



# EBM CONFERENCE

*Radiology department*

*Reporter: R1 朱孝青*

*Supervisor: VS 郭禹廷*

*2010/06/24*

**Five steps  
of EBM  
(QSAPA)**

Step 1  
Question:  
Ask answerable  
clinical  
question

Step 2  
Search:  
Acquire  
for evidence


Step 3  
Appraisal:  
Appraise above  
evidences

Step 4  
Practice:  
Apply to  
your patient

Step 5  
Audit:  
Audit and evaluation



# ASKING AN ANSWERABLE QUESTION

- 
- TACEs (transarterial chemoembolization) are the mostly performed palliative therapy for patients with HCC
  - However, TAE (transarterial embolization) without chemotherapy are also performed.



So,

TACE or TAE is more beneficial for  
patient with unresectable hepatocellular  
carcinoma?

# PICO


- Problem / Patient
  - Patient had unresectable HCC.
  - Indication → TACE/TAE.
- Intervention
  - TACE
- Compare
  - TAE
- Outcome
  - Survival rate



**ACQUIRE THE BEST EVIDENCE**

# Levels of Evidence

Level	Intervention	Diagnosis	Prognosis	Etiology
<b>I</b>	A systematic review of level II studies	Systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies
<b>II</b>	A randomised controlled trial	Cross-sectional study among consecutive presenting patients	A prospective inception cohort study	A prospective cohort study
<b>III-1</b>	A pseudo-randomised controlled trial ( eg. Alternate allocation, or some other method)	Cross-sectional study among non-consecutive patients	Untreated control patients in a randomised controlled trial	A retrospective cohort study
<b>III-2</b>	A comparative study with concurrent control group: 1. Nonrandomised experimental study 2. Cohort, case-control study	Diagnostic case-control study	A retrospectively assembled cohort study	A case-control study
<b>III-3</b>	A comparative study without concurrent control group			
<b>IV</b>	Case series	Case series	Case series, or cohort study of patients at different stages of disease	A cross sectional study

- 
- Database:
    - UptoDate
    - Pubmed
  - Key words:
    - Transarterial chemoembolization or TACE
    - Transarterial embolization or TAE
    - Hepatocellular carcinoma or HCC
  - Limitation: reviews, randomized-controlled trials, meta-analysis

Search Results for "HCC AND TACE"

Click on what you meant by **tace**: [tumor necrosis factor-alpha converting enzyme](#), [transarterial chemoembolization](#)

All search results | Prioritize adult topics | Prioritize pediatric topics | Prioritize patient topics

- Nonsurgical therapies for localized hepatocellular carcinoma
- Overview of treatment approaches for hepatocellular carcinoma
- Clinical trials in treatment of chronic hepatitis C virus infection in HIV-infected patients
- Surgical resection for hepatocellular carcinoma
- Epidemiology and etiologic associations of hepatocellular carcinoma
- Systemic treatment for advanced hepatocellular carcinoma
- Evaluation of the HIV-infected patient with chronic hepatitis C virus infection**
- Liver transplantation for hepatocellular carcinoma
- Surveillance for hepatocellular carcinoma in adults with chronic liver disease
- Staging and prognostic factors in hepatocellular carcinoma
- Clinical features and diagnosis of primary hepatocellular carcinoma
- Management of acute intermittent porphyria
- Peliosis hepatis
- Natural history and treatment of nonalcoholic steatohepatitis
- Treatment options for locally advanced cholangiocarcinoma
- Molecular genetics of acute myeloid leukemia
- What's new in oncology
- Overview of hepatitis B virus infection in children
- Overview of the complications, prognosis, and management of cirrhosis
- Approach to the patient with a focal liver lesion

Topic Outline

INTRODUCTION

INITIAL EVALUATION

- History
  - Substance abuse
  - Psychiatry history
  - Other past medical history
  - Medication history
  - Social history
  - Pregnancy
  - Family history
- Physical examination
- Laboratory screening
- Screening for tuberculosis
- Interpretation of aminotransferases
- Patients with suspected cirrhosis

DIAGNOSTIC IMAGING

- Ultrasound
  - Screening for hepatocellular carcinoma
- CT scanning
- Endoscopy

ROLE OF A LIVER BIOPSY

- Advantages
- Limitations
- When should a liver biopsy be obtained
- When should a biopsy be repeated

## Nonsurgical therapies for localized hepatocellular carcinoma

electrically dependent electrodes. Nonetheless, there is less experience with this approach than with RFA, and the technique is not widely available.

