Systematic Review of Randomized Trials for Unresectable Hepatocellular Carcinoma: Chemoembolization Improves Survival

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There is no standard treatment for patients with unresectable hepatocellular carcinoma (HCC). Survival benefits derived from medical interventions are controversial. The aim of this systematic review was to assess the evidence of the impact of medical treatments on survival. Randomized controlled trials (RCTs) that were published as full papers assessing survival for primary treatments of HCC were included. MEDLINE, the Cochrane Library, CANCERLIT, and a manual search from 1978 to May 2002 were used. The primary end point was survival, and the secondary end point was response to treatment. Estimates of effect were calculated according to the random effects model. Sensitivity analysis included methodological quality. We identified 61 randomized trials, but only 14 met the criteria to perform a meta-analysis assessing arterial embolization (7 trials, 545 patients) or tamoxifen (7 trials, 898 patients). Arterial embolization improved 2-year survival compared with control (odds ratio [OR], 0.53; 95% confidence interval [CI], 0.32-0.89; $P = .017$). Sensitivity analysis showed a significant benefit of chemoembolization with cisplatin or doxorubicin (OR, 0.42; 95% CI, 0.20-0.88) but none with embolization alone (OR, 0.59; 95% CI, 0.29-1.20). Overall, treatment induced objective responses in 35% of patients (range, 16%-61%). Tamoxifen showed no antitumoral effect and no survival benefits (OR, 0.64; 95% CI, 0.36-1.13; $P = .13$), and only low-quality scale trials suggested 1-year improvement in survival. In conclusion, chemoembolization improves survival of patients with unresectable HCC and may become the standard treatment. Treatment with tamoxifen does not modify the survival of patients with advanced disease. (HEPATOLOGY **2003;37:429-442.**)

The incidence of hepatocellular carcinoma (HCC) is increasing worldwide.[1] Liver cancer is the fifth most common cancer in the world and the third most common cause of cancer-related death.[2] Cohort studies and cost-efficiency modeling have suggested that surveillance of well-defined cirrhotic patients may decrease tumor-related mortality. However, only 30% of patients benefit from curative therapies such as resection, transplantation, or percutaneous ablation[3] and achieve 5-year survival rates of 50% to 75%.[4]

Most patients with HCC are diagnosed at intermediate to advanced stages, and there is no standard treatment for these patients.[3,4] The most reliable method to show survival advantages is to perform large randomized controlled trials (RCTs) that include more than 1,000 patients comparing treatment versus no treatment in a well-defined strata of individuals.[5-10] These investigations are lacking in patients with HCC. On the contrary, several medical interventions have been tested in the setting of small RCTs. However, the reduced size of these studies may cause questions of their statistical power when detecting survival differences, which, as in many areas of health care and oncology, are unlikely to be large. This raises the need for a systematic meta-analysis assessment, with a major role to integrate valid information and provide estimates of treatment effects when RCTs themselves are not of sufficient size.[9,10] Two systematic reviews published years ago[11,12] suggested a potential benefit for at

Abbreviations: HCC, hepatocellular carcinoma; RCT, randomized controlled trial; OR, odds ratio; CI, confidence interval.

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least 3 therapies (embolization, tamoxifen, and interferon) but emphasized that the amount of data was limited to achieve valid conclusions. Several RCTs have been published since then; thus, an up-to-date analysis may provide new and more consistent insight on the estimates of treatment efficacy.

This systematic review of RCTs aims to identify survival benefits of medical interventions for unresectable HCC in comparison with conservative management/suboptimal therapies. For this purpose, a meta-analysis was performed in 2 controversial interventions with uncertain efficacy: embolization/chemoembolization and tamoxifen. Sensitivity analysis of methodological quality was performed to control any bias in the estimates of intervention efficacy.[13-16]

Materials and Methods

Identification and Selection of Trials

The protocol of this systematic review and meta-analysis included study objectives, search strategy, selection criteria of trials, and assessment of study quality.

Study Objectives. The primary end point was to identify survival benefits of medical interventions as primary treatment of unresectable HCC, analyzed in the setting of RCTs. The secondary end point was to assess objective response rates, defined as complete and partial responses.

Search Strategy. Retrieval of studies was performed through MEDLINE on PubMed, CANCERLIT (National Cancer Institute), and the Cochrane Library database by using "hepatocellular carcinoma," "liver cancer," and "primary liver carcinoma" as free text words and/or combined with "randomized, controlled clinical trials," "clinical trials," "phase 3 studies," "double-blind," "placebo," "review," "meta-analysis," "therapy," and "treatment" as well as a manual search and review of reference lists.

Selection Criteria of Trials. We selected RCTs published as full papers in English from 1978 to May 2002 in peer-review journals, assessing survival benefits derived from medical therapies as primary treatment of unresectable HCC reporting 1- or 2-year death rates. Because evidence of survival advantages for any of the available interventions has been questionable until now,[3,4] we only included studies comparing treatment versus conservative management. In the case of trials assessing percutaneous treatments or embolization, comparison with suboptimal therapies without proven antitumoral activity and no impact on survival were also considered. Quasi-RCTs, randomized phase 2 studies, unpublished RCTs or those only reported in abstract form, RCTs published in languages other than English, and RCTs including patients with liver metastases were excluded from the analysis. The integrity of randomization of all studies was checked. During the trial selection and data extraction, we were not masked to authors, institutions, journal, or interventions assessed.

Quantitative Analysis (Meta-analysis)

The protocol proposes a meta-analysis of therapies that have been assessed in enough patients to achieve an optimum information size.[9,10] This has been defined as the minimum number of patients needed to perform a robust quantitative analysis.[9,10] However, the outcome assumptions for sample size calculation depend on the evolutionary stage at which patients are recruited in the study. For this reason, we estimated one minimum sample size for patients at intermediate stage, who are mostly included in RCTs assessing arterial embolization or intra-arterial chemotherapy, and other sample sizes for patients at advanced stages who are included in trials assessing systemic treatments. The following criteria were established.

Arterial Embolization. *Definitions.* We separately evaluated procedures aimed to achieve arterial occlusion, such as arterial embolization or chemoembolization, and others aimed to deliver nonocclusive antitumoral substances, such as arterial chemotherapy. Arterial embolization is defined as the occlusion of arterial flow by synthetic (Gelfoam [cubes or powder], Ivalon, or others) or natural particles (blood clots). It includes procedures named elsewhere as transarterial embolization, transcatheter arterial embolization, hepatic arterial embolization, hepatic arterial obstruction, or intra-arterial embolization. Chemoembolization refers to the same process preceded by the administration of chemotherapeutic agents, usually mixed with Lipiodol as a vehicle. This procedure refers to those named transarterial chemoembolization or intra-arterial chemoembolization. Arterial chemotherapy (direct arterial administration of chemotherapy or using pumps) and lipiodolization (arterial administration of Lipiodol [no antitumoral activity] or a mixture of Lipiodol as a vehicle of chemotherapy) are not aimed to achieve arterial occlusion.

