Lipiodol: Clinical Credentials, Back to Basics and Insight into the Future

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Professor of Radiology and Oncology
Yale University School of Medicine
New Haven, Connecticut
Chemoembolization: General Approach

Chemoembolization mixture administered to carcinoma through catheter.
Why Intraarterial Therapy?
Preferential arterial feeding of liver tumor

- **Tumor** ± 100% arterial
- Surrounding liver (30% arterial, 70% portal)
- Some tumors have more arteries (hypervascular)

Rationale for Hepatic Artery Injection

Hepatic artery injection: Tumor targeting

Portal vein opacification: Healthy liver sparing
How Can We Exploit These Properties to Maximize Drug Delivery?

Rationale for Hepatic Arterial Infusional Therapy
Properties of Ideal Agents for Intraarterial Hepatic Delivery

- Metabolized by liver during first pass (FUDR)
  - High local concentration + minimal systemic toxicity
  - FUDR: 94-99% extracted by liver on first-pass when given IA (7-9% when given IV)
- Steep dose-response curve = IDEAL
- High hepatic clearance = IDEAL
From HAI to Chemoembolization

ROLE OF LIPIODOL (Konno et al, Cancer 1990)

1. Lipiodol administered IA selectively remained in solid tumors
2. Lipiodol not easily removed from normal capillaries and tumor neovasculature

LIPIODOL + CHEMOTHERAPY

1. Lipiodol as a drug carrier?
2. Anti-cancer agents MUST BE SOLUBLE in Lipiodol
   BE STABLE in it
   SEPARATE gradually

Anti-cancer agents selectively remain in the tumor (14C-labeled doxorubicin)
Targeting Cancer Chemotherapeutic Agents by Use of Lipiodol Contrast Medium

Konno T. Cancer. 1990 Nov 1;66(9):1897-903

<table>
<thead>
<tr>
<th>Form of ADR</th>
<th>Radioactivity (dpm/g) of ADR at periods from injection to death*</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Immediately after</td>
<td>6 hours</td>
</tr>
<tr>
<td><strong>14C-labeled ADR/Lipiodol†</strong></td>
<td><strong>28,066</strong></td>
<td><strong>17,546</strong></td>
</tr>
<tr>
<td></td>
<td>25,806</td>
<td>9000</td>
</tr>
<tr>
<td></td>
<td>24,471</td>
<td>8947</td>
</tr>
<tr>
<td></td>
<td>20,358</td>
<td>5340</td>
</tr>
<tr>
<td><strong>14C-labeled ADR/aqueous solution plus Lipiodol</strong></td>
<td>15,309</td>
<td>1157</td>
</tr>
<tr>
<td></td>
<td>14,668</td>
<td>721</td>
</tr>
<tr>
<td></td>
<td>12,631</td>
<td>571</td>
</tr>
<tr>
<td></td>
<td>9606</td>
<td>431</td>
</tr>
</tbody>
</table>

* Two specimens from one rabbit were measured.

† Persistent high radioactivities were observed in rabbits that received 14C-labeled ADR/Lipiodol.
Chemoembolization: Importance of Lipiodol (emulsification)

**Iodized oil (Ethiodol, Lipiodol):**
- Not cleared by cancer cells (retention)
- OIL = Drug carrier + Tumor seeking + Embolic agent
  - Occlusion of hepatic arterioles at 30 µm level
  - Enters portal venules through arterioporal shunts
Lipiodol Chemoembolization
Seoul National University

Pumping method

Emulsion
Lipiodol Uptake Improved with Water in Oil Emulsion: Selective Retention in Tumors

Drug in oil emulsion with a 3 way stopcock method:
- Lower volume of drug than Lipiodol
- Push drug towards Lipiodol

30 push and pull = 30-120 μm droplets (70% = 70-100 μm)
Lipiodol Uptake Improved with Water in Oil Emulsion
Lipiodol Chemoembolization

HA

PV
Rationale for Lipiodol

SELECTIVITY FOR TUMOR  
Tumor vs liver X3 to X10  
emulsion of Lipiodol I $^{125}$

(de Baere T, Radiology. 1996)
Rationale for Lipiodol

PHARMAMOKINETIC BENEFIT

Doxorubicin (labeled iodine 131) : Hepatic Arterial Injection – Chemolipiodol – LipiodolTACE