**TRANSARTERIAL EMBOLIZATION** — The majority of the blood supply to HCCs is derived from the hepatic artery rather than the portal vein. This has led to the development of techniques designed to either eliminate the tumor's blood supply by particle embolization and/or directly infuse cytotoxic chemotherapy into the branch of the hepatic artery that feeds the tumor.

There is marked variability in the types of procedures that have been used for transarterial therapy: bland particle embolization, transarterial chemoembolization (TACE) without or with lipiodol (which is sometimes called transarterial oily chemoembolization), and transarterial chemotherapy alone or with lipiodol. Bland particle embolization, which relies solely on induction of tumor ischemia by disruption of the blood supply to the tumor, has been utilized successfully for the treatment of both unresectable and recurrent HCC [68-70]. Two meta-analyses have failed to show a significant survival difference between the two techniques, although there was a trend toward longer survival with TACE [71,72]. However, the majority of published experience is with TACE, and this is the procedure that was shown to improve survival in two randomized trials involving patients with unresectable HCC. As a result, it is the most commonly used technique. (See '[Indications and efficacy](#)' below.)

The term TACE has been used variably to refer to the injection of a chemotherapeutic agent into the hepatic artery, with or without lipiodol, and with or without a procoagulant

In comparing conventional **TACE versus bland embolization** alone (three randomized trials, 412 patients), **survival was no better with the addition of chemotherapy**, and there was no evidence of benefit from the addition of lipiodol to TACE.

- Among trials comparing TACE versus no treatment or suboptimal treatment (oral [tamoxifen](#), systemic or intraarterial chemotherapy alone), there was a significant survival benefit favoring TACE (odds ratio [OR] for death 0.705, 95% CI 0.50-0.99).

- In comparing conventional TACE versus bland embolization alone (three randomized trials, 412 patients), survival was no better with the addition of chemotherapy, and there

**TACE with Lipiodol remains the most commonly used approach** to hepatic arterial embolization.

Despite these results, TACE with lipiodol remains the most commonly used approach to hepatic arterial embolization.

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HCC AND TACE AND TAE

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tace in Drugs

Meta-Analysis, Randomized Controlled Trial, Review, English, published in the last 5 years

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**TRANSARTERIAL THERAPY FOR  
HEPATOCELLULAR CARCINOMA: WHICH  
TECHNIQUE IS MORE EFFECTIVE?  
A SYSTEMATIC REVIEW OF COHORT AND  
RANDOMIZED STUDIES Level I**

*Laura Marelli, Rosa Stigliano, Christos Triantos, Marco Senzolo,  
Evangelos Cholongitas, Neil Davies, Jonathan Tibballs, Tim Meyer, David  
W. Patch, Andrew K. Burroughs*

**CardioVascular  
and Interventional  
Radiology**

**Cardiovasc Intervent Radiol (2007) 30:6–25**

# Purposes of this systemic review

- TACE has been shown to improve survival compared with best supportive care in meta-analyses of randomized trials
- However, it is not clear whether TAE alone gives the same survival advantage.
- Whether there were specific patient characteristics and/or radiological techniques that would result in better outcomes for any of the transarterial therapies.

# Search Strategy and Selection Criteria

- Medline: "hepatocellular carcinoma" or "HCC" or "hepatic tumor" or "liver tumor" or "hepatic cancer" or "liver cancer" and "TACE" or "TAE" or "chemoembolization" or "embolization".
- Between 1982 and May 2006.
- Exclusion: liver metastases, recurrence of HCC after hepatectomy.
- 175 articles included.

- By excluding non-suitable studies (without clear patient data, advanced liver disease, PVT, etc.)
- 61 articles evaluating TACE alone (cohort studies) or TACE compared with conservative management or suboptimal therapies (RCTs and non-RCTs)

Table 1. Patient characteristics in therapeutic studies of transarterial techniques for hepatocellular carcinoma

Population (%)	Child A	Child B	Child C	Uninodular	Okuda I	Okuda II	Okuda III
Eastern (n=25)	64	26	10	34	34	64	2
Western (n=36)	66	30	4	34	49	44	7
Before 2000 (n=40)	66	28	6	33	42	52	6
After 2000 (n=21)	70	25	5	33	58	40	2
RCTs	69	25	6	34	55	40	5
Nonrandomized	56	35	9	39	45	44	11

# Chemoembolization procedure

- TACE (transarterial chemoembolization) in 40 (67%)
  - Anticancer +/- Lipiodol + embolizer
- TAE (transarterial embolization) in 7 (11%)
  - Embolizer +/- Lipiodol
- TOCE (transarterial oily chemoembolization) in 7 (11%)
  - Anticancer + Lipiodol
- TAC (transarterial chemotherapy)
  - Only anticancer
- TACE followed by systemic chemotherapy in 5 (8%), and lipiodol alone or combined with ethanol in 2 (3%).