Sample size. Arterial embolization is the first-line treatment of unresectable multinodular HCC. In modern series, the natural history of untreated patients who are the target population of these therapies shows 2-year survival figures of 20% to 50%.[17,18] Expecting a 2-year survival rate of 55% for the treatment group and 35% for the control group, with a statistical power of 90% and 2-tailed type I error of 5%, the minimal sample size for a robust meta-analysis should be 256 patients (128 per arm).

The core group was constructed with studies reporting 2-year death rates. Sensitivity analyses were performed to assess the type of embolization with or without chemotherapy, the quality profile, the effect in studies including a control group of conservative management, discarding suboptimal therapies, and the effect in all trials irrespective of follow-up length (1-year death rates).

Systemic Treatments. Hormonal compounds (tamoxifen), immunotherapy, systemic chemotherapy, and other new agents have been mostly assessed in patients with contraindications for locoregional therapies (*e.g.*, percutaneous treatments or embolization) or in those with more advanced tumoral disease. This includes patients with tumor-related symptoms, impaired performance status, or vascular invasion or extrahepatic spread (*i.e.*, lymph node involvement or metastases).

Sample size. The expected 1-year survival figures of these individuals according to the natural history of the disease account for 30% to 50%.[17,18] Expecting a 1-year survival rate of 55% for the treatment group and 40% for the control group, with a statistical power of 90% and a 2-tailed type I error of 5%, the minimal sample size for a robust meta-analysis should be 462 patients (231 per arm).

The core group was constructed with RCTs assessing tamoxifen as a primary treatment of HCC. Three sensitivity analyses were performed assessing quality profile or double-blinded RCTs, thus excluding open-label studies, or assessing all trials identified, including those using tamoxifen as adjuvant therapy of radical therapies.

Statistical Methods

The random effects model of DerSimonian and Laird was used.[19] The results are reported as pooled odds ratios (OR) and 95% confidence interval (CI). Cumulative meta-analysis was used to update the treatment effect as evidence has accumulated according to time of publication.[6-8] Heterogeneity was evaluated with a χ^2-based Q statistic of OR and defined at a P value less than .1, and potential reasons for heterogeneity were explored. All calculations were performed using Meta-analyst 1990 to 1997 (Dr. Joseph Lau, Tufts University, New England Medical Hospitals, Boston, MA). This report follows the QUORUM guidelines[20] and the Cochrane Collaboration guidelines (www.cochrane.de) for reporting meta-analysis.[21]

Qualitative Analysis

Quality assessment was performed to control the estimates of intervention effects. Any disagreement was resolved by consensus. A modification of the standard methodological quality scale of Jadad[13] was applied, including 5 components[14]: allocation sequence generation (computer-generated random numbers or similar, 2; not described or inadequate, 1); allocation concealment (central randomization, 3; sealed envelopes or similar, 2; not described or inadequate, 1); double blinding (identical placebo tablets or double dummy, 2; double blind but method not described, 1; no double blinding or inadequate method, 0); description of protocol deviations, withdrawals, and dropouts (numbers and reasons described, 1; not described, 0); and efficacy of randomization (pretreatment prognostic variables balanced and presented in tabular form, 2; described in text, 1; no information reported or variables unbalanced, 0). The 10-point score was ranked as high (>6 points) or low (<5 points). Due to the nature of the embolization treatment, double-blind or double-dummy techniques have been discarded in all studies. Thus, the maximum quality score in trials assessing embolization was 8 points.

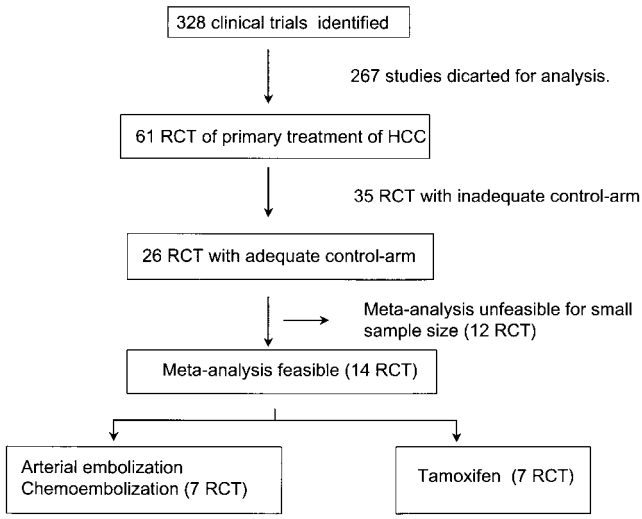

Fig. 1. Study flowchart.

Potential Conflict of Interest

This study has not received any support from industry or private corporations.

Results

Selection of Trials

After initial screening, 328 potentially relevant clinical trials of HCC were identified (Fig. 1). After subsequent evaluation for eligibility, we retained 61 published RCTs assessing primary treatments of HCC[22-82] (Table 1). The remaining studies were excluded because they were prospective cohort studies, phase 1 or random phase 2 studies, quasi-RCTs, non-English RCTs, unpublished RCTs

Table 1. RCTs Identified Assessing Primary Treatments of HCC (n = 61)