- Serum doxorubicin level after injection
- Scintigraphy of labeled doxorubicin
  liver / liver+lungs+abdomen ratio
  tumor / nontumorous liver ratio,
doxorubicin half-life in tumor

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**Serum doxorubicin level**

☐ : HAI (Hep. Artery Injection)

☑ : Chemolipiodol

Δ : Chemoembolization

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<table>
<thead>
<tr>
<th>Serum doxorubicin</th>
<th>HAI doxo</th>
<th>Chemolipiodol</th>
<th>TACE</th>
</tr>
</thead>
<tbody>
<tr>
<td>C max (ng/ml)</td>
<td>2100 ± 950</td>
<td>960 ± 300*</td>
<td>460 ± 240*†</td>
</tr>
<tr>
<td>AUC∞ (ng/ml/h)</td>
<td>1430 ± 470</td>
<td>1400 ± 770</td>
<td>740 ± 717</td>
</tr>
<tr>
<td>AUC∫ (ng/ml/h)</td>
<td>298 ± 100</td>
<td>230 ± 50*</td>
<td>89 ± 25*†</td>
</tr>
</tbody>
</table>

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**Table 2**

<table>
<thead>
<tr>
<th></th>
<th>HAI doxo</th>
<th>Chemolipiodol</th>
<th>TACE</th>
</tr>
</thead>
<tbody>
<tr>
<td>L/L + 1 + A (%)</td>
<td>28 ± 1</td>
<td>36 ± 5</td>
<td>63 ± 7*†</td>
</tr>
<tr>
<td>T/NT ratio</td>
<td>1 ± 0</td>
<td>1.5 ± 0.1†</td>
<td>4.7 ± 0.5*†</td>
</tr>
<tr>
<td>t ½ T (days)</td>
<td>0.7 ± 0.1</td>
<td>1.3 ± 0.2</td>
<td>2.6 (n = 1)</td>
</tr>
</tbody>
</table>

L/L + 1 + A: liver/liver + lungs + abdomen binding ratio; T/NT ratio: tumorous liver/nontumorous liver binding ratio; t ½ T: half-life in tumorous tissue.

* Significantly different from Grade 2.
† Significantly different from Grade 1.

(Raoul JL, Cancer 1992; 70, 585-590)
Rationale for Lipiodol: Arterio-portal Shunt

Portal Vein Pressure, after injection of Lipiodol in the hepatic artery

(de Baere T, Radiology. 1995; 194:165-170)
Hepatocellular Carcinoma: Treatment with Intraarterial Iodized Oil with and without Chemotherapeutic Agents

Complete tumor necrosis on resection specimen:

<table>
<thead>
<tr>
<th></th>
<th>Main Tumor</th>
<th>Daughter Nodules</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipiodol only (n=6)</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Dox/Lipiodol (n=15)</td>
<td>13%</td>
<td>6%</td>
</tr>
<tr>
<td>Dox/Lipiodol/Gelfoam (n=10)</td>
<td>83%</td>
<td>53%</td>
</tr>
</tbody>
</table>

\{ ns \}

\{ p < 0.01 \}

Takayasu K, Radiology 1987;163:345-51
# Rationale for Lipiodol-TACE

## Level 1 evidence in randomized control trials for intermediate stage HCC

<table>
<thead>
<tr>
<th>RTC, TACE/TAE vs conservative</th>
<th>112 unresectable HCC</th>
<th>Overall survival (OS) sequential analysis</th>
<th>Study stopped at 9th sequential inspection: TACE better than control (HR of death 0.47; 95% CI 0.25 – 0.91; p = 0.025)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>37 TAE</td>
<td>TAE (n=37)</td>
<td>TACE (n = 40) Control (n = 35)</td>
</tr>
<tr>
<td></td>
<td>40 TACE</td>
<td></td>
<td>Death</td>
</tr>
<tr>
<td></td>
<td>35 control</td>
<td></td>
<td>25 (67%) 21 (52%) 25 (71%)</td>
</tr>
<tr>
<td></td>
<td>Doxorubicin</td>
<td>1 year</td>
<td>75% 82% 63%</td>
</tr>
<tr>
<td></td>
<td>10 mL lipiodol</td>
<td>2 years</td>
<td>50% 63% 27%</td>
</tr>
<tr>
<td></td>
<td>Mean of 2.8 courses of TACE/patient</td>
<td></td>
<td>Treatment allocation was the only variable independently related to survival (Odds Ratio 0.45; 95% CI 0.25 – 0.81; p=0.02)</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>RCT TACE vs. symptomatic treatment</th>
<th>79 unresectable HCC</th>
<th>Survival rates</th>
<th>192 TACE sessions; median 4.5; range 1 – 15 per patient</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>40 TACE; 39 control</td>
<td>Tumor response</td>
<td>Survival TACE Control p</td>
</tr>
<tr>
<td></td>
<td>I Mar 1996 – Oct 1997</td>
<td></td>
<td>(n = 40) (n = 39)</td>
</tr>
<tr>
<td></td>
<td>Cisplatin</td>
<td></td>
<td>1 year 57% 32%</td>
</tr>
<tr>
<td></td>
<td>Mean of 4.5 courses of TACE/patient</td>
<td></td>
<td>2 years 31% 11% <strong>0.002</strong></td>
</tr>
<tr>
<td></td>
<td>emulsion of cisplatin with Lipiodol in a volume ratio of 1 to 1.</td>
<td></td>
<td>3 years 26% 3%</td>
</tr>
</tbody>
</table>

