Unresectable Hepatocellular Carcinoma: Randomized Controlled Trial of Transarterial Ethanol Ablation versus Transcatheter Arterial Chemoembolization

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Hepatocellular carcinoma (HCC) is one of the most common solid malignancies. Has tripled in incidence in the past 2 decades in the United States.

Transarterial therapy has been playing an important role in the treatment algorithm for:

- patients with multifocal or large intrahepatic lesions
- who are not eligible for surgical resection, transplantation, or local ablative therapy
Background

- Transarterial therapy:
  - transcatheter arterial chemoembolization (TACE),
  - bland embolization (5),
  - radioembolization
  - transarterial ethanol ablation (TEA) (7–9)

- TACE is the only one that has been proved to be of survival benefit, as opposed to best supportive care, in randomized controlled trials (RCTs) (10–12)
TEA is a hybrid of bland embolization and chemical ablation.

The treatment involves the use of:
- ethiodized oil (Lipiodol Ultrafluide; Guerbet, City, France)
- ethanol (dehydrated alcohol[absolute alcohol], Martindale Pharmaceuticals, Romford, United Kingdom),

which are mixed in a 2:1 ratio by volume to form a clear, champagne-like solution of medium viscosity.
- Ethanol produces long-lasting embolization of the arterioles and portal venules by causing endothelial damage and thrombosis, thereby leading to infarction of the affected tissue (14)

- Tissue ischemia resulting from embolization enhances the diffusion of ethanol from the tumor vasculature to the tumor cells, and the ablative effect of ethanol is synergistic to tissue ischemia to achieve complete tumor necrosis (16,17)
Objective

To compare the treatment effectiveness of TEA and TACE for patients with unresectable HCC
Materials and Methods

- Patient recruitment took place between July 2007 and May 2011.
- followed until the date of analysis in September 2012.

- The primary outcome was overall survival.

- The secondary outcomes were:
  - time to progression (TTP),
  - progression-free survival (PFS),
  - tumor response
  - treatment-related toxicity.
Assessed for eligibility (n=125)
- Excluded (n=27)
  - Not meeting inclusion criteria (n=21)
  - Declined to participate (n=6)

Randomized (n=98)

Enrollment

Allocated to TEA (n=49)
- Received TEA (n=45)
- Did not receive TEA (n=4)
  Reasons: violation of eligibility criteria due to occlusion of artery (n=1), bleeding esophageal varices (n=1), hepatic encephalopathy (n=1), tumor size 25cm (n=1)

Allocated to TACE (n=49)
- Received TACE (n=45)
- Did not receive TACE (n=4)
  Reasons: refuse study and default follow-up (n=1); confirmed not HCC (n=2); violation of eligibility criteria due to portal vein thrombosis (n=1)

Follow-Up

Lost to follow-up (n=0)
Discontinued TEA (n=0)

Lost to follow-up (n=0)
Discontinued TACE (n=0)

Analysis

Analyzed (n=45)
- Excluded from analysis (n=4)
  Reason: did not receive TEA

Analyzed (n=45)
- Excluded from analysis (n=4)
  Reason: did not receive TACE
Materials and Methods

Eligibility Criteria for Participants

1. Signed informed consent from patient

2. Age more than 18 years

3. **Child-Pugh class A or B cirrhosis**

4. Eastern Cooperative Oncology Group performance score of 2 or below

5. No serious concurrent medical illness

6. **No prior treatment or surgery for HCC**

7. (a) Histologically or cytologically proved HCC except for lesions 1 to 2 cm in diameter, with typical features of HCC with two dynamic imaging techniques or (b) lesions larger than 2 cm, with typical features with one dynamic imaging technique or (c) lesions larger than 2 cm with a-fetoprotein level . 200 ng/mL*

8. Unresectable disease **without extrahepatic involvement** at chest radiography and CT

9. Massive expansive tumor morphology with a measurable lesion at CT (characterized by a well-defined spherical or globular configuration, with or without tumor capsule or satellite lesions)

10. **Total tumor mass less than 50% liver volume**

11. Tumor size up to **15 cm** in the largest dimension

12. **Up to five tumors**
Materials and Methods

Exclusion Criteria

1. Known active malignancy within the past 3 years
2. Concurrent ischemic heart disease or heart failure
3. History of acute tumor rupture with hemoperitoneum
4. Serum creatinine level higher than 180 mmol/L
5. Biliary obstruction not amenable to percutaneous drainage
6. Child-Pugh class C cirrhosis
7. History of hepatic encephalopathy
8. Intractable ascites not controllable with medical therapy
9. History of variceal bleeding within the past 3 months; serum total bilirubin level of at least 50 mmol/L
10. Serum albumin level less than 25 g/L
11. International normalized ratio of more than 1.5
12. Extrahepatic metastasis
13. Infiltrative tumor morphology (characterized by ill-defined tumor margin and amorphous configuration) or diffuse tumor morphology (characterized by a large number of small nodules)
14. More than five tumors
15. Thrombosis of target hepatic artery
16. Partial or complete thrombosis of the main portal vein and tumor invasion of the portal branch of the contralateral lobe
17. Hepatic vein tumor thrombus
18. Arterio–portal venous shunt affecting more than one hepatic segment at CT
19. Arterial–hepatic venous shunt with the hepatic vein opacified in the arterial phase at CT
- **Two treatment** sessions conducted 2 months apart were planned.
- Arterial feeders to tumors were identified and catheterized with a microcatheter