Author (Journal, Year)	Treatment Arms (No. of Patients)	Meta-analysis (Exclusion Criteria)*
Locoregional Treatments		
Percutaneous treatments (n = 5)		Not performed
1. Bartolozzi et al. (Radiology, 1995)[22]	Chemoembolization + PEI (26) Chemoembolization (27)	Excluded (1)
2. Ohnishi et al. (HEPATOLOGY, 1998)[23]	PEI (29) Percutaneous acetic acid injection (31)	Excluded (1)
3. Koda et al. (Cancer, 2001)[24]	Chemoembolization + PEI (26) Chemoembolization (26)	Excluded (1)
4. Habib et al. (Cancer Gene Ther, 2002)[25]	PEI (5) E1B-deleted adenovirus (5)	Excluded (1)
5. Shibata et al. (Radiology, 2002)[26]	Radiofrequency ablation (36) Microwave coagulation (36)	Excluded (1)
Arterial embolization/chemoembolization (n = 17)		
Nonactive control arm (n = 7)		Performed
6. Lin et al. (Gastroenterology, 1988)[27]	Embolization (21) Embolization + IV 5-FU (21) IV 5-FU (21)	Included
7. Pelletier et al. (J Hepatol, 1990)[28]	Chemoembolization (doxorubicin) (21) Control (21)	Included
8. Group d' Etude et de Traitment du Carcinome Hépatocellulaire (N Engl J Med, 1995)[29]	Chemoembolization (cisplatin) (50) Control (46)	Included
9. Bruix et al. (HEPATOLOGY, 1998)[30]	Embolization + coils (40) Control (40)	Included
10. Pelletier et al. (J Hepatol, 1998)[31]	Chemoembolization (cisplatin) (37) Tamoxifen (36)	Included
11. Lo et al. (HEPATOLOGY, 2002)[32]	Chemoembolization (cisplatin) (40) Control (39)	Included
12. Llovet et al. (Lancet, 2002)[33]	Embolization (37) Chemoembolization (doxorubicin) (40) Control (35)	Included
Potentially active control arm (n = 10)		
13. Kasugai et al. (Gastroenterology, 1989)[34]	Chemoembolization (doxorubicin) (20) Chemoembolization (doxorubicin) (25) Chemoembolization (cisplatin) (52)	Excluded (1)
14. Kawai et al. (Cancer Chemother Pharmacol, 1992)[35]	Embolization (148) Chemoembolization (doxorubicin) (141)	Excluded (1)
15. Okamura et al. (Cancer Chemother Pharmacol, 1992)[36]	Chemoembolization (farmorubicin) (58) Chemoembolization (doxorubicin) (59)	Excluded (1)
16. Kawai et al. (Cancer Chemther Pharmacol, 1994)[37]	Chemoembolization (farmorubicin) (208) Chemoembolization (doxorubicin) (207)	Excluded (1)
17. Chang et al. (Cancer, 1994)[38]	Embolization (24) Chemoembolization (cisplatin) (22)	Excluded (1)
18. Hatanaka et al. (Radiology, 1995)[39]	Embolization (90) Chemoembolization (cisplatin, doxorubicin)(92) Lipiodolization (cisplatin, doxorubicin) (184)	Excluded (1)
19. Ikeda et al. (Am J Clin Oncol, 1995)[40]	Embolization (20) Embolization + oral tegafur/uracil (20)	Excluded (1)
20. Ikeda et al. (Am J Clin Oncol, 1997)[41]	Embolization (20) Embolization + oral 5′-DFUR (20)	Excluded (1)
21. Kwok et al. (J Hepatol, 2000)[42]	Embolization (52) Embolization (blood clot) (48)	Excluded (1)
22. Kawata et al. (Br J Cancer, 2001)[43]	Embolization + oral 5-FU + pravastatin (41) Embolization + oral 5-FU (42)	Excluded (1)
Arterial lipiodolization/arterial chemotherapy (n = 10)		Not performed
23. Kajanti et al. (Am J Clin Oncol, 1992)[44]	Arterial chemotherapy (epidoxorubicin + 5-FU) (10) IV epidoxorubicin + 5-FU (10)	Excluded (1)
24. Ikeda et al. (Cancer Chemother Pharmacol, 1992)[45]	Arterial lipiodolization (ADMOS) (59) Arterial lipiodolization (ADMOS + CDPP) (76)	Excluded (1)
25. Uchino et al. (Am J Clin Oncol, 1993)[46]	Arterial chemotherapy (ADM + CDPP + oral 5-FU (15) Arterial chemotherapy (ADM + CDPP + oral 5-FU + tamoxifen + MPA (15)	Excluded (1)

Table 1. (Cont'd.)

Author (Journal, Year)	Treatment Arms (No. of Patients)	Meta-analysis (Exclusion Criteria)*
	Arterial lipiodolization (ADMOS + CDPP) (76)	
26. Madden et al. (Gut, 1993)[47]	Arterial lipiodolization (5-epidoxorubicin) (25)	Excluded (2)
	Control (25)	
27. Watanabe et al. (Cancer Chemother Pharmacol, 1994)[48]	Arterial lipiodolization (doxorubicin) (38)	Excluded (1)
	Arterial lipiodolization (epidoxorubicin) (39)	
28. Yoshikawa et al. (Cancer Chemother Pharmacol, 1994)[49]	Arterial chemotherapy (epidoxorubicin) (17)	Excluded (1)
	Arterial lipiodolization (epidoxorubicin) (19)	
29. Bhattacharya et al. (Cancer, 1995)[50]	Arterial lipiodolization (epirubicin) (17)	Excluded (1)
	Intra-arterial ^{131}I (11)	
30. Kawai et al. (Semin Oncol, 1997)[51]	Arterial lipiodolization (epidoxorubicin) (208)	Excluded (1)
	Arterial lipiodolization (doxorubicin) (207)	
31. Chung et al. (Cancer, 2000)[52]	Arterial chemotherapy (cisplatin) + IFN-α (19)	Excluded (2)
	Arterial chemotherapy (cisplatin) (23)	
	Control (26)	
32. Chen et al. (World J Gastroenterol, 2002)[53]	Arterial lipiodolization 20 mL (epirubicin + mitomycin) (216)	Excluded (1)
	Arterial lipiodolization 5-15 mL (epirubicin + mitomycin) (257)	
Internal radiation (n = 3)		Not performed
33. Order et al. (Int J Radiat Oncol Biol Phys, 1991)[54]	IV antiferritin ^{131}I (crossover treatment) (n = 48)	Excluded (1)
	IV doxorubicin + 5-FU (n = 50)	
34. Raoul et al. (J Nucl Med, 1994)[55]	Intra-arterial ^{131}I (14)	Excluded (2)
	Suboptimal treatments (tamoxifen, 5-FU) (n = 13)	
35. Raoul et al. (HEPATOLOGY, 1997)[56]	Intra-arterial ^{131}I (n = 73)	Excluded (1)
	Chemoembolization (cisplatin) (n = 69)	
Systemic treatments		
Hormonal compounds		
Antiestrogens: tamoxifen (n = 8)		
Nonactive control arm (n = 7)		Performed
36. Elba et al. (Ital J Gastroenterol, 1994)[57]	Tamoxifen 60 mg/d (11)	Included
	Placebo (11)	
37. Martinez-Cerezo et al. (J Hepatol, 1994)[58]	Tamoxifen 20 mg/d (20)	Included
	Control (16)	
38. Castells et al. (Gastroenterology, 1995)[59]	Tamoxifen 20 mg/d (58)	Included
	Placebo (n = 62)	
39. Manesis et al. (HEPATOLOGY, 1995)[60]	Tamoxifen 30 mg/d + triptorelin (33)	Included
	Flutamide + triptorelin (23)	
	Placebo (29)	
40. CLIP Group (Lancet, 1998)[61]	Any treatment + tamoxifen 40 mg/d (237)	Included
	Any treatment + control (240)	
41. Riestra et al. (J Clin Gastroenterol, 1998)[62]	Tamoxifen 40 mg/d (40)	Included
	Placebo (37)	
42. Liu et al. (Am J Gastroenterol, 2000)[63]	Tamoxifen 30 mg/d (61)	Included
	Placebo (58)	
Inadequate control arm (n = 1)		
43. Melia et al. (Cancer Treat Rep, 1987)[64]	IV doxorubicin + tamoxifen (29)	Excluded (1)
	IV doxorubicin (30)	
Other hormonal compounds (n = 3)		Not performed
44. Grimaldi et al. (J Clin Oncol, 1998)[65]	Anandron + placebo (60)	Excluded (2)
	LHRH agonist + placebo (62)	
	Anandron + LHRH agonist (62)	
	Placebo + placebo (60)	
45. Kouroumalis et al. (Gut, 1998)[66]	SC octreotide (29)	Excluded (2)
	Control (29)	
46. Villa et al. (Br J Cancer, 2001)[67]	Megestrol (21)	Excluded (2)
	Control (24)	
Systemic chemotherapy (n = 9)		Not performed
47. Falkson et al. (Cancer, 1978)[68]	Oral 5-FU (43)	Excluded (1)
	Oral 5-FU + streptozotocin (33)	
	Oral 5-FU + methyl CCNU (44)	
	IV doxorubicin (36)	
48. Melia et al. (Cancer, 1983)[69]	IV doxorubicin (n = 21)	Excluded (1)
	IV VP 16 (n = 14)	
49. Choi et al. (Cancer, 1984)[70]	IV doxorubicin (n = 20)	Excluded (1)
	IV 5-FU + MTX + Cyclophos + incristine (n = 19)	
50. Falkson et al. (J Clin Oncol, 1984)[71]	IV neocarzinostatin (28)	Excluded (1)
	IV doxorubicin (29)	
	IV m-AMSA (24)	