Multivariate Cox analysis:
Relative risk of death TACE vs. control: 0.49; 95% CI 0.29 – 0.81; p =0.006
EASL–EORTC Clinical Practice Guidelines: Management of hepatocellular carcinoma

Levels of evidence:

1. Adjuvant therapy after resection
   - LDLT
   - Internal radiation
   - OLT-extended
   - Neo-adjuvant therapy in waiting list

2. Resection
   - RF (<5 cm)
   - RF/PEI (<2 cm)

3. Down-staging
   - External/palliative radiotherapy

Grade of recommendation:

1 (strong)
2 (weak)
Survival: Oil +/- Particles
Lipiodol chemoembolization (solid line) vs. Lipiodol without embolization (dotted line) matched by propensity score

HR 0.70 [0.63-0.76]  
p=0.0001
Prospective nonrandomized observational cohort study over 8 years.
Among 11,030 patients with HCC
8,507 TACE
2,523 iodized oil + anticancer agent

With embolization
Without embolization

HR 0.70 [0.63-0.76] p=0.0001
cTACE: The Technique Matters

- Selectivity: Microcatheter placement
- Endpoint: Angiography (2-5 heart beats)
Rationale for Lipiodol: Arterio-portal Shunt

Grade 0
No visualization

Grade 1
Visualization adjacent to the tumor

Grade 2
Visualization in the whole or extending embolized area

(Miyayama S 2007 JVIR 18:365-376)
Rationale for Lipiodol:
Arterio-portal Shunt (peribiliary plexus)
Long lasting uptake of lipiodol

Local Recurrence / Portal Vein Visualization (by a Single TACE Session)

Local recurrence rates

292 HCCs (≤5cm) in 174 pts, 2002.10—2006.12

Grade 0 (n=32, 11%)
66%
74%
P <0.0001*

Grade 1 (n=122, 42%)
38%
42%
42%
P =0.0150*

Grade 2 (n=138, 47%)
16%
16%
16%
19%
19%
P =0.0150*

*Generalized Wilcoxon test

Interventional Oncology: Imaging Tools for Improved Tumor Targeting
Intraarterial Therapy for Liver Cancer

1. Can we see the tumor every time?

2. Can we target & reach the tumor every time?

3. If so can we treat it successfully?

4. What about assessing tumor response?

NIH/NCI R01 CA160771  $2.74 M X5 years
“AJAX” Project at Johns Hopkins
EmboGuide – New Guidance System = more confidence in selective therapy

EmboGuide software to plan optimal access to tumor and injection locations
Usefulness of cone beam CT
## Meta-Analysis of TACE for HCC

### Study Patients Odds ratio (95% CI)

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lin, Gastroenterology 1998</td>
<td>63</td>
<td>0.53</td>
<td>0.32–0.89</td>
<td>0.017</td>
</tr>
<tr>
<td>GETCH, NEJM 1995</td>
<td>96</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bruix, Hepatology 1998</td>
<td>80</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pelletier, J Hepatol 1998</td>
<td>73</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lo, Hepatology 2002</td>
<td>112</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>503</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Expected median OS vs. BSC: ≈ 20 vs. 16 months

3-year overall survival (OS): 26% – 29%

Outcome assessed = 2-year survival

- Child-Pugh B <10% of all patients
- Around 10% had tumor portal vein thrombosis
- In most trials no selective TACE

