood flow occlusion with chemoembolization was to decrease heat dispersion during consequent RFA treatment. During follow-up complete response was obtained in 70.3% of lesions <5cm, while only 41.7% complete response was reached in lesions >5cm.¹⁴ Concerns for RFA following TACE approach include possibility of decreased efficacy of the drugs including doxorubicin and mitomycin when exposed to high temperatures and persistence of neoplastic microsatellite foci around dominant HCC lesion.¹⁴

Combined Therapy: DEB-TACE after RFA

Experimental animal tumor models have shown that combining sub-lethal heating with cell exposure to chemotherapeutic agents increases tumor necrosis.¹⁵ Embolic microspheres that actively sequester doxorubicin, like doxorubicin eluting beads (DEB)*, release it in a controlled and sustained fashion improving tumor response. As previously discussed, RFA's limitations are that viable neoplastic cells survive at the periphery of the lesion due to suboptimal heat propagation. On the other hand, RFA prior to DEB-TACE increases vascular endothelial pore size, causes reversible damage to the membrane efflux pump and leads to transient hyperemia at the rim of the lesion, allowing more DEB to be deposited than after TACE without prior RFA. A pilot study by Lencioni et al. demonstrated that DEB-TACE, after RFA enhanced the effect of RF ablation leading to a high rate of complete response in HCC tumors incompletely treated with standard RFA.¹⁵ At our institution we retrospectively evaluated patients with HCC who undergone RFA/DEB-TACE between May 2008 – November 2011. Administration of a total of 150mg doxorubicin dose in 100-300 micron and 300-500 micron LC beads after RFA led to an 85% complete response at 1 month of follow up.

RFA PATIENT SELECTION

The decision to proceed for loco-regional therapy is best addressed with a multidisciplinary approach. Patients are often not surgical candidates or may elect percutaneous approach. Considerations include size of the lesion, proximity to vessels, vital structures and extent of disease. These vary with the involved organ, and the neoplasm. In regards to size, tumor recurrence rates are determined predominantly by lesion size, with hepatocellular carcinoma, lesions <3.0cm, yielding a successful treatment in the vast majority. Complete local response decreases with tumors between 3.0 and 5.0cm, and drops further to approximately 25% in large tumors over 5cm in diameter. With successful ablation, 5-year survival rates of 40-50% have been reported.¹⁶

For lesions between 3-5cm in size transarterial chemoembolization (TACE) may be performed in combination to better address margins. Adequate treatment margins is most highly associated with complete response, therefore lesion size must be adequately covered with either single or multiple probes during ablation.

Given that RFA is a thermal ablative technique, lesions are ideally >1cm away from critical structures such as the hepatic hilum, diaphragm, gallbladder or bowel wall. Patients with disseminated disease in multiple organs or with very numerous lesions likely will not benefit from local ablative therapy and are not ideal candidates.

*There are currently no FDA approved drug-eluting beads available for sale in the U.S.

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WHERE DOES RFA EXCEL?

RFA vs. Microwave

Microwave ablation has been reported to be more effective in treating larger lesions. It is also less susceptible to heat sink effect, and has consistently higher intratumoral temperatures.¹⁷ Microwave ablation times are shorter, however, the intended ablation zone is more variable with Microwave ablation.

RFA vs. Cryoablation

Cryoablation is susceptible to the warming effect of large adjacent vessels. There is also an increased risk of hemorrhage in the event that the “ice ball” should fracture.¹⁸ Unique to cryoablation is the complication of cryoshock after hepatic cryoablation where the release of free radicals can lead to multi-organ failure.