Table 1. (Cont'd.)

Author (Journal, Year)	Treatment Arms (No. of Patients)	Meta-analysis (Exclusion Criteria)*
51. Falkson et al. (Cancer, 1984)[72]	IV doxorubicin (50) Oral 5-FU + streptozotocin (49) Oral 5-FU + methyl CCNU (55) Oral 5-FU + methyl CCNU + IV doxorubicin (38)	Excluded (1)
52. Bezwoda et al. (Oncology, 1987)[73]	IV doxorubicin + VM26 + 5-FU (n = 24) IV m-AMSA + VM26 + 5-FU (n = 24)	Excluded (1)
53. Lai et al. (Cancer, 1988)[74]	IV doxorubicin (60) Control (46)	Excluded (2)
54. Falkson et al. (Am J Clin Oncol, 1990)[75]	IV deoxydoxorubicin (n = 30) Acivicin (n = 26)	Excluded (1)
55. Ishikawa et al. (J Gastroenterol Hepatol, 2001)[76]	Oral tegafur/uracil (28) Control (20)	Excluded (2)
Immunotherapy (n = 4)		Not performed
56. Lai et al. (Br J Cancer, 1989)[77]	IM IFN-α 18 $\times$ 10^6 (n = 50) IV doxorubicin (n = 25)	Excluded (1)
57. Lai et al. (Hepatology, 1993)[78]	IV IFN-α 50 $\times$ 10^6 MUI (35) Control (36)	Excluded (2)
58. Falkson et al. (Am J Clin Oncol, 1995)[79]	IV + IFN-β (31) IV menogaril (34)	Excluded (1)
59. Llovet et al. (Hepatology, 2000)[80]	IM IFN-α 3 $\times$ 10^6 MUI (30) Control (28)	Excluded (2)
Other treatments (n = 2)		Not performed
60. Lai et al. (World J Surg, 1986)[81]	Arterial dearterialization (33) Hepatic arterial ligation + arterial chemotherapy (30) Hepatic arterial ligation + portal chemotherapy (29) External radiation (37) Control (37)	Excluded (2)
61. Van der Merwe et al. (Prostaglandins Leukotr Essent Fatty Acids, 1990)[82]	Oral linolenic acid (31) Placebo (31)	Excluded (2)

NOTE. Fourteen RCTs were included in the meta-analysis.

Abbreviations: PEI, percutaneous ethanol injection: IV, intravenous; 5-FU, 5-fluorouracil; 5′, DFUR, doxifluridine; ADMOS, adriamycin/mitomycin C oil suspension; CDPP, Cis-diammine-dichloroplatinum; MPA, medroxyprogesterone acetate; IFN, interferon; LHRH, luteinizing hormone-releasing hormone; SC, subcutaneous; CCNU, lomustine; MTX, methotrexate; m-AMSA, amsacrine.

*Exclusion criteria: 1, inadequate control arm including treatments potentially active; 2, there are only a few RCTs assessing this treatment, with overall insufficient sample size to perform a meta-analysis.

or published only in abstract form, included patients with liver metastases, or assessed primary or secondary prevention of HCC.

Fourteen full-length published RCTs were adequate for the meta-analysis[27-33,57-63] because they fit with the inclusion criteria and overall provided a sufficient sample size for a given option. The remaining 47 studies were excluded, either because they compared 2 active antitumoral treatments in 35 cases (involving percutaneous treatments [5],[22-26] arterial embolization or chemoembolization [10],[34-43] arterial lipiodolization or arterial chemotherapy [8],[44-46,48-51,53] internal radiation [2],[54,56] systemic chemotherapy [7],[68-73,75,76] immunotherapy [2],[77,79] and tamoxifen [1][64]) or because of an insufficient sample size to perform a meta-analytic approach in 12 cases (including arterial chemotherapy [2 studies, 118 patients],[47,52] systemic chemotherapy [2 studies, 154 patients],[74,76] interferon [2 studies, 129 patients],[78,80] antiandrogens [1 study, 244 patients],[65] octreotide [1 study, 58 patients],[66] megestrol [1 study, 45 patients],[67] internal radiation ^{131}I [1 study, 27 patients],[55] external radiation [1 study, 166 patients],[81] and linolenic acid [1 study]).[82]

Meta-analysis

Two meta-analyses were performed to assess arterial embolization/chemoembolization in 545 patients (7 RCTs[27-33]) (Tables 2 and 3) and tamoxifen in 898 patients (7 RCTs[57-63]) (Tables 4 and 5).