Treatment of HCC

Transarterial chemoembolization (TACE)

- Optimal candidates for TACE: Patients with preserved liver function (Child–Pugh A) without extrahepatic spread or vascular invasion (BCLC B)
- Median survival: 16 months without treatment
  > 24 months with TACE
- Contraindications: Poor liver function, compromised portal flow, extrahepatic disease, vascular invasion, presence of cancer related symptoms
- What about TACE in presence of partial portal vein thrombosis? Depends who you believe
  - Treat with sorafenib
  - Emerging data on combination sorafenib and TACE
Lack of Response after Initial Chemoembolization for Hepatocellular Carcinoma: Does It Predict Failure of Subsequent Treatment?\(^1\)

- Retrospective study at Johns Hopkins Med Center
  - 116 consecutive patients with unresectable HCC who underwent at least two TACE procedures
  - Tumor response using MRI: EASL and mRECIST
  - Survival rate for each patient calculated and correlated with response
  - KM estimates used to construct survival curves

Lack of Response after Initial Chemoembolization for Hepatocellular Carcinoma: Does It Predict Failure of Subsequent Treatment?¹

TACE also in BCLC C-Patients?

Pinter et al., Radiology 2012; 263: 590

- 228 TACE-patients, Medical University of Vienna
- 144 Sorafenib-Patients, 11 Centers Austria
  - Exclusion: OLT, resection, TACE (Sorafenib-group)
  - BCLC C, retrospective: 34 TACE vs. 63 Sorafenib

Whole Cohort

Survival T vs. S: 9.2 vs. 7.4 months, p=0.377

CP A + MVI, EHS (T 15 vs. S 26 pat.)

14 vs. 9.7 months, p=0.49
Lipiodol Retention: Possible Biomarker of Tumor Response?

Degree of Lipiodol uptake predictive of efficacy

Assuming that retained lipiodol within the tumor = necrotic tissue

(Takayasu, K. AJR2000;175:699-704)
Prospective Study of Transcatheter Arterial Chemoembolization for Unresectable Hepatocellular Carcinoma: An Asian Cooperative Study between Japan and Korea

99 HCC ineligible for curative treatment, without main PVT
PS = 0–2; Child-Pugh A or B
- Epirubicin = 45 mg/body [10–70]
- Doxorubicin = 40 mg/body [10–60]
- Lipiodol = 5 mL [1.5–20]

2-year OS : 75.0% (95% CI, 65.2%–82.8%)
Med. OS : 3.1 years
Med. TTP : 7.8 months
mRECIST : CR:42%, PR=31%,
Grade 3–4 toxicities :
    ALT level 36%,
    AST level 35%,
    thrombocytopenia 12%,
    abdominal pain in 4%

Ikeda M. J Vasc Interv Radiol 2013; 24:490–500
"For comparison with the results of Llovet et al., the eligibility criteria except age and cardiac ejection fraction, and study endpoints were set to be same"
Conclusions

- Lipiodol: Track record and credentials established
- TACE officially in all the treatment guidelines (Gold standard)
- Only level 1 evidence for any IA therapy
- Technical considerations critical (superselective TACE, water in oil emulsion, CBCT imaging for visualization and targeting)
- Future: Can we design an even better and more effective oily medium? Improved drug retention? Increased potency?
## Major Complications of Hepatic Arterial Chemoembolization

<table>
<thead>
<tr>
<th>Major complication</th>
<th>Reported rate (%)</th>
<th>Suggested threshold (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abscess with biliary enteric anastomosis/biliary stent/sphincterotomy</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>Post-embolization syndrome requiring extended stay or readmission</td>
<td>4.6</td>
<td>10</td>
</tr>
<tr>
<td>Liver failure</td>
<td>2.3</td>
<td>4</td>
</tr>
<tr>
<td>Death within 30 days</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Abscess with functional sphincter of Oddi</td>
<td>&lt;1</td>
<td>2</td>
</tr>
<tr>
<td>Biloma requiring percutaneous drainage</td>
<td>&lt;1</td>
<td>2</td>
</tr>
<tr>
<td>Surgical cholecystitis</td>
<td>&lt;1</td>
<td>1</td>
</tr>
<tr>
<td>Pulmonary arterial oil embolus</td>
<td>&lt;1</td>
<td>1</td>
</tr>
<tr>
<td>Gastrointestinal hemorrhage/ulceration</td>
<td>&lt;1</td>
<td>1</td>
</tr>
<tr>
<td>Iatrogenic dissection preventing treatment</td>
<td>&lt;1</td>
<td>1</td>
</tr>
</tbody>
</table>

Brown et al. 2006. Quality improvement guidelines for transhepatic arterial chemoembolization, embolization and chemotherapeutic infusion for hepatic malignancy.