- Therapeutic agent:
  - ethiodized oil–ethanol solution for TEA
  - cisplatin–ethiodized oil emulsion in a concentration of 0.5 mg *cisplatin* (Platosin; Pharmachemie, Eindhoven, the Netherlands) per milliliter, followed by 1mm of gelatin-sponge pellets per milliliter, for TACE (9).

- Before delivery of ethiodized oil–ethanol solution, 1 mL of 1% *lidocaine* (Pfizer [Perth], Bentley, Australia) was instilled intraarterially through the microcatheter at each site of solution administration for pain control.
Materials and Methods

Treatment Procedures

- Stopped when evidence of intraarterial flow stasis or until the maximum dose was reached.
- The maximum total volume of ethiodized oil–ethanol solution or cisplatin emulsion to be delivered in one treatment session was 60 mL, for a maximum cisplatin dose of 30 mg in one treatment session.

- Patients in both groups were treated with paracetamol (Endopain II; Medipharma, Hong Kong) for fever or pain after treatment.
Materials and Methods

Treatment Procedures

- CT was performed at 3-month intervals after the onset of the first treatment for assessment of tumor response.

- Further treatment sessions were administered when there was CT evidence of residual tumors or occurrence of new hepatic tumors.

- There was no limit on the total number of treatment sessions.

- If progression - These patients were subsequently treated with sorafenib (Bayer, Leverkusen, Germany) if there was no contraindication.
Materials and Methods

- Clinical Outcome
- Tumor Response of Individual Tumors
- Overall Tumor Response of Individual Patients
- Treatment-related Toxicity
Results

Baseline Characteristics
There was no significant difference in the other baseline characteristics between the two arms

Treatment
- The mean number of treatments administered per patient:
  - TEA arm 2.4 ± 1.4;
  - TACE arm 3.0 ± 1.7

- The duration of the hospital stay for patients was similar in both groups: a median of 2 days
Clinical Outcome

- The median overall survival of patients tended to be longer in the TEA

  TEA, 24.3 months, 95% confidence interval [CI]: 12.8, 32.7;
  TACE, 20.1 months, 95% CI: 9.3, 31.2),

although there was no significant difference (log-rank test, $P = .513$).
- The median **TTP** and **PFS** for any disease progression in the TEA arm were longer
  - TTP for 
    - TEA 8.4 months [95% CI: 5.3, 11.4]
    - TACE 4.4 months [95% CI: 1.7, 7.1]
  - PFS for
    - TEA 6.5 months [95% CI: 7.8, 9.2]
    - TACE 4.4 months [95% CI: 1.6, 7.2]),

- The differences were not significant ($P = .128$ and $P = .16$, respectively)
- When the subclasses of disease progression were analyzed the differences were significant ($P = .028$ and .029, respectively)
Results

Tumor Response

- the complete response rate was persistently and significantly higher in the TEA arm

  3 months (62 of 88 [70%] vs 39 of 76 [51%], \( P = .012 \)),
  6 months (64 of 88 [73%] vs 41 of 76 [54%], \( P = .012 \)),
  12 months (66 of 88 [75%] vs 45 of 76 [59%], \( P = .031 \))

-The median percentage volume reduction of individual tumors at 6 months compared with baseline was:

  66% (95% CI: 37, 83) for the TEA group
  54% (95% CI:0, 87.5) for the TACE group (\( P = .55 \)).
Results

Treatment-related Toxicity

- There was no treatment-related death.

- **Fever** was more common in the **TEA** arm (33 vs 22 incidences, \( P = .017 \)).

- **Vomiting** was more common in the **TACE** arm (21 vs six incidences, \( P = .001 \)).

- Most abdominal pain in the TEA arm was of grade 1 (23 of 33 incidences, 70%). Grade 1 abdominal pain occurred in 52% (13 of 25 incidences) of the TACE arm.

- Cardiac ischemia, renal impairment, hepatitis reactivation, and posttreatment tumor rupture occurred rarely and only in the TACE arm.

- Temporary respiratory decompensation due to intralesional arteriovenous shunting occurred rarely in the TEA arm.
These results show that TEA tends to result in

(a) *a much better complete tumor* response rate when compared with conventional TACE or drug-eluting beads by using doxorubicin

(b) longer survival when compared with 90Y radioembolization involving TheraSphere (Nordion) or SirSphere (Sirtex).
- No significant difference in overall survival
- TEA was associated with significantly better tumor response in terms of
  - complete response
  - longer time to intralesional progression
  - longer survival free from intralesional progression.