Arterial Embolization. Characteristics of the studies included in the meta-analysis are detailed in Table 2. The core group was constructed with 6 studies including 503 patients[27,29-33] reporting 2-year death rates, whereas an additional study reporting 1-year survival figures was used in the sensitivity analysis.[28] Regarding the core group, 4 studies compared treatment versus conservative management[29,30,32,33] and 2 compared treatment versus suboptimal therapies (one using systemic chemotherapy with 5-fluorouracil[27] and one using oral tamoxifen[31]). Four studies included 2

Table 2. Characteristics of RCTs Included in the Meta-analysis of Arterial Embolization/Chemoembolization Versus Conservative Management/Suboptimal Therapies

	Mean No. of Sessions	No. of Patients	Etiology HCV/HBV/alcohol (%)	Percent With Cirrhosis (% With Child A)	Okuda Stage I/II/III (%)	Segmental Portal Thrombosis (%)	Objective Responses (%)	Survival (%)	
								1 Year	2 Years
Lin et al. (Gastroenterology, 1988)[27]		63	–/80/–	Not described	Not described	Not described			
TAE (Ivalon + Gelfoam powder/cubes)	(2.1 ± 1)	21					13 (61.9)*	42	25
TAE + IV 5-fluorouracil (1g/m^2/5 days)	(1)	21					10 (47.6)*	20	20
IV 5-fluorouracil		21					2 (9.5)	13	13
Pelletier et al. (J Hepatol, 1990)[28]		42	–/7/70	88	26/52/22	Not detailed			
TACE (Gelfoam powder, doxorubicin [50 mg])	(2)	21					7 (33)†	24	NA
Conservative management		21					0	33	NA
Group d'Etude et de Traitment du Carcinome Hépatocellulaire (N Engl J Med, 1995)[29]		96	8/5/78	91 (100)	90/10/0	7 (7.2)			
TACE (Gelfoam particles, cisplatin [70 mg])	(2.9)	50					7 (16)†	62	38
Conservative management		46					2 (5)†	43	26
Bruix et al. (HEPATOLOGY, 1998)[30]		80	62/4/4	100 (82)	67/23/0	0			
TAE (Gelfoam) + coils	(1.4)	40					22 (55)*	70	49
Conservative management		40					0	72	50
Pelletier et al. (J Hepatol, 1998)[31]		73	15/16/53	89 (76)	60/40/0	0			
TACE (Gelfoam, cisplatin [2 mg/kgl]) + tamoxifen	(2.8)	37					9 (24)	51	24
Tamoxifen		36					2 (5.5)	55	26
Lo et al. (HEPATOLOGY, 2002)[32]		79	–/80/–	Not described	47/53/0	21 (26)			
TACE (1 Gelfoam, cisplatin [maximum 30 mg])	(4.8)	40					11 (27)‡	57	31
Conservative management		39					1 (2.6)	32	11
Llovet et al. (Lancet, 2002)[33]		112	85/6/7	100 (70)	65/35/0	0			
TAE (Gelfoam)	(3.08)	37					16 (43)§	75	50
TACE (Gelfoam, doxorubicin [25–75 mg/m^2])	(2.8)	40					14 (35)§	82	63
Conservative management		35					0	63	27

Abbreviations: HCV, hepatitis C virus; HBV, hepatitis B virus; TAE, arterial embolization; IV, intravenous; TACE, chemoembolization.
Objective responses sustained for 1*, 2†, 3‡ and 6§ months.

arms,[29-32] and 2 studies included 3 arms.[27,33] Two studies applied a sequential design.[29,33] Four studies assessed chemoembolization, 1 with doxorubicin[33] and 3 with cisplatin,[29,31,32] whereas 3 studies evaluated embolization alone.[27,30,33] The embolization agent was Gelfoam cubes in all studies (one combined with coils[30] and one with powder and Ivalon[27]), except in one that used Gelfoam powder as the sole embolizing agent.[28] The mean number of treatment sessions ranged between 1 and 4.8 courses. Five of the core

Table 3. Methodological Characteristics of RCTs Included in the Meta-analysis of Embolization/Chemoembolization

Author (Journal, Year)	Methodological Quality					
	Allocation Generation	Allocation Concealment	Double Blinded	Adequate Follow-up	Efficacy of Randomization	Quality Score*
Lin et al. (Gastroenterology, 1988)[27]	1	1	0	1	2	5
Pelletier et al. (J Hepatol, 1990)[28]	1	2	0	1	2	6
Group d'Etude et de Traitment du Carcinome Hépatocellulaire (N Engl J Med, 1995)[29]	1	3	0	1	2	7
Bruix et al. (HEPATOLOGY, 1998)[30]	2	2	0	1	2	7
Pelletier et al. (J Hepatol, 1998)[31]	2	3	0	1	2	8
Lo et al. (HEPATOLOGY, 2002)[32]	1	2	0	1	2	6
Llovet et al. (Lancet, 2002)[33]	2	2	0	1	2	7

*≥6, high-quality trials.

Table 4. Characteristics of RCTs Included in the Meta-analysis of Tamoxifen Versus Conservative Management

	No. of Patients	Etiology HCV/ HBV/alcohol (%)	Cirrhosis (%) (Child A/B/C)	Okuda Stage I/II/III	Performance Status (0/1–2)	Portal Vein Thrombosis (%)	1-Year Survival (%)
Elba et al. (Ital J Gastroenterol, 1994)[57]	22	Not described	100 (18/4/0)	5/16/1	Not described	Not described	
Tamoxifen 60 mg/d	11						72
Placebo	11						45
Martinez-Cerezo et al. (J Hepatol, 1994)[58]	36	31/3/5	100 (18/13/5)	Not described	15/21	6 (16)	
Tamoxifen 20 mg/d	20						50
Control	16						6
Castells et al. (Gastroenterology, 1995)*[59]	120	92/4/9	100 (score 6.4 ± 1)	52/68/0	54/66	42 (35)	
Tamoxifen 20 mg/d	58						51
Placebo	62						43
Manesis et al. (HEPATOLOGY, 1995)[60]	85	11/53/21	82 (score 8.3 ± 2)	Not described	ECOG: 1.4 ± 0.9	Not described	
Tamoxifen 30 mg/d + triptorelin 3.75 mg/mo	33						31
Flutamide 750 mg/d + triptorelin 3.75 mg/mo	23						18
Placebo	29						10
CLIP Group (Lancet, 1998)†[61]	477	344/47/13	91 (206/181/60)	208/169/35	Not described	77 (16)	
Any treatment + tamoxifen 40 mg/d	237						55
(no treatment + tamoxifen 40 mg/d)	128						30
Any treatment + control	240						56
(no treatment)	125						35
Riestra et al. (J Clin Gastroenterol, 1998)[62]	80	45/5/25	100 (score 6.8)	29/31/17	Not described	18 (23)	
Tamoxifen 40 mg/d	40						30
Placebo	37						38
Liu et al. (Am J Gastroenterol, 2000)*[63]	119	–/93/–	65/37/17	10/83/26	ECOG: 1	Not described	
Tamoxifen 30 mg/d	61						2
Placebo	58						0

Abbreviations: HCV, hepatitis C virus; HBV, hepatitis B virus; ECOG, Eastern Cooperative Oncology Group; PEI, percutaneous ethanol injection; TACE, chemoembolization.

*Objective responses reported in the studies by Martinez-Cerezo et al.[58] (1 partial response, tamoxifen arm), Castells et al.[59] (1 partial response, placebo arm), and Liu et al.[63] (no partial responses).

