Chemoembolization For Hepatocellular Carcinoma

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Hepatocellular Carcinoma

- Incidence 2.99 per 100,000 (~10,000 cases per year)
- Most cases associated with cirrhosis
- Accounts for 65% of liver cancer in the U.S
- Between 1976 and 2000, incidence increased by >90%
  - Young white men had an increase of 432%

World Wide Mortality

Deaths per 100,000 people from HCC

El–Serag HB et al. Hepatocellular Carcinoma: Epidemiology and Molecular Carcinogenesis Gastroenterology 2007; 132: 2557
Therapy Options

• Surgery
  – Resection
  – Transplantation
  – Best therapy but < 30 % are candidates

• Systemic chemotherapy
  – Sorafenib (oral multikinase inhibitor)
  – Trial limited to Childs Class A/B

• External Beam Radiation

• Regional therapy
  – Trans-arterial chemoembolization (TACE)
  – Percutaneous tumor ablation
Principles of Regional Cancer Therapy

- Anatomically confined tumor
- Therapeutic advantage
- Technical feasibility
- Clinical benefit
Transcatheter Therapy

- Hepatic artery infusion chemotherapy
  - single/multi-shot, port-a-cath, hypoxic perfusion
  - high response rate, no survival benefit
- Hepatic artery embolization
  - effective for neuroendocrine tumors
- Lipiodol embolization
- Chemoembolization
  - combination of oily HA embo and local chemo
- Yttrium-90 glass microspheres
- Gene therapy
TACE

- First described in 1982
- Injection of a 1:1 mixture of lipophilic chemotherapeutic agents and Lipiodol into the hepatic artery branches supplying a HCC
- Lipiodol acts as a reservoir for the chemotherapy and slowly releases it (1 month)
- Preferential uptake in tumor cells (Raoul 1988)

Chemoembolization Physiology

• Dual blood supply
  – Normal liver
    • 75% portal vein
    • 25% hepatic artery
  – HCC
    • > 95% hepatic artery
    • Hypervascular

• TACE leads to tumor ischemia and local drug concentrations 10-25x over systemic administration
Chemoembolization

Hepatic artery embolization combined with local infusion of chemotherapeutic drugs emulsified in lipiodol

• Aim
  – tumor ischemia $\rightarrow$ necrosis
  – ↑ tumor drug concentrations (10-25x)
  – ↑ dwell time of drug (up to 1 month)
  – ↓ systemic toxicity (85% retained in liver)
Chemoembolic Agents

• Chemotherapeutic agents
  – doxorubicin
  – cisplatin
  – mitomycin C

• Embolic agent
  – lipiodol
  – gelfoam - temporary embolic agent
  – PVA particles - 150-250 micron
Lipiodol
PROPERTIES

• Iodinated ethyl esters of poppy seed oil
• Preferential uptake in tumor cells (Raoul 1988)
  – penetrates tumor cells
• Plastic embolic agent
  – enters portal venules
• Acts as a reservoir for anticancer drugs
  – slow release of drugs from emulsion
• Selectivity for large arteries
Patient Selection

• Unresectable, liver-dominant tumor

• Contraindications
  – to angiography
  – to hepatic embolization
    • encephalopathy
    • >50% liver replaced by tumor
    • AST > 100, LDH > 425, Bili >2
    • biliary obstruction
    • portal vein occlusion (relative)
  – to chemotherapy
    • severe leukopenia or thrombocytopenia
    • renal or cardiac insufficiency
Pretreatment Assessment

- Patient education (PES, complications, etc)
- Cross-sectional imaging
  - MRI or CT
- Labs
  - CBC, PT/PTT, creat, LFT’s, tumor markers
- Diagnostic visceral arteriography
  - portal vein patency, variant anatomy
Technique

• Conventional Angiography
  – Confirms diagnosis (if no biopsy performed or biopsy non-diagnostic)
  – Map arteries for embolization

• Selective embolization
  – Maximizes intra-tumoral concentration of chemotherapy
  – Blocks small arterioles to promote tumor ischemia
  – Minimizes embolization of normal liver
Chemo-embolization

• 10-mL chemotherapy solution (cisplatin 100 mg [Bristol Myers Squibb, Princeton, NJ], doxorubicin 50 mg [Adriamycin; Pharmacia & Upjohn], and mitomycin C 10 mg [Bedford Laboratories, Bedford, OH]) dissolved in ionic contrast (Renografin)
• Mix in 1:1-2:1 volume ratio with Lipiodol (Savage Laboratories, Melville, NY)
Selective Injection

Super-selective Injection
Post TACE Angiogram

No tumor blush on post-treatment angiogram
Hepatocellular Carcinoma
Pre-treatment CT
Typical findings of hepatocellular carcinoma (HCC)
HCC Lipiodol Accumulation

Sequential non-contrast CTs

2 months  8 months  18 months
Clinical Response to TACE

- There is a survival benefit in selected patients with unresectable hepatocellular carcinoma (HCC) successfully treated with TACE.
- Careful patient selection, technique, and follow-up are important to the technical success of TACE and in achieving good outcomes.
- Incomplete embolization is associated with residual tumor at follow-up imaging and poor clinical results.

