IMAGE-GUIDED ABLATION (PERCUTANEOUS)

Session 2: The patient with early stage disease: what is the first line therapy?

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Goals

• Define percutaneous image-guided local ablation
• Review methods of image-guided ablation
• Review results of image-guided ablation
• Identify the role of image-guided ablation in early stage hepatocellular carcinoma
Early and Very Early Stage Hepatocellular Carcinoma

- Limited size and number of tumor(s)
  - ≤3 localized tumors
  - one 2-5 cm, two or three 2-3 cm
  - Very early stage: one ≤2 cm

- Preserved liver function

- Preserved overall function
Therapies for Hepatocellular Carcinoma

- Liver transplantation
- Surgical resection – typically ≤10-20% eligible
- Ablation – percutaneous and operative
- Transarterial therapy
  - embolization
  - chemoembolization
  - radioembolization
- Systemic therapy
- Best supportive care
Therapies for Early Stage HCC
BCLC Staging & Treatment Algorithm

From Forner, Lancet 2018
Percutaneous Image-guided Local Ablation: *Concept*

- Introduction of drug, chemical, or energy directly into tumor under imaging guidance (US, CT, MRI) → destruction of visualized tumor plus a surrounding zone of liver
  - margin 5-10 mm (larger probably better)
- Considered a curative therapy
Percutaneous Image-guided Local Ablation: *Methods*

- Typically involves placing ≥1 needle(s) into tumor
- Avoid damage to biliary, vascular, or sensitive extrahepatic structures
Local Ablative Therapies: *Types*

- **Chemical injury**
  - ethanol
  - acetic acid

- **Thermal injury**
  - radiofrequency
  - microwave
  - cryotherapy
  - ↑ intensity focused US
  - hot saline
  - laser

- **Biological**
  - gene therapy

- **Bioelectrical**
  - irreversible electroporation
HCC Local Ablative Therapies: Types

- **Ethanol ablation**
  - early modality, surpassed by ↑ results w RFA

- **Radiofrequency ablation**
  - most extensively studied

- **Microwave ablation**
  - growing experience, favorable, replacing RFA

- **Cryoablation**
  - limited experience in HCC

- **Irreversible electroporation**
  - limited experience in HCC
Percutaneous Ethanol Ablation Therapy for HCC

• Mechanism
  – local cytotoxicity (cell dehydration, protein denaturation, tumor vessel occlusion)
  – EtOH diffuses into “soft” HCC but contained by surr firm, cirrhotic liver & any capsule, but also by intratumoral septa

• Technique
  – 20-22 G needle, may use mult needles/locations
  – volume calculated with extra 0.5-1 cm radius
  – usu limit to ~10 ml/Rx, so typically ≥ 2-4 Rx’s
  – guidance: US > CT
67 yo man w HCC, S/P R lobe chemoemb & resection & later wedge resect & RFA L lobe foci. New 1.6 cm caudate mass.
Ethanol Ablation: Complications

• Rates: major 0.28-7.4%  
  death 0.14-1.3%

• Types
  – transient pain & fever ~50%  
  – rarely (usually with larger EtOH volumes):
    - PV thrombosis
    - hemorrhage ~0.6%
    - cholangitis, bil obstr
  – tumor seeding of needle track ~0.1%
  – EtOH “intoxication” with larger volumes
  - pleural effusion
  - infect/lvr abscess
Hyperthermic Ablation (RFA & MWA): Goal

- Generate adequate elevation of temperature throughout target volume to produce nonviable tissue
  - $>60^\circ$ C $\rightarrow$ immediate protein denaturation with irreversible cell damage, coagulative necrosis
  - lower temperatures $\rightarrow$ longer time
Percutaneous Hyperthermic Ablation: Methods

• Perc 14-17 G needle access w US or CT guid

• Probe size/#: lesion size + 5-10 mm surr zone

• Traverse nl tissue, if poss, & coagulate track?
  – ↓ risks: blding & seeding

• Heavy moderate sedation
  – alternatively, GA

• Outpatient, occasionally require admission

• Treatment sessions: typically expect one
Hyperthermic Ablation (RFA & MWA): General Limitations

- **Size abl zone achievable about applicator**
  - typically ≤3+ cm

- **Avoid injury to adjacent vital structures**
  - GB, bowel, central bile duct, heart?
    - hydrodissect, artif ascites, surg abl, nontherm abl

- **Thermal sink from adjacent vessels, ≥3 mm**
  - MWA ↓ affected – nonthermal ablative options