†A total of 253 patients (53%) received only tamoxifen,[61] and 224 patients (47%) also received the following treatments: liver transplantation (3), resection (20), PEI (124), TACE (68), resection + PEI (2), PEI + TACE (6), and resection + PEI + TACE (1).

studies showed a high quality score of 6 to 8 points.[29-33] Four studies were from Europe[29-31,33] and included hepatitis C virus or alcohol-related cirrhotic patients in 88% to 100% of cases, mostly from Child-Pugh A class. Two Asian studies[27,32] included hepatitis B virus–induced chronic liver disease in 80% of cases, although the rate of cirrhotic patients was not described. Two studies treated patients with segmental portal branch tumoral thrombosis.[29,32] The 2-year survival rate in the treated group was 41% (range, 19%-63%) versus 27% (range, 11%-50%) in the control group. Treatment response assessed 1 to 6 months after the procedure showed objective responses in 35% (range, 16%-61%) of patients (108 of 307). Two studies iden-

Table 5. Methodological Characteristics of RCTs Included in the Meta-analysis of Tamoxifen Versus Conservative Management

	Methodological Quality					
Author (Journal, Year)	Allocation Generation	Allocation Concealment	Double Blinded	Adequate Follow-up	Efficacy of Randomization	Quality Score*
Elba et al. (Ital I J Gastroenterol, 1994)[57]	1	1	0	0	0	2
Martinez-Cerezo et al. (J Hepatol 1994)[58]	0	2	0	0	2	4
Castells et al. (Gastroenterology, 1995)[59]	2	3	2	1	2	9
Manesis et al. (HEPATOLOGY, 1995)[60]	1	2	2	1	2	8
CLIP Group (Lancet, 1998)[61]	1	3	0	1	2	7
Riestra et al. (J Clin Gastroenterol, 1998)[62]	1	2	2	0	2	7
Liu et al. (Am J Gastroenterol, 2000)[63]	1	2	0	0	2	5

*≥6 points, high-quality trials.

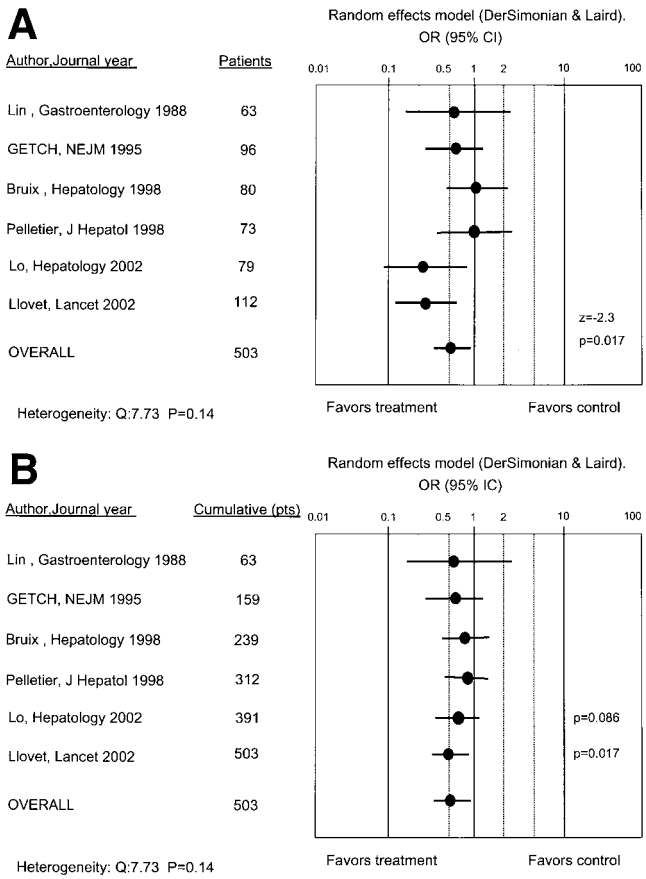

Fig. 2. (A) Meta-analysis of RCTs comparing 2-year survival with chemoembolization/embolization versus conservative management or suboptimal therapies for unresectable HCC (core group). Random effects model (OR, 0.53; 95% CI, 0.32-0.89; $P = .017$). (B) Cumulative meta-analysis according to time of publication.

tified survival benefits favoring treatment,[32,33] and 2 described a trend.[27,29] Meta-analysis of the core group showed a significant improvement in 2-year survival favoring treatment (OR, 0.53; 95% CI, 0.32-0.89; $P = .017$) (Fig. 2).

Sensitivity analysis. Four sensitivity analyses were performed (Fig. 3). When assessing the 4 RCTs (367 patients) with a control arm of conservative management,[29,30,32,33] the results were consistent favoring treatment (OR, 0.46; 95% CI, 0.23-0.89). Similarly, when including high-quality trials (5 RCTs, 440 patients),[29-33] the results were confirmed (OR, 0.53; 95% CI, 0.29-0.97). Sensitivity analysis showed a significant benefit of chemoembolization with cisplatin or doxorubicin assessing 323 patients in 4 studies[29,31-33] (OR, 0.42; 95% CI, 0.20-0.88) but none with embolization alone assessing 215 patients in 3 studies[27,30,33] (OR, 0.59; 95% CI, 0.29-1.20). Overall meta-analysis including 545 patients in 7 studies[27-33] reporting 1-year survival rates showed an OR of 0.64 (95% CI, 0.41-1.01). Heterogeneity among the trials was nonsignificant for the core group ($Q = 7.73$; $P = .14$) and for any of the sensitivity analyses.

Tamoxifen. Characteristics of the studies included in the meta-analysis are detailed in Table 4. The core group was constructed with 7 RCTs (689 patients) assessing tamoxifen as a primary treatment of HCC.[57-63] This accounted for patients from all studies, except for one in which we included 253 patients who received tamoxifen as a primary treatment but discarded 224 patients in which tamoxifen was administered as adjuvant therapy.[61] Six studies included 2 arms, and one included 3 arms.[60] Four studies showed a high-quality score (7-9 points),[59-62] and 3 showed a low score (2-5 points).[57,58,63] Three studies were double blinded,[59,60,62] and 4 were single blinded or open.[57,58,61,63] Six European studies[57-62] included cirrhotic patients (81%-100%) mainly due to hepatitis C virus, and one Asian study[63] reported hepatitis B virus–related liver disease (78%). Two studies excluded Child-Pugh C patients,[57,59] and one excluded patients with Okuda stage III.[59] Half of the patients presented abnormal performance status in the studies in which it was described.[58-60,63] Portal vein thrombosis accounted for 16% to 35% of cases in the studies in which it was reported.[59-62] Tamoxifen was administered orally at a daily dose ranging between 20 and 60 mg. Five studies used placebo in the control arm,[57,59,60,62,63] and 2 used symptomatic therapy.[58,61] The 1-year survival rate was 23% (range, 2%-72%) in treated patients and 22% (range, 0%-46%) in control patients. Partial response to tamoxifen was described in one patient.[58] Meta-analysis of the core group showed no impact of tamox-

