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

Simon Chun Ho Yu, FRCR; Joyce Wai Yi Hui, FRCR; Edwin Pun Hui, FRCP; Stephen Lam Chan, FRCP; Kit Fai Lee, FRCS; Frankie Mo, PhD; John Wong, FRCS; Brigette Ma, FRCP; Paul Lai, FRCS; Tony Mok, FRCP; Winnie Yeo, FRCP

Radiology: Volume 270: Number 2—February 2014 n radiology.rsna.org

Background

-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)

Background

- 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.

Background

-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

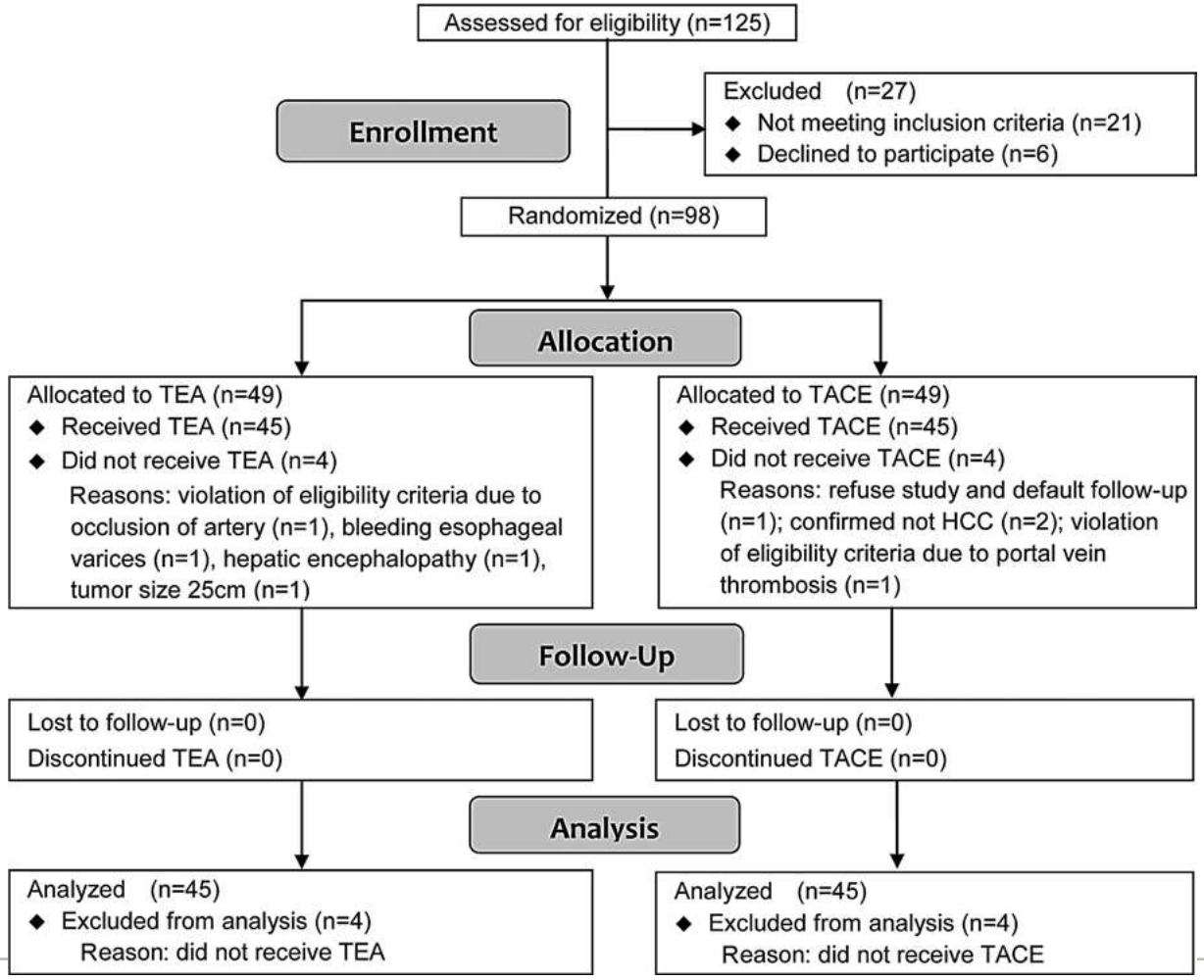
Materials and Methods

- 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.

Materials and Methods



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

Materials and Methods

Treatment Procedures

-**Two treatment** sessions conducted 2 months apart were planned.