RFA vs. PEI

Percutaneous ethanol injection (PEI) has high local recurrence rates and often requires multiple sessions. A single PEI needle with multiple retractable prongs and four terminal side holes (Quadra-Fuse™ Device; Rex Medical, Conshohocken, PA) has been developed to address some of the limitations. However, multiple randomized control trials have showed better local control of disease in the treatment of early-stage HCC and an improved overall survival benefit for tumors larger than 2cm with RFA vs PEI.¹⁹

RFA vs. IRE

Although IRE (irreversible electroporation) has advantages over other modalities in select cases as it is a predominantly non-thermal energy, IRE has to be cardiac gated and is contraindicated in patients with a history of cardiac arrhythmias or instability. Also, IRE requires multiple needle placements which must be rather exactly spaced and can be more time consuming. General anesthesia with complete muscle paralysis is mandatory for IRE and patients with multiple comorbidities may not be candidates.

KEY TECHNIQUES THAT MAY ENHANCE SUCCESS

Several techniques can be employed to enhance success during RFA procedures.

Pre-procedural or same day triple phase CT scan is followed by post-procedure CT scan allows better assessment of ablation target and extent of ablation.

Chasing the contrast bolus with saline cuts the contrast dose in half.

Ideal tumor size <3 cm, with a spherical geometry located at least 1cm from vital structures or large vessels.

Bowel preparation is recommended in patients who have biliary stents, biliary drainage catheters or reconstruction of the ampulla that in turn increases risk of cholangitis.

General anesthesia assists with respiratory variation, pain control and patient motion during the ablation.

Avoid direct puncture of capsular lesions, instead entering the liver through normal tissue to prevent back bleeding and tract seeding.

COMPLICATIONS

Common complications include but are not limited to pain, low-grade fever, abscess, tumor seeding, hemorrhage, pneumothorax, pleural effusions, and skin burns. To limit pain, general anesthesia is recommended and used in all cases at our institution. Lesions that are large, subcapsular, involving the porta hepatis or abutting the diaphragm produce more pain. The latter can refer pain to the shoulder. Low-grade fever where fevers less than 101 F may be seen for several days are associated with post RFA syndrome which is less severe than arterial post embolization syndrome. Abscesses rarely form however fevers greater than 101 F should alert the clinician to their presence. Larger lesions and patients with biliary stents are at a higher risk for abscess formation. Tumor seeding and back bleeding can be avoided by ablating the needle track and entering capsular lesions via normal tissue. Pneumothoraces can be seen with ablations of hepatic or lung lesions and even with upper pole renal lesions and adrenal lesions. Small asymptomatic pneumothoraces may be managed conservatively but larger ones respond well to catheter drainage. Pleural effusions can result after lung ablations or treatment of hepatic lesions abutting the diaphragm. These may take several weeks to resolve. Skin burns related to grounding pad issues can occur and can be reduced by preventing creases in the grounding pads and assuring their correct placement prior to the ablation session.

POST PROCEDURE CARE AND FOLLOW-UP

In our institution, patients undergo general anesthesia for ablation procedures. Patients are placed on patient controlled analgesia (PCA) systems overnight for pain control and are switched to oral medications typically the next morning when taking adequate PO. IV antibiotics are given pre and post procedure and patients are typically sent home on several days of PO antibiotics. A contrast enhanced CT is obtained pre and post ablation during the procedure and again at 4 weeks. If the patient had a PET avid lesion pre-ablation, a repeat PET/CT is obtained the morning after the ablation. The patient is followed up in clinic after the 4 week CT scan and any relevant tumor markers are obtained.

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CASE 1

78 YEAR OLD FEMALE WITH RENAL CELL CARCINOMA POST RIGHT NEPHRECTOMY WITH METASTASIS TO LEFT ADRENAL GLAND.

The adrenal lesion had a safe access and location and RFA was chosen as the treatment option. RFA of the adrenal gland is safe and feasible.