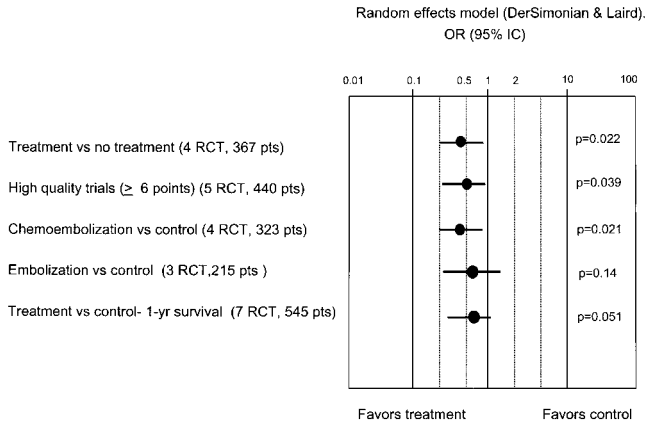

Fig. 3. Sensitivity meta-analysis of the core group (6 RCTs) reporting 2-year survival assessing embolization of RCTs with a control arm of conservative management (4 RCTs),[28,29,32,33] the effect of chemoembolization (4 RCTs),[29,31-33] embolization (3 RCTs),[27,30,33] and high-quality trials (5 RCTs).[29-33] Sensitivity analysis including all studies reporting 1-year survival rates (7 RCTs).[27-33]

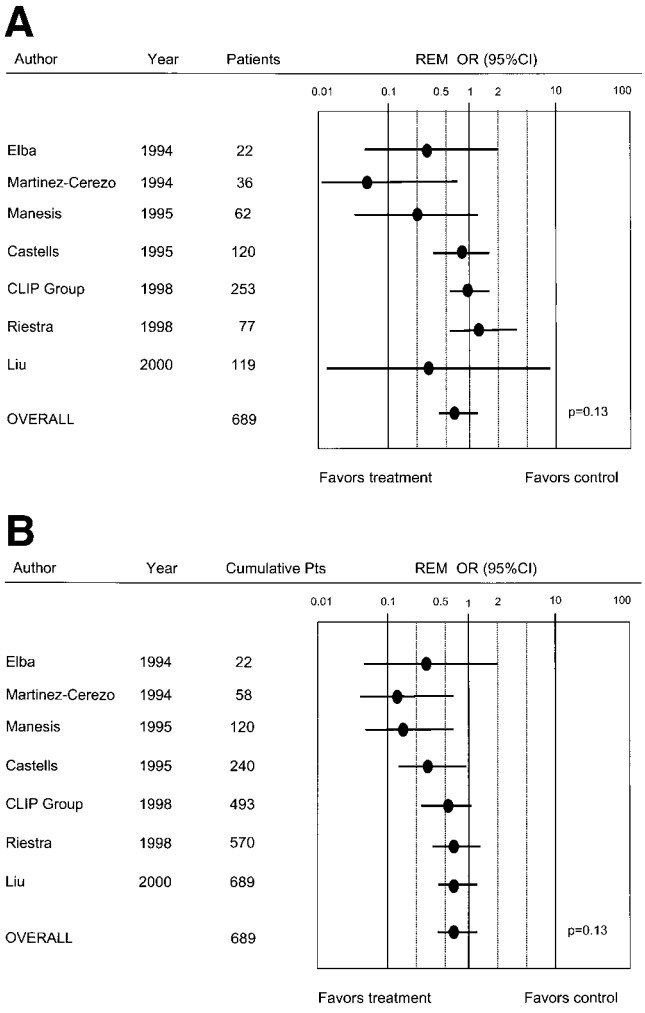

Fig. 4. (A) Meta-analysis of randomized trials comparing 1-year survival with tamoxifen versus conservative management for unresectable HCC. Random effects model (OR, 0.64; 95% CI, 0.36-1.13; $P = .13$). (B) Cumulative meta-analysis according to time of publication.

ifen therapy on 1-year survival (OR, 0.64; 95% CI, 0.36-1.13) (Fig. 4).

Sensitivity analysis. Three sensitivity analyses were performed (Fig. 5). Methodological quality assessment shows negative results for the 4 high-quality trials with 512 patients[59-62] (OR, 0.85; 95% CI, 0.53-1.37) but significant positive benefits favoring tamoxifen when assessing the 3 low-quality trials including 177 patients[57,58,63] (OR, 0.19; 95% CI, 0.05-0.68). Sensitivity analysis of 3 double-blinded, placebo-controlled trials (259 patients)[59,60,62] confirmed the absence of survival benefit (OR, 0.73; 95% CI, 0.34-1.61). The inclusion of all patients randomized in the 7 trials (898 patients),[57-63] also considering tamoxifen as adjuvant therapy in one study,[61] showed similar negative results (OR, 0.65; 95% CI, 0.37-1.15). Heterogeneity among the trials was nonsignificant for the core group ($Q = 10.75$; $P = .22$) and for any of the sensitivity analyses.

Discussion

Despite the fact that surveillance programs have been widely implemented, curative therapies can only be applied to less than 30% of patients with HCC.[3,4] Thus, most patients are diagnosed at more advanced stages and receive palliative interventions that have not shown any unequivocal long-term impact. The lack of standard therapy justifies that active interventions should be explored through RCTs comparing active versus nonactive treatment in carefully selected populations. Phase 3 studies are commonly performed in oncology but few include an untreated control arm, which is mandatory to show outcome benefits. Our systematic review shows that this is also the case for HCC in the past 25 years. Sixty-one RCTs[22-82] assessing primary treatments of HCC have been identified, although meta-analysis was only feasible in 14 studies evaluating embolization[27-33] or tamoxifen.[57-63] The remaining RCTs either did not include a control arm of untreated patients or included a small number of individuals to enable robust conclusions. The present study therefore provides the available data for evidence-based medicine in the HCC field for the past 2 decades.