- **Subcapsular lesions, direct puncture?**
  - perhaps greater risk of tumor seeding
  - risk of intraperitoneal hemorrhage?
HCC: subcapsular and colon anteriorly
Radiofrequency Ablation

• **Mechanism:** EM energy deposition
  – needle electrode in lesion + dispersive electrode (typically external grounding pads)
  – altern current → altern electric field in tissue → agitation ions surrounding electrode → heat

• **Avoid temperature >100° C**
  – tissue vaporizes & carbonizes → $\uparrow$ impedance
    → limits dispersion of electrical field

• **Pacemaker:** possibly an issue if in the path of current between electrode and grounding pads
RFA: *Intrinsic Limitation*

- Limit tiss vol ablatable w 1 probe: typ ≤3 cm
- To increase volume
  - modified electrodes
    - *internal cool* (Cool-tip): ↓ overheat about electrode
    - *expandable electrode needles*: retractable tines
  - multiprobe arrays (e.g. Cluster Cool-tip)
  - saline injections to improve conduction
  - ↓ vasc-rel heat sink - emb HA/tumor feeding art
    - occl balloon in HA or HV
  - overlapping ablations – particularly for >3 cm
  - bipolar arrays
**RFA: Devices**

- **Radiotherapeutics (Boston Scientific)**
  - expandable LeVeen electrode with multiple tines in umbrella shape

- **RITA – Angiodynamics**
  - expandable electrode with multiple tines

- **Cool-tip (Covidien Valleylab)**
  - single or cluster (3) internal-cooled electrode(s)
76 yo man w CAD & HBV

Initial US 2.8 cm

Biopsy: Well diff HCC

Tines within lesion

S/P RFA
Microwave Ablation

• **Mechanism**: needle antenna → high frequency oscillating EM field → agitation polar molecules (water) → kinetic energy → friction → heat

• **Compared to RFA**
  – larger radius/ablation volumes (larger tumors)
  – faster
  – higher target lesion temperatures
  – more homogenous
  – less affected by rising tiss imped (e.g., charring)
  – less affected by adjacent vessels/heat sink
  – easier multiple simultaneous applications
Postablation Side Effects

• Early pain

• Postablation syndrome
  – common side effect, ~1/3 of patients
  – typically between days 3-10
  – symptoms
    ♦ pain
    ♦ nausea
    ♦ fever
    ♦ chills
    ♦ malaise and fatigue
    ♦ anorexia
Radiofrequency Ablation for Very Early & Early HCC: Results

- **Tumors ≤3 cm**
  - complete ablation on imaging >90%
    - if ≤2 cm, then >95%
  - 5 year survival 61-86%

- **Tumors >3 cm to ≤5 cm**
  - complete ablation on imaging ↓ to ~74%
RFA for Very Early & Early HCC: *Pathological Results*

- **Serra (2018)**
  - 78 patients undergoing transplantation after treatment of 125 HCCs
  - imaging response pre-transplant 78%
  - complete pathological response 62%
    - <2 cm: 77%, 2-3 cm: 55%, >3 cm: 31%
    - near vessel: 50%, distant 69% (p=0.039)
RFA & Ethanol Ablation: Meta-Analysis of Five Randomized Trials*

• RFA significantly better in all categories

<table>
<thead>
<tr>
<th></th>
<th>RFA</th>
<th>EtOH</th>
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<tbody>
<tr>
<td>Early complete abl</td>
<td>96%</td>
<td>88-92%</td>
</tr>
<tr>
<td>No. sessions</td>
<td>1.1-2.1</td>
<td>2.7-6.5</td>
</tr>
<tr>
<td>Local recurr at 3 y</td>
<td>14-18%</td>
<td>31-33%</td>
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<table>
<thead>
<tr>
<th>Surv (RFA/EtOH) %</th>
<th>2 y</th>
<th>3 y</th>
<th>4 y</th>
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<tbody>
<tr>
<td>- overall</td>
<td>81-98/63-88</td>
<td>74/51-55</td>
<td>74/57</td>
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<tr>
<td>- cancer-free</td>
<td>59-60/43-45</td>
<td>37-43/20-23</td>
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• NSD in adverse events in most studies

*Orlando, Am J GE, 2009
Microwave Ablation for Very Early & Early HCC: *Results*

- **Complete ablation >90%**
  - for tumors >3 cm to ≤5 cm, improved complete ablation rates of 90%
    - superior to RFA