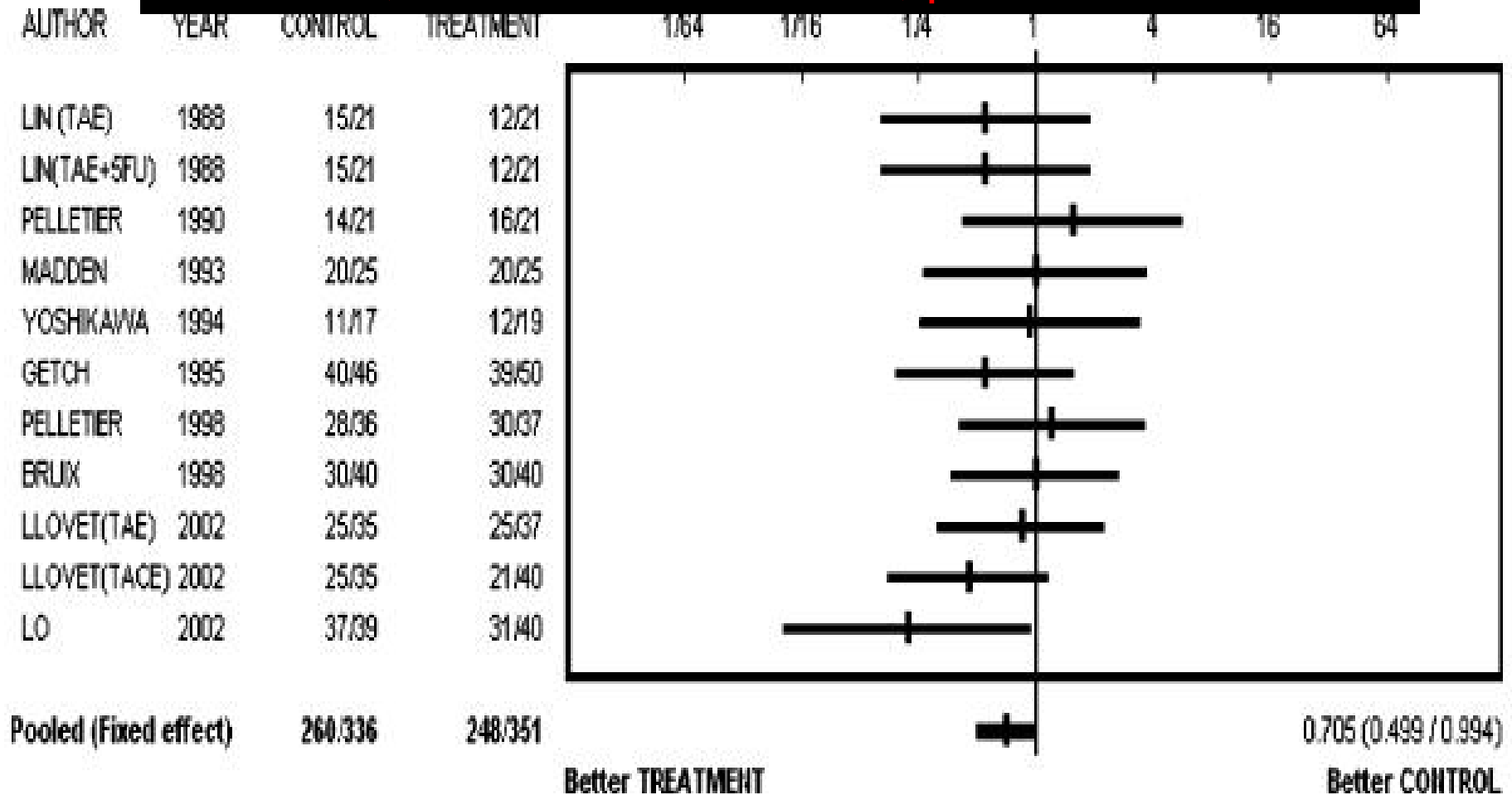
# TACE/TAE/TOCE vs Conservative Management or Suboptimal