Bruix J. Gastroenterology 2004; 127: s179
Incomplete Embolization

• Associated with residual tumor at follow-up

• More common when angiography demonstrates:
  – Complex arterial supply (e.g. central lesions)
  – Lesions poorly visualized on angiography
Causes of Incomplete Embolization

• Hypovascular lesions only seen on pre-procedure MRI
  – May be difficult to identify at angiography
  – Lesions may be atypical HCC (hypovascular) or mis-diagnosis
  – Diagnostic Lipiodol injection with follow-up CT

• Hypervascular lesions with poor uptake of chemoembolization
  – Likely to have poor clinical response

• Lesions that are only visible on non-selective injections
  – Multiple vessel supply (common with central lesions)
Dyna CT

- Cone beam CT (CBCT) (Dyna CT, Siemens Medical Solutions) improves tumor visualization during diagnostic angiography
- Helps the operator identify which vessels are supplying a tumor
- Better defines the tumor embolization endpoint by confirming Lipiodol uptake prior to leaving procedure room
Segment V-VIII HCC on MRI

56 y/o with Hepatitis C, cirrhosis and new hypervascular mass
Replaced Right Hepatic Angiogram Demonstrates Tumor Blush
Segment VIII Arteriogram

Tumor blush not visible on conventional angiography
Segment V Artery Dyna CT
Segment VIII Large Volume Dyna CT
Incorporation of Dyna CT into TACE Planning

- Celiac arteriogram
- Common hepatic angiogram in three views
- Selective right and left hepatic angiography (3 views or Dyna Vision)
- Dyna CT of right or left hepatic artery
- Super-selective angiography
- Repeat Dyna CT of segmental arteries as needed
CBCT Sensitivity

• Forty-nine consecutive patients (52 suspicious lesions) were prospectively examined

• Conventional DSA plus CBCT was superior to DSA alone for identifying areas of tumor blush

• In 42 of the 52 lesions (81%), CBCT provided additional useful information for therapeutic decision making

Kakeda S. Usefulness of Cone-Beam Volume CT with Flat Panel Detectors in Conjunction with Catheter Angiography for Transcatheter Arterial Embolization. JVIR 2007; 18: 1508
Follow-up CT Confirms Lipidol Uptake

LV Dyna CT Multi-planar reconstruction

Follow-up CT MPR
Ethiodol uptake

- HCCs with complete uptake of iodized oil after TACE are considered to be completely necrotic
- HCCs with only partial uptake of iodized oil after TACE may have residual viable tumor
- We perform a post embolization Dyna CT or LV Dyna CT on every case

50 y/o with HCC in Segment IV

Gadolinium enhanced T1W axial image
Selective Angiography

Left gastric angiogram demonstrates lesion
Lesion identified on LV Dyna-CT

LV Dyna-CT confirms entire lesion fed by replaced hepatic artery arising from the left gastric artery.
TACE Injection
Post TACE LV Dyna CT

Density is provided by Lipiodol uptake
Area of No Lipiodol Accumulation Adjacent to Tumor

Area of hypo attenuation not identified at time of this study
One Month CT Demonstrates Residual Tumor Enhancement

- Lipiodol in tumor
- Contrast enhancement - Residual tumor
Repeat TACE

Complete filling of tumor with Lipiodol
Repeat LV Dyna-CT

Lipiodol uptake in the tumor is improved

Complete left lobe lateral segment opacification with Lipiodol
CBCT Effect on Outcome

- Initial treatment of 265 tumors in 79 HCC patients using CT-guided TACE
- Overall local recurrence-free rates after a single TACE session at 6, 12, and 36 months were 67%, 49%, and 28%
- With complete lipiodol accumulation confirmed by CBCT, the results were 82%, 68%, and 41%, respectively

