RFA II: Review of the Technique, Clinical Applications and Possibilities.

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October 2002
What is Radiofrequency Ablation (RFA)?

- RFA is a minimally invasive strategy for local treatment of solid malignancies.
- The technique utilizes radiofrequency (RF) as a thermal energy source for percutaneous, image-guided tumor ablation.
Mechanism

To accomplish RFA of a tumor, thin (usually 21-14 gauge) needle – like electrodes are placed directly into the tumor with the use of US, CT or MR guidance.

The RF electrode typically is comprised of a metal shaft, which is insulated except for an exposed conductive tip, as well as a wide grounding pad placed on the patients skin.

Courtesy of Dr. N Goldberg
The RF generator supplies RF power to the tissue through the electrode.

It produces RF voltage between the electrode and the grounding pad, which establishes lines of electric field. Resistive energy loss results in frictional heat which kills tissue.

Courtesy of Dr. N Goldberg
Coagulation Necrosis

The volume of tissue destroyed by RFA depends on the temperature distribution of the RFA treated lesion.

Courtesy of Dr. N Goldberg
Coagulation Necrosis (cont)...

- The highest temperature, and therefore the highest degree of necrosis, occurs in the center of the RFA lesion.
- Untreated tumor cells can remain at the periphery where temperatures are not high enough.

Courtesy of Dr. N Goldberg
Thermal Ablation Therapy: Temperature/Tissue Interactions

- 35 - 40°C  Normothermia
- 42 - 46°C  Hyperthermia
- 46 - 48°C  Irreversible cellular damage @ 45 min.
- 50 - 52°C  Coagulation necrosis, 4 - 6 min.
- 60 - 100°C Near instantaneous coag. necrosis
- > 110°C  Tissue vaporization
The goal is to destroy an entire tumor by killing malignant cells in a homogenous fashion, and in a wide enough radius to cover the entire tumor and surgical margin (0.5-1cm) without damaging the surrounding tissues.
Strategies to Optimize Effects of Thermal Ablation

These can be determined by applying Goldberg’s “simplified bioheat equation:”

\[ \text{Tissue} = \text{Energy} \times \text{Tissue} - \text{Heat} \]
\[ \text{Coagulation} - \text{Deposited} \times \text{Interactions} - \text{Loss} \]

Therefore, to increase the size of the RFA lesion, you can:
1) Increase the energy deposited,
2) Increase tissue interactions,
3) Decrease heat loss.
Increasing Energy Deposition:

Can increase the voltage on the generator:

While this seems logical, the approach does not work for two reasons:

i) Increasing the voltage on the generator will also increase the voltage to the grounding pad and result in skin burns.

ii) Temperatures > 105-115 °C cause tissue boiling, vaporization and carbonization. These gases insulate heat and decrease the radius of ablation.
Monopolar electrodes: produce small and specific lesions (1.6 cm diameter).

Increasing the electrode length, increases the longitudinal axis of necrosis without increasing the diameter.

Courtesy of Dr. N Goldberg
Approaches to Increasing Spherical Energy Deposition

- Multiprobe Arrays
  - Bipolar
  - Free-standing
  - Hooks
- Internally-cooled electrodes
- Pulsing
Multiprobe Arrays: Bipolar

Heat is generated around the active and the ground needle. This results in larger, elliptical zones of coagulation necrosis.

Courtesy of Dr. N Goldberg
Multiprobe Arrays: Free-standing

- Same concept as bipolar, but it is difficult to insert and position multiple needles correctly.

Courtesy of Dr. N Goldberg
Multiprobe Arrays: Hooked

- Multiple curved-tip wires that come out of a 14-16 gauge needle in an umbrella shape.
- Allows greater coagulation temperatures in a 3-5 cm diameter lesion (vs. 1.6 cm with monopolar).

Courtesy of Dr. N Goldberg
Internally-cooled Electrodes

- These electrodes have hollow lumina that allow for continuous circulation of cooling material and removal of warmed effluent from the tip:

- This produces a heat-sink effect that minimizes tissue heating at the center of the lesion – this decreases impedance, and results in greater current deposition to increase the diameter of heating.

Courtesy of Dr. N Goldberg
Pulsed RF: Deposition

- Periods of high-energy are alternated with periods of low energy deposition.