- Lo CM et al. (2002). Lancet 359:1734–1739
- Lo CM TACE vs. TAE vs. controls 4–1171
- Groupe d'Etude et de Traitement du Carcinome Hepatocellulaire (1995). *N Engl J Med* 332:1256–1261
- Bruix J et al. (1998). *Hepatology* 27:1578–1583
- Lin DY et al. (1988). Gastroenterology 94:453–456
- Pelletier Multiple TAE vs. one TAE + 5-FU vs. control 4
- Pelletier G et al. (1990). *J Hepatol* 11:181–184
- Madden MV et al. (1993). *Gut* 34:1598–1600
- Yoshikawa M et al. (1994). *Cancer Chemother Pharmacol* 33[Suppl]:S149–S152

9 RCTs

- 5 trials lasted 2 years or more and 4 trials lasted less than 2 years.
- 6 studies:
  - intraarterial treatment vs. conservative management
- 3 studies
  - intraarterial treatment vs. therapies not shown to have effects on survival
    - (systemic chemotherapy with 5-fluorouracil, oral tamoxifen)
- Total of 11 comparisons

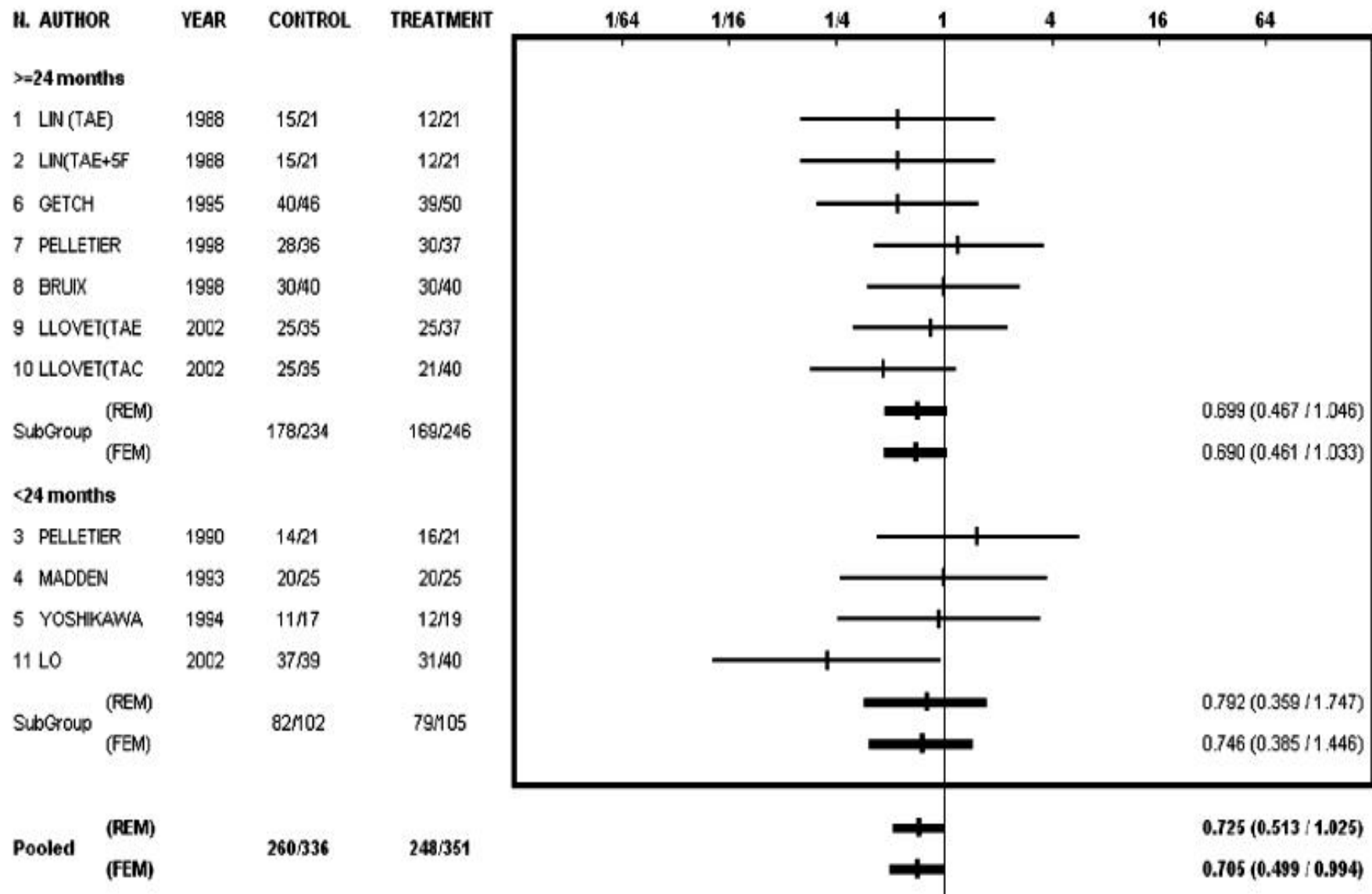
**OR 0.705; 95% CI 0.499–0.994; p = 0.0026**