(Brown D J Vasc Interv Radiol 2012; 23:287–294)
20 patients
38% OS at 1 year (patient without portal vein thrombosis)

1989: Ohnishi K, (Radiology; 170: 783-786)
100 patients
53.8% OS at 1 year, 33.3 OS at 2 years

40 & 39 patients
35 - 39% OR
26 - 63% OS at 2 years

2013: Ikeda M, (JVIIR; 24: 490-500)
99 patients
OR: 73%
2-year OS: 75% (95% CI, 65.2%-82.8%), Med OS: 3.1 years
**Lipiodol-TACE, is the only treatment that demonstrated superiority to supportive care in intermediate HCC**

- No comparative study with OS endpoint
- Comparative study (response endpoint) failed to demonstrate superiority (non-significant results in a superiority trial is not a proof of equivalence)

**Lipiodol-TACE**

- Demonstrates a pharmacokinetic benefit
- Has the unique advantage of tumor selectivity
- Has the unique advantage of reaching peritumoral portal branches
- Provides long lasting tagging of tumors: helps in combine treatment
- Could be improved on drug used, formulation of emulsion & embolic
E1208

A Phase III Randomized, Double-Blind Trial of Chemoembolization with or without Sorafenib in Unresectable Hepatocellular Carcinoma (HCC) in Patients with and without Vascular Invasion
**ECOG Phase III Study: TACE With or Without Sorafenib**

- Phase III randomized, double-blind trial of TACE with or without sorafenib in patients with unresectable HCC
- Status: recruiting
- Contact information: ECOG Group Chair’s Office

**Eligibility criteria**
- Unresectable HCC
- Child–Pugh A or B7
- ECOG PS 0–1

**Exclusion criteria**
- EHS
- Main portal vein invasion
- Ascites

**Randomization**
1:1 (n = 400)

**Treatment arms**
- Sorafenib 400 mg b.i.d. and TACE (doxorubicin, mitomycin C and cisplatin)
- Placebo and TACE (doxorubicin, mitomycin C and cisplatin)

**Primary end-point**
- PFS

**Secondary end-points**
- OS
- Toxicity

ECOG Phase III Study: TACE With or Without Sorafenib

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Sorafenib 400 mg b.i.d. and TACE (doxorubicin, mitomycin C and cisplatin)

Placebo and TACE (doxorubicin, mitomycin C and cisplatin)

Primary end-point
- PFS

Secondary end-points
- OS
- Toxicity

Combining loco-regional and systemic therapies: A top priority for clinical research in HCC

Design and Endpoints of Clinical Trials in Hepatocellular Carcinoma

Josep M. Llovet, Adrian M. Di Bisceglie, Jordi Bruix, Barnett S. Kramer, Riccardo Lencioni, Andrew X. Zhu, Morris Sherman, Myron Schwartz, Michael Lotze, Jayant Talwalkar, Gregory J. Gores; for the Panel of Experts in HCC-Design Clinical Trials

- **Early HCC**: Surgery / Ablation
- **Intermediate HCC**: TACE
- **Advanced HCC**: Sorafenib

**Standard of care**
- **1st line**: Placebo vs Drug
- **2nd line**: Placebo vs Drug

**Primary treatment**
- **TACE vs TACE + drug**
- **Sorafenib vs Sorafenib + drug**
Thank you
Figure 5 Comparison of outflow ratio (area under plasma concentration curve [AUC<sub>0-60</sub>] / total infused dose of anticancer drug) for cisplatin, mitomycin and epirubicin among the hepatic arterial infusion (HAI), HAI with lipiodol (Lp-HAI) and transcatheter arterial chemoembolization with Lp plus particles (Lp-TACE) groups.
Roles Played by Chemolipiodolization and Embolization in Chemoembolization for Hepatocellular Carcinoma: Single-Blind, Randomized Trial