Our meta-analysis shows a significant survival benefit in patients with unresectable HCC treated by arterial embolization. Although this was the most used treatment worldwide, robust evidence of survival advantages has not been available until now. Two previous systematic reviews reported controversial results.[11,12] A more recent meta-analysis suggested small benefits favoring chemoembolization, but this study had several flaws.[83] Chemoembolization and arterial chemotherapy are analyzed as a single treatment approach, the handling of 3-arm trials is controversial,

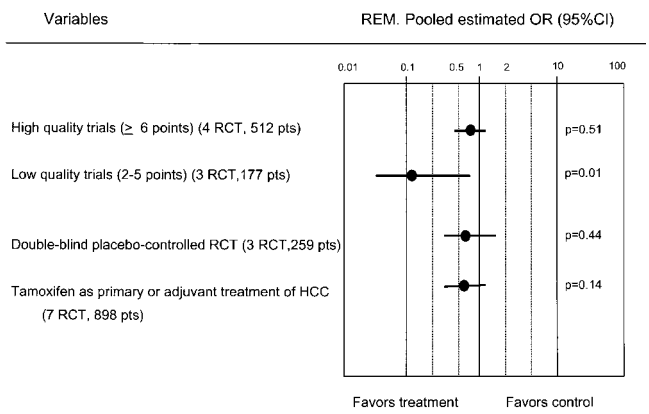

Fig. 5. Sensitivity meta-analysis of tamoxifen assessing 1-year survival. Assessment of high-quality[59-62] versus low-quality trials,[57,58,63] only double-blinded, placebo-controlled studies,[59,60,62] and including all patients randomized also including tamoxifen as an adjuvant treatment of HCC.[57-63]

and some studies published at that time are missing[28,36,43,44,46,47,50,52] whereas quasi-RCTs are included.[84] Seven new RCTs assessing embolization have been published since the first review,[30-33,41-43] 4 of which include an untreated control arm.[30-33] These new data provide the rationale to propose arterial chemoembolization as the standard therapy in a subset of patients with unresectable HCC.

Now the issue is which patients may benefit from treatment and which schedule should be applied. Selection of candidates is a key point. Most of the studies include Child-Pugh A patients (70%-100% of reported cases), Okuda stage I (47%-90% of cases), with multinodular HCC without vascular invasion (overall >95%). In contrast, 2 studies reporting the lowest control rate have included patients at very advanced stages[28] (74% Okuda stage II-III) or with segmental vascular invasion[32] (26% of cases). Thus, patients with well-preserved liver function and multinodular HCC without vascular invasion seem the best target population. However, not all of these patients respond to therapy, and this should be the major effect leading to improvement in survival. Objective responses lasting 1 to 6 months were achieved in 35% of cases and associated with a significantly lower incidence of portal vein thrombosis in 2 studies.[29,33] Furthermore, response to treatment was identified as an independent predictor of survival.[33] Therefore, well-selected candidates achieving treatment response may be those who will obtain the major survival advantage. However, it has to be considered that these studies were not designed to address this issue and thus do not provide enough information to perform a sensitivity analysis. A meta-analysis of individual data is recommended to further explore the optimal target population.

The type of embolization agent and the treatment schedule to be applied was partially explored in the sensitivity analysis. Survival benefits were identified with chemoembolization (doxorubicin or cisplatin) but not with embolization alone, although these results should be considered with caution because of the small sample size of the studies. Benefits were identified in 2 RCTs using chemoembolization,[32,33] and a trend was recognized in another trial also using chemotherapeutic agents.[29] It is still unknown whether adding chemotherapy to the embolization agent enhances its antitumoral effect.[35,37-39] Studies from Japan suggest that chemoembolization with doxorubicin provides a higher antitumoral effect compared with embolization alone.[35] Other collaborative studies identified survival benefits favoring chemoembolization with doxorubicin compared with farmorubicin.[37] All of these issues should be clarified in further RCTs comparing 2 active therapies. Regarding the treatment schedule, the 2 positive RCTs applied an active retreatment schedule with 2.9 to 4.8 treatments per patient.[32,33] This schedule may be tolerated by patients with preserved liver function, in which the potential benefit is not offset by treatment-induced liver failure.

Only 7 RCTs exploring embolization and including an untreated arm have been produced in the HCC field in 25 years: 5 in Europe[28-31,33] and 2 in Asia.[27,32] Therefore, concerns arise regarding the heterogeneity of the population studied. French studies[28,29,31] include mostly patients with alcohol-induced cirrhosis, those from the Barcelona group[30,33] include patients with hepatitis C virus–induced cirrhosis, and Asian studies[27,32] include patients with hepatitis B virus–induced cirrhosis. Whether the outcome may vary according to the cause of the disease, particularly in active alcoholic patients with alcohol-induced extrahepatic disease, is not clearly known. As previously mentioned, the control rate was lower in Asian trials. Although heterogeneity among the trials was not statistically significant, we used the random effect approach to control that potential flaw. Another concern regards the strict criteria applied for selecting RCTs in the meta-analysis that may lead to publication or location bias.[85] We included only published full-length papers with an untreated controlled arm, because they provide the minimum information to properly analyze the primary end point of the study. In our opinion, the inclusion of trials assessing different active interventions may lead to confounding results. We excluded non-English studies because language-restricted meta-analysis does not induce any bias in the estimates of intervention effectiveness.[86] We established a stringent minimum sample size in the design of meta-analysis to avoid nonrobust conclusions. However, we are aware that the possibility of a degree of "file drawer effect" or publication bias cannot be ruled out in a study with 7 small RCTs including 545 patients. In this sense, we encourage all unpublished studies or ongoing trials to be published, although new evidence from megatrials (with >1,000 patients) including an untreated controlled arm are not expected in this field and may nowadays be unfeasible.

The efficacy of antiestrogen therapy in advanced HCC has also been controversial. Our meta-analysis shows that tamoxifen does not provide significant antitumoral effect or survival benefits and that the positive results identified in the early 1990s were due to a methodological bias and random error of small-sized studies.[57,58] In fact, the inclusion of double-blinded, placebo-controlled studies with large series of patients in cumulative meta-analysis shows a completely negative overall effect.[59,60,62] These results are reinforced when particularly focusing on high-quality trials.[59-62] It has to be noted that none of the trials in-

cluded in the meta-analysis had by itself enough sample size to reach a robust conclusion. Concerns of publication bias due to the nature of our strict selection criteria can again be raised because we have only accepted published RCTs in peer-review journals reporting 1-year survival rates. However, at least 3 additional RCTs[87-89] have been reported in abstract form, including about 800 patients both in Europe and Asia, all of which report negative results when comparing tamoxifen with control. Therefore, a bias in the estimates of treatment effect is unlikely and the final publication of these 3 RCTs is not expected to change the results. In any case, with the data available, there is no rationale to further assess the usefulness of this treatment in patients with advanced HCC.

Several treatments of unresectable HCC, such as immunotherapy with interferon,[78,80] antiandrogen therapy,[65] internal radiation,[55] and arterial[47,52] or systemic chemotherapy,[74,76] have also been evaluated in comparison with conservative management. However, none included a sufficient number of patients to guarantee a robust analysis. Although meta-analysis is technically possible, it is not clinically sound and the potential bias in the estimates of treatment effect may not be properly controlled. Therefore, further studies should be published to ensure a solid assessment, mainly in reference to therapies with acceptable response rates, such as internal radiation[54-56] or arterial chemotherapy.[44-50]

In summary, the present systematic review provides consistent evidence that arterial chemoembolization may benefit a subset of patients with unresectable HCC and thus proposes this therapy as the standard intervention in these cases. The data are relevant for the decision-making process of these patients, who at present do not have any option for cure.

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