**Significant decrease in mortality favoring treatment, confirming that chemoembolization improves survival.**

- 3 sensitivity analyses assessing
  - (1) different duration of follow-up (mean more or less than 2 year)
  - (2) different treatments (TACE, TAE or TOCE)
  - (3) different management of the control groups (no treatment or suboptimal treatment)

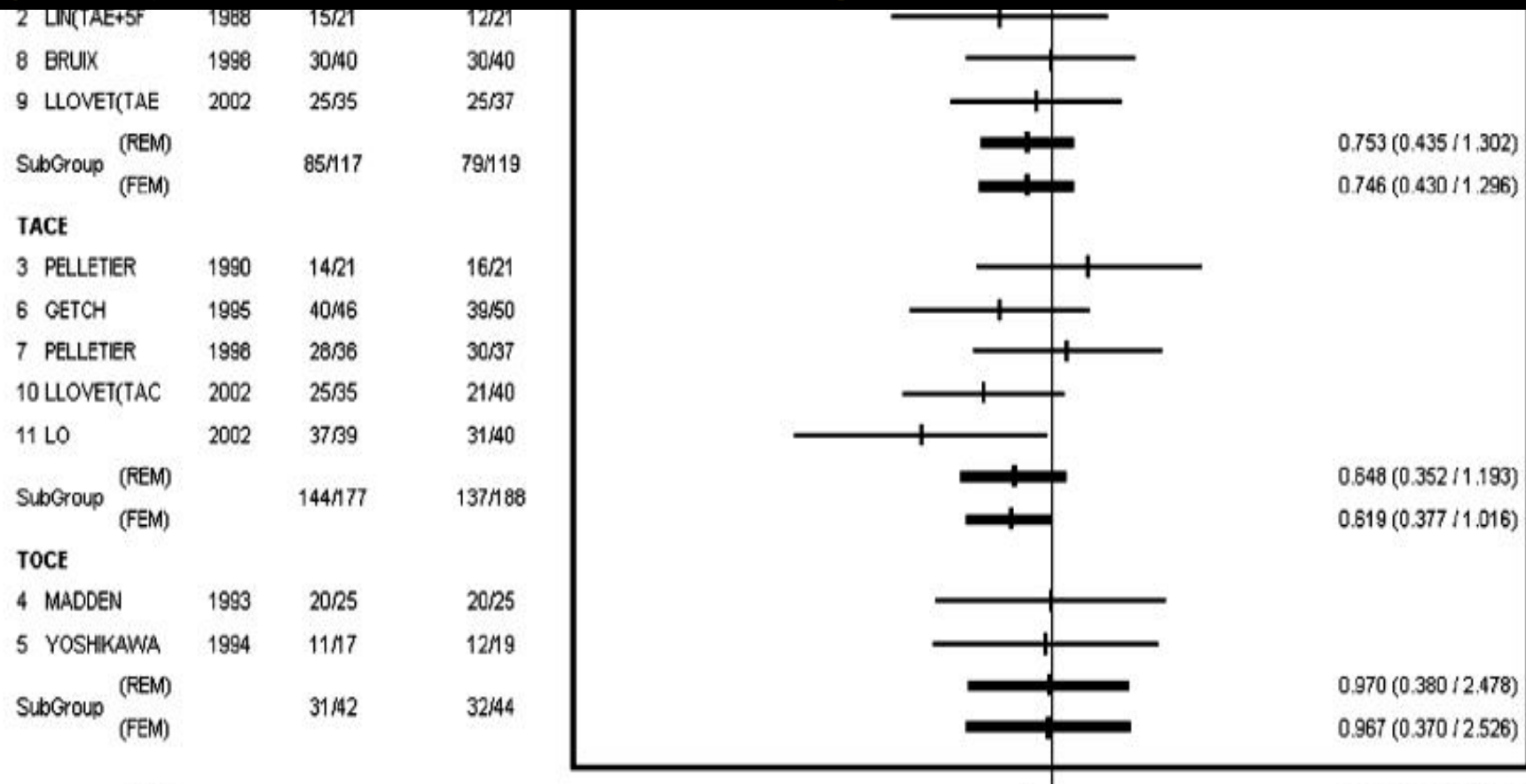
# Different follow-up duration



**No alteration of the results of the main meta-analysis**

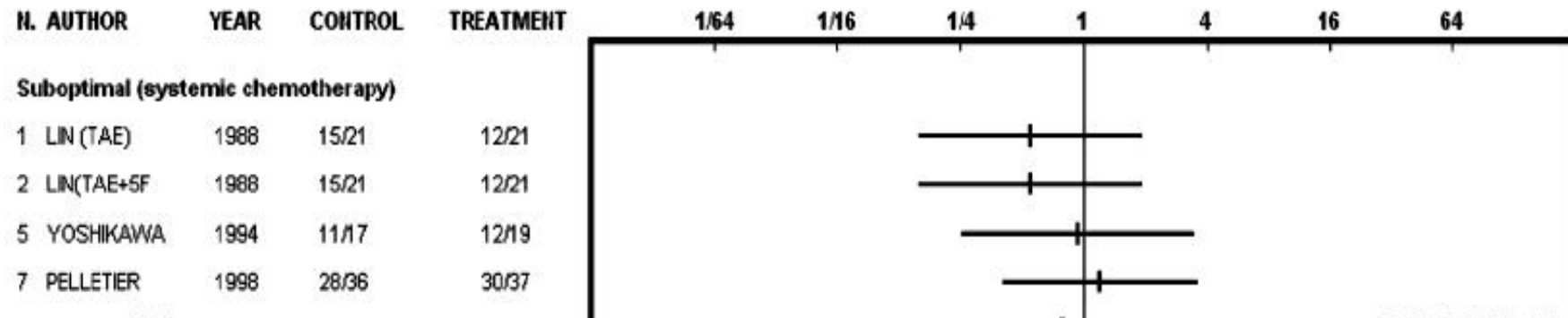
# Different treatments (TACE, TAE or TOCE)

Chemoembolization (TACE) and embolization alone (TAE) achieved the same improvement in survival



Lipiodolization (TOCE) without embolization was less effective than both of them.

# Different management of the control



The benefit of chemoembolization is independent of whether the control group was untreated or treated with suboptimal therapies

8	BRUIX	1998	30/40	30/40
9	LLOVET(TAE	2002	25/35	25/37
10	LLOVET(TAC	2002	25/35	21/40

Suggesting that systemic or intra-arterial chemotherapy does not have therapeutic benefit in hepatocellular carcinoma.