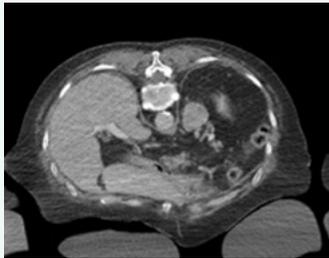


Figure 1a:
Pre ablation CT scan

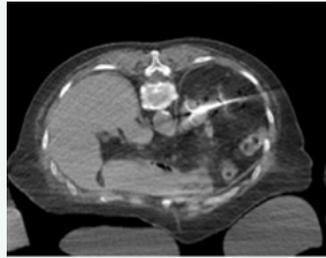


Figure 1b:
Radiofrequency Ablation
of adrenal gland

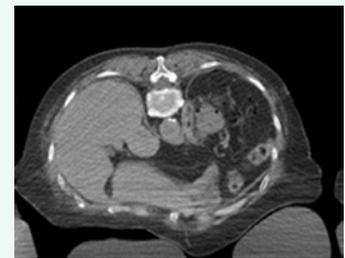


Figure 1c:
Immediate Post ablation CT scan



Figure 1d:
Pre ablation PET/CT adrenal



Figure 1e:
Immediate Post ablation PET/CT

CASE 2

57 YEAR OLD MALE WITH POORLY DIFFERENTIATED NEUROENDOCRINE TUMOR WITH METASTASES TO THE LIVER.

This patient has the lesion close to the capsule. A subcapsular location has a higher risk of bleeding and approaching this lesion from a lateral approach directly into the lesion will not be the best method. It was accessed from an anterior approach with the probe traversing normal liver parenchyma to reach the lesion. This helps to tamponade any bleed that may occur. It is also important to track ablate as the probe is being pulled back and removed after the ablation.

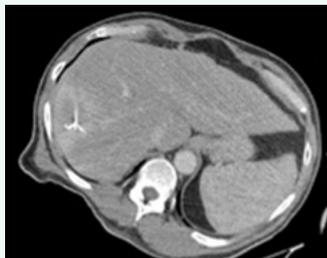


Figure 2a:
Pre ablation CT Scan



Figure 2b:
Ablation CT scan



Figure 2c:
One month post Ablation CT scan. The lesion previously measured 5.0 x 5.0 cm and now measures 4.5 x 5.0 cm. It shows no evidence of enhancement that would suggest the presence of residual tumor.

CASE 3

75 YEAR OLD MALE WITH PRIMARY HCC SEPTEMBER 2009.

This patient had a treatment with TACE using doxorubicin coated drug eluting beads (DEBDOX) with a partial response on the first follow-up. Given the size of the lesion it was elected to treat this again with a combined RFA and DEBDOX. This case demonstrated the synergy of the combined approach using RFA and drug eluting beads. In carefully selected patients with intermediate size lesions combination of RFA and TACE can provide good local control.



Figure 3a:
HCC lesion treated with RFA, day 1

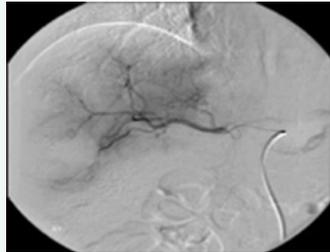


Figure 3b:
Pre DEB-TACE angiogram, day 2

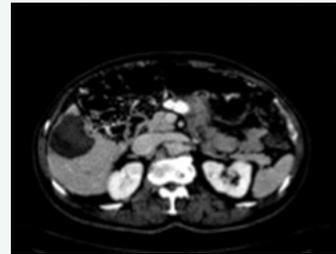


Figure 3c:
One month post Ablation CT scan. Contrast CT at 1 month follow-up shows non-enhancing zone in the area of the lesion

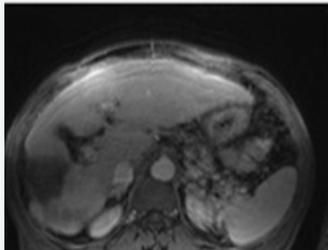


Figure 3d:
18 month follow up contrast MRI confirms lack of enhancement or tumor progression

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LEVEEN NEEDLE ELECTRODE FAMILY