Post TACE Dyna-CT and Conventional CT

Incomplete uptake suggests poor outcome

Large volume Dyna-CT immediately post embo

Conventional unenhanced CT 4 weeks later
Chemoembolization
COMPLICATIONS

• Major (3 - 4 %)
  – hepatic insufficiency or infarction
  – biliary necrosis
  – hepatic abscess
  – tumor rupture
  – surgical cholecystitis
  – nontarget embolization of gut

• Other (~ 1%)
  – renal insufficiency
  – anemia requiring transfusion
Gallbladder Embolization

pre

post
Postprocedure / Follow up

• Posttreatment care
  – manage post-embolization syndrome (supportive)
  – avg hospital stay: 1-2 days, discharge abx/meds

• Follow up
  – repeat chemoembolizations at ~ monthly intervals: avg 2-3 sessions
  – assess response/recurrence at 1/3/6/12 months by lab tests and cross-sectional imaging
Hepatoma - Survival

• Untreated
  – median survival 3-6 months
  – 0% at 1 year

• Surgical resection
  – 1/2/3 yr survival → 60/50/40 %

• Systemic chemo
  – 70 % response—tumor stabilization
  – Impact on survival similar to TACE
Results of Chemoembolization
HEPATOMA

• Response rate to chemoembolization
  – ↓AFP and/or tumor volume → 60 - 83 %

• Cumulative survival (n=800)

  - 1yr → 72 % (55 - 76 %)
  - 2yr → 53 % (33 - 64 %)
  - 3yr → 40 % (15 - 51 %)
Results of Chemoembolization HEPATOMA

- Bronwicki et al, Cancer 1994
- Simultaneous case-control study

<table>
<thead>
<tr>
<th>survival</th>
<th>chembo</th>
<th>support</th>
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<tr>
<td>1yr</td>
<td>64 %</td>
<td>18 %</td>
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<tr>
<td>2yr</td>
<td>38 %</td>
<td>6 %</td>
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<tr>
<td>3yr</td>
<td>27 %</td>
<td>5 %</td>
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<tr>
<td>4yr</td>
<td>27 %</td>
<td>0 %</td>
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RCT
HONG KONG DATA

• 387 consecutive patients with HCC
  – 108 patients sent for surgery
  – 199 excluded (vascular, mets, poor function)
  – 80 patients entered into study
    • 40 control / 40 TACE

• TACE
  – 192 courses of therapy (1 - 15, median 4.5)
  – Cisplatinum/Lipiodol & 1mm gelatin-sponge particles
  – Median chemo volume  20 ml (2 - 60 ml)
  – 38/40 had treatment stopped
    • progressive dx/liver failure/death/refusal/AE/thrombosis
RCT
HONG KONG DATA

• Survival at 1, 2, & 3 years
  – TACE 57%, 31%, and 26%
  – Control 32%, 11%, and 3%

Fig. 2. Probability of survival in patients treated with chemoembolization and in patients of the control group (log-rank test, $P = .002$).
RCT
BARCELONA DATA

• Multicenter trial
• Strict selection with aggressive retreatment
• Mild hepatic dysfunction (Okuda I, II)
• Primarily white patients with Hepatitis C
• Stopped after 4 years for statistically significant results
RCT
BARCELONA DATA

• Evaluated 903 patients with newly diagnosed HCC
  – Excluded 791 patients
  – Randomized 112
    • 37 Bland embolization
    • 40 TACE
    • 35 Control
RCT
BARCELONA DATA

• Survival at 1, 2, & 3 years
  – TACE 82%, 63%, & 29%
  – Bland embo 75%, 50%, & 29%
  – Control 63%, 27%, & 17%

<table>
<thead>
<tr>
<th>Deaths</th>
<th>Embolisation (n=37)</th>
<th>Chemo-embolisation (n=40)</th>
<th>Control (n=35)</th>
<th>Total (n=112)</th>
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<tbody>
<tr>
<td>Cause of death</td>
<td>25 (67%)</td>
<td>21 (52%)</td>
<td>25 (71%)</td>
<td>71 (63%)</td>
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<td>Tumour progression</td>
<td>20</td>
<td>14</td>
<td>23</td>
<td>57</td>
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<tr>
<td>Hepatic failure with stable disease</td>
<td>4</td>
<td>5</td>
<td>2</td>
<td>11</td>
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<tr>
<td>Other</td>
<td>1*</td>
<td>2†</td>
<td>0</td>
<td>3</td>
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</table>

*Neoplasm of lung. †Neoplasm of tongue and treatment-related death (septic shock).
Figure 3: Survival curves of the chemoembolisation and control groups
Percutaneous Tumor Ablation