Better TREATMENT

Better CONTROL

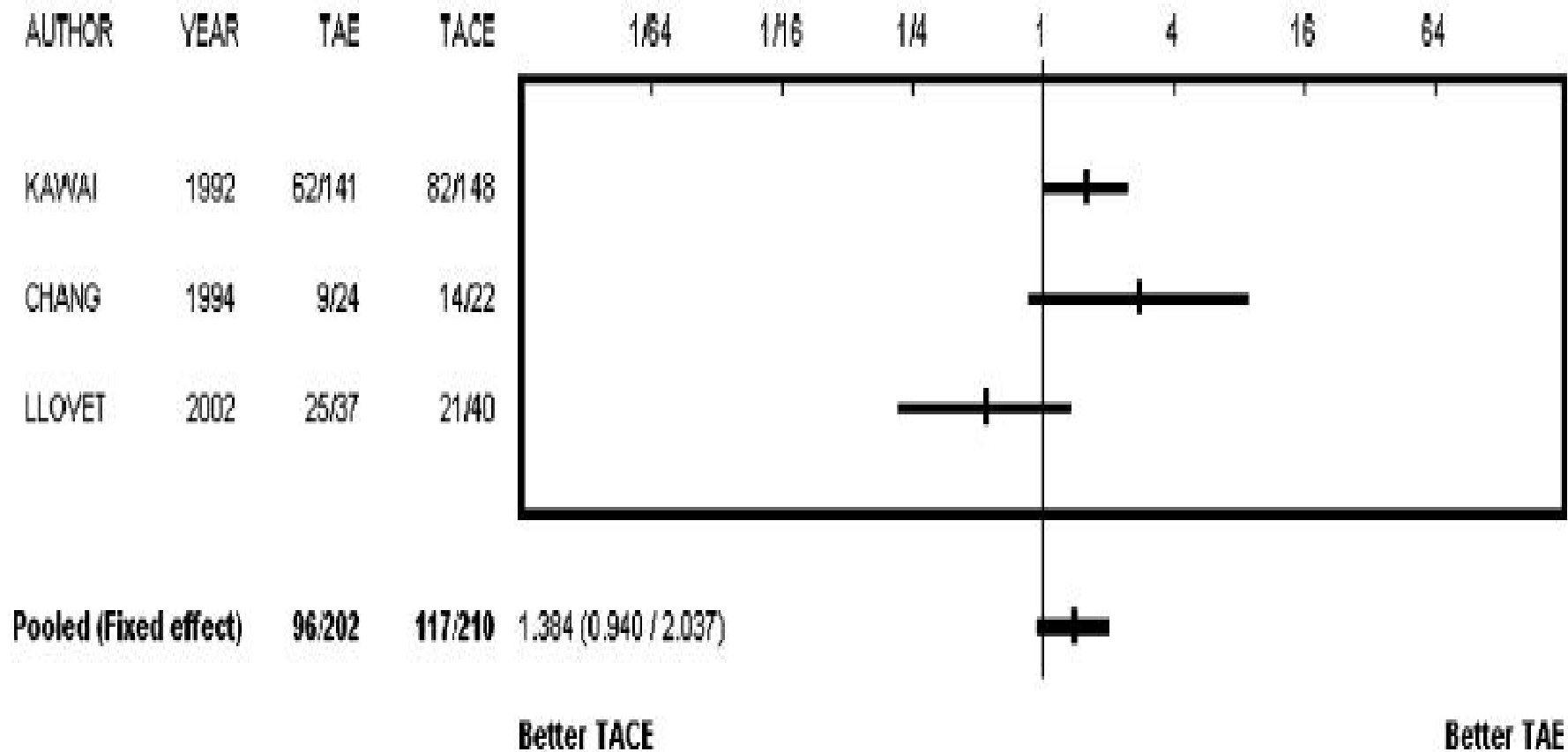


# Embolization (TAE) Versus Chemoembolization (TACE)

- Meta-analysis with 3 RCTs (412 patients) comparing TAE versus TACE, using the number of patients reported as dead during follow-up.
  - Llovet JM et al.(2002). Lancet 359:1734–1739
  - Chang JM et al.(1994). Cancer 74:2449–2453
  - Kawai S et al.(1992). Cancer Chemother Pharmacol 31[Suppl]:S1–S6
- The mean duration of follow-up was 2 years in two studies and 1 year in one.

- TACE : doxorubicin or cisplatin mixed with lipiodol and then gelatin sponge particles
- TAE: lipiodol with gelatine sponge particles or gelatine sponge particles alone.
- The mean number of courses per patient was three in two studies and 1.4 in the other and similar between TAE and TACE.

**OR 1.384; 95% CI 0.94–2.04; p = 0.052**



**No statistical difference between therapies, with 2 trials favoring TAE, and 1 favoring TACE.**

**Further trials comparing these treatments are needed to resolve this issue.**

# Conclusion

- Lack of adequately powered trials: most are very small (20–40 patients in each arm) and short in duration (1–2 years of follow-up).
- Intraarterial therapy with embolization either with or without chemoagents better than conservative or suboptimal therapy.

- 5 following features:

- Most frequently the anticancer drugs: **doxorubicin** (50 mg), **epirubicin** (50 mg) or **cisplatin** (92 mg), either alone or in combination
- **Lipiodol** was frequently used but there is no evidence of its benefit
- Embolizing agents most frequently used were **gelatin sponge particles** given after injection of the chemotherapeutic agent.
- Selective or superselective (segmental or subsegmental) rather than a lobar embolization
- **Repeated courses** “on demand” (tumor response, patient tolerance) are used most often.

- Side effects: acute liver failure (7.5%), acute renal failure (1.8%), upper gastrointestinal bleeding (3%) and hepatic or splenic abscess (1.3%); treatment-related **mortality was 2.4%**.

- Intraarterial therapy does improve survival (OR 0.705; 95% CI 0.499–0.994; p = 0.0026)
- TACE versus TAE alone demonstrated no survival difference.
- HCC is known to be insensitive to chemoagents the role of embolization might be more important than chemotherapy.
- **Maximizing ischemia** or using a **more distal embolizing agent** such as **PVA** should be evaluated further in comparative trials.