Number at risk

<table>
<thead>
<tr>
<th>Arm</th>
<th>Number</th>
<th>Time after randomization (months)</th>
<th>Median survival, months (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm 1</td>
<td>122</td>
<td>55, 30, 26</td>
<td>10.5 (8.3 to 12.8)</td>
</tr>
<tr>
<td>Arm 2</td>
<td>121</td>
<td>54, 33, 29</td>
<td>10.1 (6.2 to 14.0)</td>
</tr>
<tr>
<td>Arm 3</td>
<td>122</td>
<td>32, 20, 18</td>
<td>5.9 (4.2 to 7.6)</td>
</tr>
</tbody>
</table>

Roles Played by Chemolipiodolization and Embolization in Chemoembolization for Hepatocellular Carcinoma: Single-Blind, Randomized Trial

Triple arm RCT with 122 Hcc patients per arm
- tumor size med. 10.9 cm (7–22), 100% CHILD A, 1/3 BCLCC stage C & 2/3 B

- Lobaplatin (50 mg) / epirubicin (50 mg) / mitomycinC (6 mg) + Lipiodol (10 ml) + gelfoam
- Lobaplatin (50 mg) / epirubicin (50 mg) / mitomycinC (6 mg) + Lipiodol (10 ml)
- Epirubicin (50 mg) + Lipiodol (10 ml) + gelfoam

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Arm 1, n = 122</th>
<th>Arm 2, n = 121</th>
<th>Arm 3, n = 122</th>
<th>P</th>
<th>Arm1 vs Arm 2</th>
<th>Arm1 vs Arm 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival, months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>10.5</td>
<td>10.1</td>
<td>5.9</td>
<td></td>
<td>.20†</td>
<td>&lt;.001†</td>
</tr>
<tr>
<td>95% CI</td>
<td>8.3 to 12.8</td>
<td>6.0 to 14.0</td>
<td>4.2 to 7.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to radiological progression,</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>3.6</td>
<td>3.1</td>
<td>3.1</td>
<td></td>
<td>.89†</td>
<td>.071†</td>
</tr>
<tr>
<td>95% CI</td>
<td>2.4 to 4.8</td>
<td>1.6 to 4.5</td>
<td>2.0 to 4.2</td>
<td></td>
<td></td>
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<tr>
<td>Tumor response evaluation, %</td>
<td></td>
<td></td>
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<tr>
<td>Objective response</td>
<td>45.9</td>
<td>29.7</td>
<td>18.9</td>
<td></td>
<td>.009†</td>
<td>&lt;.001†</td>
</tr>
</tbody>
</table>

Single-center Comparison of Three Chemoembolization Regimens for Hepatocellular Carcinoma

122 patients with 228 treatments:
- 59 with Doxorubicin / Lipiodol + Gelfoam
  - 51% OR / 37% PD
- 30 with Cisplatin-Adriamycin-Mitomycin / Lipiodol
  - 81% OR / 13% PD
- 33 with Doxorubicin Eluting Beads
  - 84% OR / 9% PD

No differences in TTP, and less treatment session in DEB and CAM group.

(Petrucci NJ. 2013 J Vasc Interv Radiol; 24:266–273)
Take home message 1

- A non-significant result NEVER implies that the treatments are EQUALLY GOOD.
- One can NEVER prove that treatments are EQUALLY GOOD.
- If we believe that 2 treatments are EQUALLY GOOD, then another design is needed ⇒ EQUIVALENCE TRIAL.
Take home messages

- **Non-significant result** with a superiority trial is **NOT** a proof of equality.
- Goals for the three designs are different:
  - **Superiority trial**: (say) E is **better** than C
  - **Equivalence trial**: E is **not too different** from C
  - **Non-inferiority trial**: E is **not much** worse than C

- (Equivalence and) non-inferiority depend on **choices of the trialist**:
  - Interval of clinical (equivalence) non-inferiority
  - 90% ⇔ 95% C.I.

- **NI trials**
  - **Make life complicated** ⇒ if possible use placebo-controlled RCT
  - **Unethical?** (Garattini & Bertele, The Lancet, 2007)
Tips for reading (NI trials)

- Look carefully at the definition of non-inferiority. This is of crucial importance for the appreciation of the result.
- Check if definition of non-inferiority is well justified for a clinical viewpoint.
- When comparing non-inferiority studies, check that definition of NI is the same
- Check the conduct of the trial. All aspects which reduce the quality of the trial will help “showing” not-inferiority!
- Non-inferiority CAN NOT be defined/claimed a posteriori!