- This allows for intermittent cooling of the tissue adjacent to the probe, with repetitive heating driving temperature deeper into surrounding tissues...this increases the diameter of the RFA lesion.
Tissue interactions:

In-vivo, there are multiple, tissue-specific limitations that prevent heating of the entire tumor volume:

a) poor heat conduction in tissue,

b) total energy tolerance limited by tissue boiling,

c) variable (cell specific) toxicity with heating at 45-55°C.
Altering Tissue Conductivity

- A primary factor that can alter the extent of coagulation necrosis is tissue composition.
- Heat conducts poorly though bone and better through soft tissue.
- Tissue conductivity can be altered by the injection of saline.
- The heated liquid spreads thermal energy further and faster by increasing the tissue ionicity.
# Rf Ablation: Effects of NaCl injection

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Saline</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Current (mA)</strong></td>
<td>1,600 pulsed</td>
<td>2,000 cont.</td>
</tr>
<tr>
<td><strong>Heating (@ 2 cm)</strong></td>
<td>55°</td>
<td>103° C</td>
</tr>
<tr>
<td><strong>Coagulation</strong></td>
<td>3.7 cm</td>
<td>7.1 cm</td>
</tr>
</tbody>
</table>

- Both saline volume and concentration effect RF heating and coagulation.
Tissue = Energy X Tissue - Heat
Coagulation Deposited Interactions

- **Heat Loss:**
hheat from RFA is lost by circulating blood which carries thermal energy away from the focal lesion.

\[ y = -0.0129x + 3.5153 \]

\[ R^2 = 0.7779 \]

Courtesy of Dr. N Goldberg
Attempts to Decrease Blood Flow

- Portal inflow occlusion: Pringle maneuver,
- Balloon occlusion,
- Embolotherapy – using lipiodal prior to RFA,
- Pharmacologic alteration,
- Anti-angiogenesis factors
Ultimate Goal = Tumor Death

- RFA provides a new approach to killing tumors, but for the best possible outcome, it should be combined with other therapies.
- RFA provides the ideal environment for drug deposition because the heat produces hyperemic tissue with leaky vessels at the thermal lesion periphery.
...therefore, drugs are deposited where they are needed most – in the peripheral zones.
Question is …how do we get the drugs there?

- Answer: Liposomes.
- At 40-42°C, blood vessels become leaky
- This allows liposomes to extravasate.
- Liposomes dump payload
- Extravasation decays back to baseline at 6 hours.

http://www.collabo.com/liposome.htm#Types
Fluorescent-labelled 100nm liposomes, 60 min after hyperthermia

Extravasation decay after 42°C for 60 min.

Liposome Payloads

- Drugs (Doxorubucin, Bleomycin, Cisplatin)
- Contrast
- Viral vector
- Genes
- Cytotoxins
- Antibody
  etc…
Combination of RF ablation therapy with adjuvant treatments increases the extent (and possibly the homogeneity) of induced tissue coagulation.

Courtesy of Dr. N Goldberg
Further research will determine which of these strategies will ultimately prove most clinically beneficial by providing predictable, reproducible large volume tumor destruction.
Example of an Ideal RFA Candidate

A 30 year old man was diagnosed with large B cell lymphoma following a kidney transplant. Multiple cycles of chemotherapy resulted in near-complete resolution of disease. However, a PET scan revealed a single active lesion, which persisted unchanged in the liver.
Lesion measures 4.5cm in diameter

- The patient underwent pulsatile RFA of the lesion with an internally cooled tip probe, and was discharged home two days later.
Follow-up MRI and Pet scans 15 months following RFA

Follow-up PET scans taken 15 months after RFA, revealed no metabolic activity in the treated lesion.
Clinical Opportunities for RF Ablation

- Hepatic Tumors – most widely used application for RFA:
  - procedural morbidity // mortality = 1.7% // 0.2%
  - surgical mortality for hepatic resection = 2-10%

- In contrast to surgery, RFA:
  - is less invasive,
  - is less expensive,
  - can be applied to non-surgical candidates.
RFA has been applied to treat

- HCC or colorectal metastases to the liver < 3.5 cm in diameter.
- Osteoid osteomas and metastatic bone disease.
- Head and neck cancers.
- Breast cancer.
- Lung cancer.
- Tumors of the adrenal gland.
- Renal tumors.
- Pelvic tumors.
Next Steps

- Combining RFA with targeted treatment.
- Understanding tumor heat, and which genes are expressed.
- Understanding tumor heterogeneity in relation to angiogenesis.
- Clinical trials for liposomes with RFA.
- Etc…
References


- Wood, BJ. “Freeze, Fry or Shake: Opening the Door to Drug Delivery”. SIR; Current Strategies in the Treatment of Hepatic Malignancies, Tyson’s Corner, VA, Sept 20.
Acknowledgements

- Dr. N. Goldberg
- Dr. G. Leiberman
- Ms. Pam Lepkowski
- Larry Barbaras

…….THANKS!!!