- If TACE is used, no drug or combination has been shown to be better than single-agent doxorubicin.

→ RCTs assessing new drugs or combinations might resolve this issue.

- Lipiodol may not be able to slowly release the anticancer drugs into the tumor because of the instability of the preparation.

- Prophylactic antibiotics are not helpful to treat post-TACE syndrome (fever, chills, abdominal pain) but they may be necessary to prevent infective complications (abscesses and sepsis)

# TRANSARTERIAL CHEMOTHERAPY ALONE VERSUS TRANSARTERIAL CHEMOEMBOLIZATION FOR HEPATOCELLULAR CARCINOMA: A RANDOMIZED PHASE III TRIAL

Takuji Okusaka, Hiroshi Kasugai, Yasukazu Shioyama, Katsuaki Tanaka,  
Masatoshi Kudo, Hiromitsu Saisho, Yukio Osaki, Michio Sata, Shigetoshi Fujiyama,  
Takashi Kumada, Keiko Sato, Seiichiro Yamamoto, Shiro Hinotsu, Tosiya Sato

JOURNAL  
OF HEPATOLOGY  
Official Journal of the European Association for the Study of the Liver

Journal of Hepatology 51 (2009) 1030–1036

- Between 1999/10 and 2003/06, total 161 patients were provisionally enrolled in the study at 10 Japanese centers.
  - TACE group (79 patients)
  - TAI group (82 patients). (transarterial infusion chemotherapy)
- Agents: **Zinostatin stimalamer (SMANCS)** with or without gelatin sponge.
- SMANCS is a **lipophilic** anti-cancer agent that dissolves in lipiodol to form a stable solution

- At the time of the final analysis, 51 patients in the TACE group and 58 patients in the TAI group had died.
- The median overall survival time was 646 days in the TACE group and 679 days in the TAI group.
- The estimated 2-year survival rate was 48.2% for the TACE group and 49.6% for the TAI group.
- No significant difference in survival was seen between the two groups ( $p = 0.383$ )

The final analysis (57 months later)	TACE group (79 patients)	TAI group (82 patients)
Number of death	51	58
Median overall survival time	646 days	679 days
Estimated 2-year survival rate	48.2%	49.6%


No significant difference in survival was seen between the two groups ( $p = 0.383$ )

# Discussion

- No any significant survival advantage of TACE over TAI.
  - SMANCS (lipophilic) as the anticancer agent → favorable results in the TAI group, long-lasting or slow-release with Lipiodol
  - The infrequent protocol treatment repetition in this study (avg. 2.3 times)
  - The enrollment of many patients with far-advanced HCC

# Conclusion

- Adding embolization did not increase the survival of HCC patients over SMANCS transarterial chemotherapy alone.
- The results of this study must be interpreted with caution because current TACE protocols have evolved thanks to the implementation of updated devices including **new embolic agents** and **improved catheters**.
- Additional studies will be required.



# **TRANSARTERIAL CHEMOEMBOLIZATION, TRANSARTERIAL CHEMOTHERAPY, AND INTRA-ARTERIAL CHEMOTHERAPY FOR HCC TREATMENT**

*Emmanuel A. Tsochatzis, Giacomo Germani, and Andrew K. Burroughs*


*Seminars in Oncology, Vol 37, No 2, April 2010, pp 89-93*



# Conclusion-Future


## Directions

- Intra-arterial therapies undoubtedly offer a survival benefit in patients with unresectable HCC, but **not standardized**
  - different embolic and chemotherapeutic agents, different arterial selectivity, and different schedules and indications for repeat sessions
- It remains unclear if chemotherapy adds to embolization, as no clear advantage has been demonstrated to date.

- 
- **Gelatine sponge particles**, the most commonly used in previous RCTS provides short-term artery occlusion (2 weeks)
  - Whereas **polyvinyl alcohol particles (PVA)**, now used in many centres, result in permanent artery occlusion
  - A randomised trial of TAE vs. TACE with PVA particles in both arms are being conducted



# OUR PRACTICE

- 
- Transarterial chemoembolization (TACE) improves survival in cirrhotic patients with hepatocellular carcinoma (HCC).
  - The optimal schedule, best anticancer agent and best technique are still unclear.
  - TACE may not be better than transarterial embolization (TAE).
  - HCC is very chemoresistant, thus embolization may be more important than chemotherapy.



**THANKS FOR YOUR ATTENTION**