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INTENDED USE/INDICATIONS FOR USE: The LeVeen Needle Electrode Family is intended to be used in conjunction with the RF 3000 Generator for the thermal coagulation necrosis of soft tissues, including partial or complete ablation of nonresectable liver lesions. These procedures should only be performed by physicians and staff familiar with the equipment and techniques involved. **PRECAUTION:** Before using, inspect the package for any breach to the sterile barrier and inspect product for any damage. If package is broken or product is damaged DO NOT USE. Immediately return package and product to Boston Scientific. **WARNINGS:** • The colored insulated cannula must be used at all times when accessing tissue. Use of the electrode without the colored insulated cannula may result in serious burns to the patient and/or user. Damage to the insulation of the introducer may result in serious burns to the patient and/or user. **Precaution:** The LeVeen Needle Electrode Family must be used in conjunction with the Boston Scientific RF 3000™ Generator. For patients with permanent pacemakers and Implantable Cardiac Defibrillators (ICD) additional precautions should be taken. **ADVERSE EVENTS:** Reported complications associated with radiofrequency (RF) ablation of liver tissue include, but are not limited to: • Abscess • ARDS (Acute Respiratory Distress Syndrome) • Arrhythmia • Ascites • Biloma • Burn • Death • Delayed hemorrhage into ablated tissue • Diarrhea • Electric Shock • Fistula, including biliary fistula • Hematoma • Hemorrhage • Infection • Liver Failure • Liver Insufficiency • Pain • Perforation • Peritonitis • Persistent Fever > 39° C • Pleural Effusion • Renal Failure • Tumor Recurrence • Tumor Seeding

RF3000 RADIO FREQUENCY GENERATOR

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The RF 3000 Radio Frequency (RF) Generator is intended for thermal coagulation of soft tissue with electrodes separately cleared by the United States FDA. The generator delivers an isolated RF output of up to 200 watts to the electrode. Full power is available in the impedance range of 25Ω to 100Ω at a constant RF voltage; lower powers are available outside this range. Power can be adjusted manually; however, changes in load impedance will change the actual power delivered (a safety feature described more fully in "Passive Power Limitation"). When power is on, actual delivered RF power and impedance are displayed. The Operation and Service Manual is intended as an instructional guide only. **General Procedure Safety WARNING!** Safe and effective electrosurgery is dependent not only on equipment design, but also, to a large extent, on factors under the control of the operator. It is important that the instructions supplied, both with this equipment and the accessories, be read, understood, and followed in order to ensure safety and effectiveness. **WARNING!** No modification of this equipment is allowed. **WARNING!** The use of RF energy can produce unintended neuromuscular stimulation. **Electromagnetic Interference WARNING!** The use of electrosurgical devices can cause electromagnetic interference (EMI) in other devices, particularly cardiac pacemakers. Precautions should be taken to ensure that the patient's well-being is maintained in the event of such interference. **WARNING!** The use and proper placement of dispersive electrodes (return pads) is a key element in the safe and effective use of monopolar electrosurgery, particularly in the prevention of burns. Follow the manufacturer's Instructions for Use.

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INTENDED USE/INDICATIONS FOR USE: The Soloist Single Needle Electrode is intended to be used in conjunction with the RF 3000 Generator for the thermal coagulation necrosis of soft tissues, including partial or complete ablation of nonresectable liver lesions. **CONTRAINDICATIONS:** None known. **WARNINGS:** Damage to the insulation of the introducer or needle may result in serious burns to the patient and/or user. **Precaution:** The Soloist™ Single Needle Electrode must be used in conjunction with the Boston Scientific RF 3000™ Generator. For patients with permanent pacemakers and Implantable Cardiac Defibrillators (ICD) additional precautions should be taken. **ADVERSE EVENTS:** Reported complications associated with radiofrequency (RF) ablation of liver tissue include, but are not limited to: • Abscess • ARDS (Acute Respiratory Distress Syndrome) • Arrhythmia • Ascites • Biloma • Burn • Death • Delayed hemorrhage into ablated tissue • Diarrhea • Electric Shock • Fistula, including biliary fistula • Hematoma • Hemorrhage • Infection • Liver Failure • Liver Insufficiency • Pain • Perforation • Peritonitis • Persistent Fever > 39° C • Pleural Effusion • Renal Failure • Tumor Recurrence • Tumor Seeding

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