• Advantages
  – spares functioning liver tissue
  – easily repeatable
  – can treat multiple lesions
  – outpatient procedure
  – low cost (ethanol)

• Disadvantages
  – size limitations
  – tissue inhomogeneity
Percutaneous Tumor Ablation

• Chemical
  – ethanol injection
  – acetic acid
  – hot saline

• Thermal
  – radiofrequency
  – interstitial laser photocoagulation
  – microwave coagulation
  – cryotherapy
Percutaneous Ethanol Injection

• Widely used to treat hepatoma, not effective against colorectal mets
• Coagulation necrosis, fibrosis, cell death
• Prognostic factors
  – solitary lesion < 3 cm
  – Child class A
  – initial AFP level < 200 mcg/L
Percutaneous Ethanol Injection
## Percutaneous Ethanol Injection

### HEPATOMA SURVIVAL

- Livrahgi et al, Radiology 1995
- Lencioni et al, Radiology 1995

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<thead>
<tr>
<th></th>
<th>1yr</th>
<th>2yr</th>
<th>3yr</th>
<th>4yr</th>
<th>5yr</th>
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<tr>
<td>Child A &lt;3cm</td>
<td>99 %</td>
<td>96 %</td>
<td>86 %</td>
<td>69 %</td>
<td>48 %</td>
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<tr>
<td>Child C &lt;5cm</td>
<td>64 %</td>
<td>12 %</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>AFP&lt;200</td>
<td>100%</td>
<td>_</td>
<td>69 %</td>
<td>_</td>
<td>32 %</td>
</tr>
<tr>
<td>AFP&gt;200</td>
<td>77 %</td>
<td>_</td>
<td>57 %</td>
<td>_</td>
<td>29 %</td>
</tr>
</tbody>
</table>
Radiofrequency Ablation

- RF energy → Ion agitation → Friction → Heat → Coagulation necrosis

- Procedure:
  - Image-guided (US/CT/MR) percutaneous electrode placement/real-time monitoring
  - Percutaneous/laparoscopic/open
  - Conscious sedation/anesthesia
  - Prophylactic ABX
  - Grounding pads
Radiofrequency Ablation

- Various electrode designs
  - monopolar/bipolar
  - multiprobe arrays/ hooked arrays
  - cluster probes/internally cooled electrodes
- Lesions > 4-5 cm: overlapping ablations
- Try to obtain 1 cm margins
- Temp/impedance/time monitored depending on manufacturer
Radiofrequency Ablation

RESULTS

• Local recurrence 2-40% at 1 year
• Survival
  – 1 yr  96%
  – 3 yr  64%
  – 5 yr  40%
Dome lesions
Follow-up

• CT or MR
• May get immediate CT/MR
• MR/CT at 1, 3, 6, mo
• Treat any evidence of recurrence or residual disease
• Post Ablation syndrome
Radiofrequency Ablation

COMPLICATIONS

• De Baere et al, AJR 2003, n=350
  – Total AE 10.6%, Mortality 1.4%
  – Abscess n=7 (bilioenteric anastomosis)
  – Pleural effusion n=5
  – Skin burn n=5
  – Pneumothorax n=3
  – Subcapsular hematoma n=2
  – Hemoperitoneum n=1
  – ARF n=1
  – Needle-tract seeding n=1
Combination Therapy

• Chemoembolization / perc. ethanol injection
  – Best for large solitary lesions
  – Randomized trials: chembo/PEI vs repeat chembo
    • significantly improved response and survival

• HA balloon occlusion or embo / RF ablation
  – Rossi et al, Radiology 2000
  – Hepatoma nodules 3.5-8.5 cm
  – 1 yr survival 87 %
Dome Lesion Not Seen with US or CT
Conclusions

- Chemoembolization is effective and well tolerated for palliation of hepatoma and hypervascular metastases
- There are many unanswered questions
  - optimal technique
  - role in neoadjuvant therapy
  - relative role to other treatment modalities
  - role of ablation techniques/combination
Conclusions

• Careful technique with thorough embolization is essential to achieving satisfactory results

• In high risk patients, super selective embolization should be performed

• CBCT (Dyna CT) improves our ability to localize and selectively embolize HCC

• Large volume Dyna CT improve the diagnostic utility of the routine post TACE CBCT
Conclusions

• Percutaneous tumor ablation appears to be efficacious for treatment of HCC and mets <4-5cm

• Promising procedures evolving
  – combination of embolization and ablation
  – portal vein embolization
  – radioembolization, gene therapy, ...

• Controlled studies are needed