- **Five year survival**
  - ~78%
MWA Compared to RFA for Early Stage HCC

- **Liu, 2018**: retrospective, MWA 126/RFA 436 pts
  - 5 year survival after propensity score matching
  - overall survival signif ↑ MWA 79.3% 68.4%
  - recur-free surv signif ↑ MWA 27.9% 6.4%

*but for*
- solitary HCC ≤3 cm
  - OS survival NSD 81.2% 66.3%
  - RFS survival NSD 37.7% 17.4%

→ Conclusion: RFA inferior to MWA for HCC within Milan criteria but comparable if ≤3 cm
Survival after HCC Thermal Ablation: Poor Prognostic Factors

- Poor liver function
- Poor performance
- Local tumor progression
- Aggressive tumor biology
  - microvascular invasion
  - high AFP
  - poorly differentiated
## Percutaneous RFA and MWA: Complications

### Rates

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<thead>
<tr>
<th></th>
<th>RFA</th>
<th>MWA</th>
<th>(PEI)</th>
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<tbody>
<tr>
<td>major</td>
<td>4.1%</td>
<td>4.6%</td>
<td>(2.7%)</td>
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<tr>
<td>death</td>
<td>0.15%</td>
<td>0.23%</td>
<td>(0.59%)</td>
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### More common types of major complications

- tumor seeding (0.5%)
- hemorrhage (intraperitoneal, hemothorax) (0.45%)
- liver abscess (0.32%)
- ascites (0.27%)
- pleural effusion (0.14%)
- hepatic infarction (0.13%)
- liver failure (0.11%)
- GI perforation (0.11%)
Cryoablation

• Mechanism
  – $\geq 1$ needle(s) w compressed gas $\rightarrow$ expands $\rightarrow$ hypothermia $\rightarrow$ cell destruction from ice crystals, dehydration, & protein denaturation
  – most reliable cell death w $T \leq 20^\circ C$

• Advantages-disadvantages
  – visible ice ball
  – likely less injurious to surrounding critical structures (e.g., bile ducts)
  – possible $\uparrow$ risk hemorrhage
Small central segment 4a HCC
Near central structures, including major bile ducts

Cryoablation
MRI FU: nonviable and no injury.
Cryoablation for HCC

- Limited clinical data

- **Xu, 2018:** SEER database analysis
  - propensity-matched cohort of patients with localized HCC – stage I or II (can be >early stage) – treated with cryoablation or RFA
  - similar
    - overall survival
    - liver cancer specific survival
Irreversible Electroporation

• **Mechanism**
  - 2 or more needles $\rightarrow$ high voltage applic $\rightarrow$ irreversible $\uparrow$ cell membr porosity $\rightarrow$ cell death

• **Compared to thermal ablative methods**
  - more sharply marginated
  - not limited by flowing blood
    - can ablate up to margin of vessels
  - connective tissue unaffected
  - preservation of adjacent structures

• **Insufficient clinical data**
Ablation or Resection
RFA-Resection for Early Stage HCC: *Randomized Trials*

- Inconsistent results

- Comparable OS & recurrence free survival
  - Chen, 2006, solitary $\leq 5$ cm HCC, 1-4 years
  - Feng, 2012, solitary HCC, 1-3 years
  - Fang, 2014, $\geq 1$ tumor $< 3$ cm, 1-3 years
RFA-Resection for Early Stage HCC: Randomized Trials

• Comparable OS but reduced RFS
  – Ng, 2017, solitary tumor \( \leq 5 \) cm or \( \leq 3 \) tumors each \( \leq 3 \) cm
    ✷ NSD OS 1-10 y, trend towards poorer disease-free survival starting at 2 y
    ✷ but NSD for <2 cm and solitary tumors
  – Lee, 2018, solitary 2-4 cm HCC
    ✷ NSD OS 3 & 5 y dis-free survival but RFA had higher local recurrence
    ✷ similar distant intrahepatic and extrahepatic recurrence
RFA-Resection for Early Stage HCC: *Randomized Trials*

- Resection providing superior overall survival
  - Huang, 2010, HCC within Milan
    - OS & local recurrence worse with RFA
    - questions of adequate ablation technique
    - some patients had benign disease

- Post-operative complications and hospital stays typically significantly higher with resection in all studies
RFA-Resection: *Outcomes from US Nat’l Cancer Database (Uhlig, 2018)*

- **18,296 patients**: RFA 8211, resect 10,085
  - variable sizes & # – propensity score matched