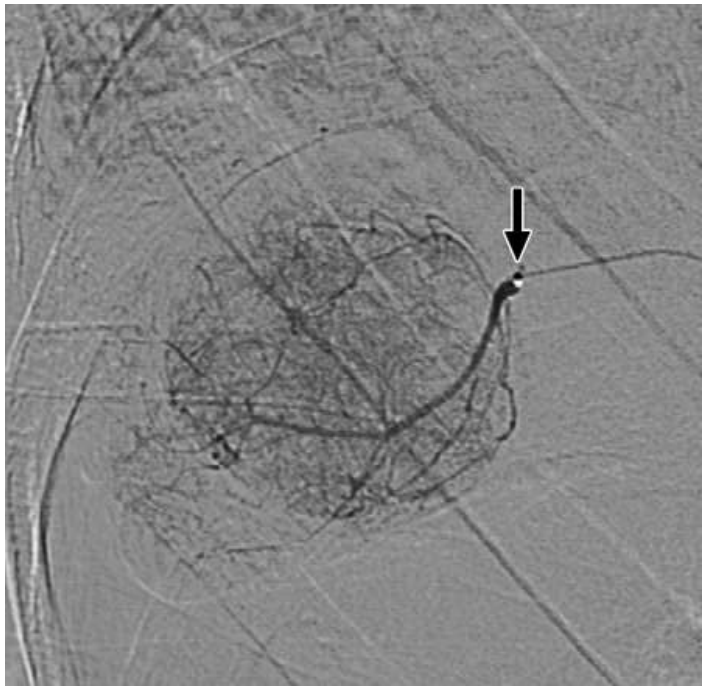
- Arterial feeders to tumors were identified and catheterized with a microcatheter

-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

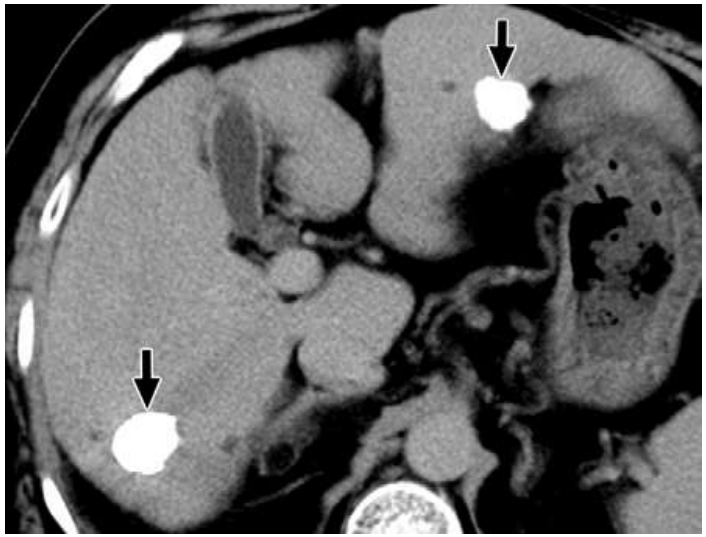
Treatment Procedures

-**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

Results

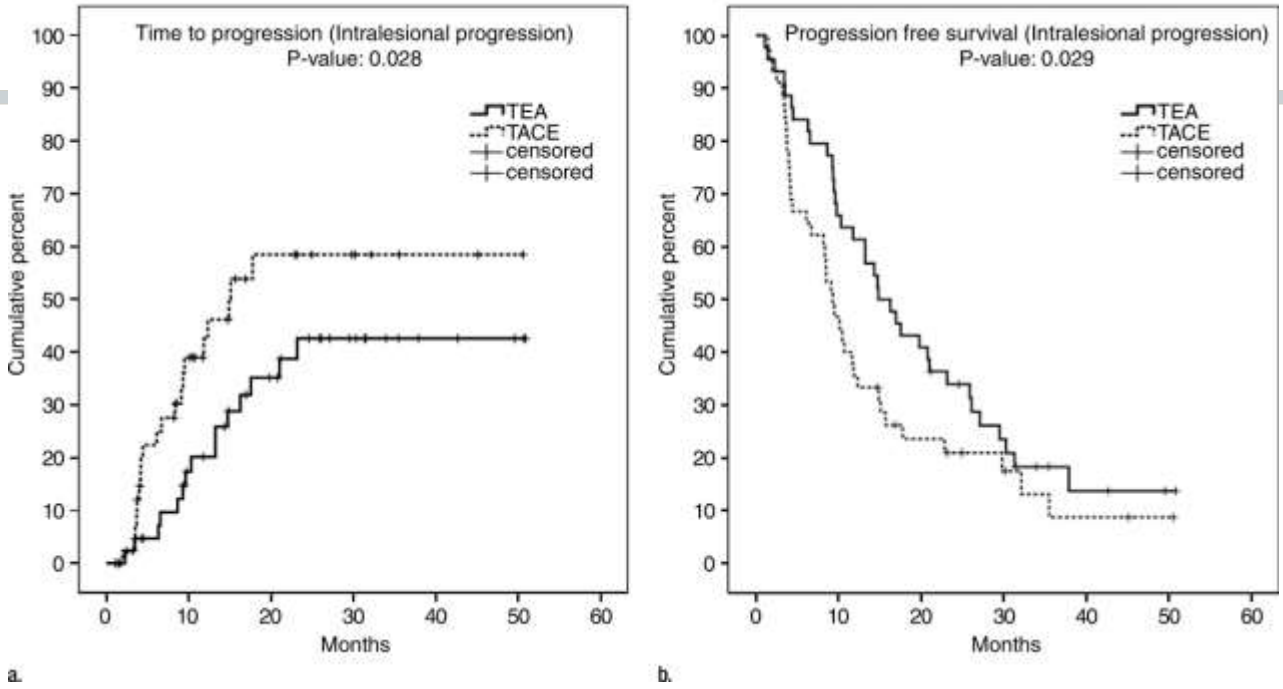
Clinical Outcome

- 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).*

Results



-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

Discussion

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).

Conclusion

- 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.