- **RFA**: better post-treatment outcomes
  - hospital length of stay – 30 & 90 d mortality
  - unplanned readmissions

- **Full cohort OS better for resection**

- **Overall survival (5 y) comparable in those**
  - w severe liver fibrosis/cirrhosis (37.3%/39.4%)
  - >65 y.o.(21.9%/26.5%)
  - HCC <1.5 cm (49.7%/52.3%)
RFA-Resection for Very Early Stage HCC ($\leq 2$ cm): *Nonrandomized*

- **Huang, 2018**
  - 833 patients from US National Cancer Database
  - RFA 620, resection 213
  - NSD OS 1, 2, 3 years
    - RFA: 90%, 64%, and 47%
    - resection: 89%, 75%, and 62%

- **Yin, 2018**
  - meta-analysis, 5 studies
  - 729 patients
  - OS NSD at 1 y but resection better at 3 and 5 y
MWA-Resection for Early Stage HCC

- Zhang, 2017: meta-analysis
  - 9 studies, 1480 patients, fu 1-184 months
  - no signif difference between MWA & resection
    - overall survival
    - disease-free survival
    - tumor recurrence
    - including subgroup analysis HCC <3 cm
      - HCC >3 cm?
  - MWA significantly
    - shorter operative times
    - less blood loss
    - fewer complications
Ablation + Other Therapies
Combination Therapy for HCC

- Two image-guided Rx’s (ablation + HA Rx)
- Surgery + image guided therapy(ies)
- Above + systemic therapy
- LRT + liver transplantation

- As one planned treatment regimen
- At different times for evolving management of HCC
Chemoembolization + Local Ablation for HCC

- Chemoembolization before thermal ablation can ↑ necrosis volume
  - likely from ↓ heat sink
- No definite benefit for solitary tumors ≤3 cm
  - Shibata, 2009: randomized trial, RFA: NSD
- Beneficial for solitary tumors >3 to ≤5-7 cm
- Uncertain benefit for tumors >5-7 cm
- Possibly beneficial for 2-3 tumors ≤3 cm
Chemoembolization + Local Ablation for HCC Larger than 3 cm

• Peng, 2013
  – randomized trial TACE-RFA (94 pts)/RFA (95)
    ◇ solitary ≤7 cm or up to three ≤3 cm
  – significantly improved overall/recurrence-free survivals

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<thead>
<tr>
<th></th>
<th>TACE-RFA</th>
<th>RFA</th>
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<tbody>
<tr>
<td>1 y</td>
<td>92.6/79.4</td>
<td>85.3/54.8</td>
</tr>
<tr>
<td>3 y</td>
<td>66.6/60.6</td>
<td>59.0/66.7</td>
</tr>
<tr>
<td>4 y</td>
<td>61.8/54.8</td>
<td>45.0/44.2</td>
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Chemoembolization + Local Ablation for HCC Larger than 3 cm

• Lu, 2013
  – meta-analysis randomized trials RFA+TACE or RFA alone: 7 trials
  – RFA+TACE significantly improved survival at 1 and 3 years only for HCC>3 cm

• Abdelaziz, 2017
  – TACE + either RFA (22 pts) or MWA (45 pts)
  – TACE-MWA → better response than TACE-RFA for tumors 3-5 cm
  – no difference in survival rates
82 yo man with probable ethanol cirrhosis & 4.1 cm mid liver biopsy-proven HCC: Chemoembolization & RFA

40 months later
CT: ↓↓ size (1.8 cm) & no enhancement
Combination Local Ablation + Other Therapies for Early Stage HCC

- Lin, 2018: network meta-analysis
  - local tumor progression at 3 years
    - RFA plus radiotherapy and TACE better than resection, although resection better than RFA alone
  - overall recurrence
    - resection best for <3 y
    - RFA + adjuvant therapies better if >3 y
Advantages of Percutaneous Ablation Therapy

- Minimally invasive
- Outpatient or minimal hospital stay
- Low mortality and morbidity
  - less than surgery
- Minimal damage of non-neoplastic liver tissue
- Usually easily repeated
Conclusions

• Hyperthermic ablation: highly effective local control of very early & early stage HCC

• MWA appears better for control of early stage tumors >3 cm

• Local ablation is probably comparable to resection for very early stage HCC (≤2 cm)

• Resection may be better than RFA for HCC>2-3 cm but
  – better results w MWA & LA+transarterial Rx