

# Systematic review: evidence-based management of hepatocellular carcinoma – an updated analysis of randomized controlled trials

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## SUMMARY

The treatment strategy of hepatocellular carcinoma applied following scientific guidelines is only supported by 77 randomized controlled trials published so far, a figure that clearly pinpoints hepatocellular carcinoma as an 'orphan' cancer in terms of clinical research when compared with other high-prevalent cancers worldwide.

A systematic review analysing 61 randomized controlled trials (1978–2002) showed a modest survival benefit from chemoembolization in patients with intermediate tumours, and the lack of an effective first-line treatment option for patients with advanced disease. These conclusions have been endorsed by the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases.

The present updated evidence-based approach includes 16 randomized controlled trials published from 2002 to 2005 assessing percutaneous ablation (seven), other loco-regional therapies (three) and systemic therapies (six). Eight showed high-quality methodological profiles.

Four randomized controlled trials demonstrated a better local hepatocellular carcinoma control in tumours larger than 2 cm treated by radiofrequency ablation compared with ethanol injection. No survival advantages were obtained from systemic treatments in patients with advanced hepatocellular carcinoma, an area that is an unmet need. Therefore, there is an urgent request to conduct well-designed phase III investigations in hepatocellular carcinoma patients.

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## INTRODUCTION

Hepatocellular carcinoma (HCC) is a major health problem, being the fifth most common cancer worldwide with 626 000 new cases in 2002.<sup>1</sup> The incidence of HCC is increasing in Europe and the US,<sup>2</sup> and is currently the leading cause of death amongst cirrhotic patients.<sup>3</sup> HCC has been classically considered a neoplasm with a dismal prognosis. However, with the advent of surveillance programmes, the scientific community has experienced a switch in the type of tumours detected and the medical interventions potentially effective for them. Nowadays, the majority of HCC patients are diagnosed at stages in which new loco-regional and systemic treatments can be tested within clinical investigations.<sup>4, 5</sup> Therefore, there is a growing interest in understanding the advantages of these treatments from an evidence-based perspective.

In oncology, the benefits of treatments should be assessed through randomized controlled trials (RCTs) and meta-analysis. Other sources of evidence, such as non-randomized clinical trials or observational studies are considered less robust. RCTs should be conducted when there is uncertainty on the final outcome comparing two arms. No such approach is justified, however, if the results obtained in the setting of cohort studies are clearly better compared with the natural course of the disease. This is the case of resection, liver transplantation and percutaneous ablation as therapies for early HCC tumours, which provide survival rates better than their untreated counterparts (5-year survival rates of 40–70% vs. <20%).<sup>4</sup> By contrast, at more advanced stages there is uncertainty in whether any treatment approach may enhance survival, and thus RCTs are needed. The primary end-point of these studies should be overall survival or cancer-specific death, whereas other end-points such as time-to-progression or quality of life might be considered surrogates.

Few medical interventions have been thoroughly tested in HCC, in contrast with other cancers with a high prevalence worldwide, such as lung, breast, colorectal and stomach cancer. Unfortunately, the fact that HCC is a tumour with a low incidence in developed countries has resulted in that the amount of information coming from controlled studies is scarce. There are no mega-RCTs (with >1000 patients) or meta-analysis of individual data in the HCC field, which are considered the 'best source of evidence'. Thousands of RCTs evaluating therapeutic interventions have been

published in each of the major cancers, for only about 80 RCTs in HCC. As a result, the strength of evidence for any intervention in HCC is far behind the most prevalent cancers worldwide. There is an urgent need to conduct randomized investigations in liver cancer, which at this point can be considered as an 'orphan' neoplasm in terms of clinical research.

## REVIEW OF RANDOMIZED CONTROLLED TRIALS AND LEVELS OF EVIDENCE

The Barcelona 2000 HCC Conference endorsed by the European Association for the Study of Liver<sup>6</sup> and the 2005 Conference endorsed jointly by the American Association for the Study of Liver Diseases–European Association for the Study of the Liver–Japanese Society of Hepatology defined the need of assessing new treatments for HCC in the setting of multicentre, large, well-designed RCTs. Following those mandates, we present herein the evidence of treatment benefits for HCC patients based on a comprehensive analysis of all RCTs published until December 2005. To that end, we have updated the systematic review published by Llovet and Bruix, analysing 61 RCTs–phase III studies between January 1978 and May 2002.<sup>7</sup> The methods used for the current review are summarized in Table 1. In brief, we have included RCTs published between June 2002 and December 2005 in English as full manuscripts and assessing primary treatments of HCC. All other clinical investigations, such as observational studies, cases series, case–control studies, non-randomized clinical trials or randomized phase IIb studies have been excluded. Among 223 clinical trials identified during this period, only 16 studies were published according to the above-mentioned characteristics, while the remaining 207 were excluded from the current analysis (Tables 2–5). These randomized investigations tested percutaneous ablative therapies ( $n = 6$ ), other loco-regional approaches ( $n = 4$ ) and systemic treatments ( $n = 6$ ) (Table 3). Four of these studies were conducted in Europe and 12 in Asia. Four RCTs included more than 200 patients. Survival was considered as primary end-point in twelve cases. The methodological quality was thoroughly reviewed following a modification of the standard scale of Jadad including five components that provide a 10-point score<sup>7, 8</sup> (Table 1). As a result, half of the trials showed a high-quality score, a trend similar to the previous period (Table 6).

The present review aims to provide and update comprehensive analysis of the estimates of benefits for all

**Table 1.** Characteristics of the search and selection of randomized controlled trials (RCTs) assessing primary treatments for hepatocellular carcinoma (HCC)**Study objectives**

The primary end-point was to analyse the RCTs assessing medical interventions as primary treatment of HCC published as full papers. The secondary end-point was to assess the methodological quality of the studies included in the review

**Selection criteria of trials**

RCTs published as full papers in peer-review journals, assessing medical therapies as primary treatment of HCC

Period: June 2002 to December 2005

Language: English

Characteristics: we included studies comparing two or more active antitumoral treatments, treatment vs. conservative management or suboptimal therapies. Quasi-RCTs, randomized phase II 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

**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 III studies,' 'double-blind,' 'placebo,' 'review,' 'meta-analysis,' 'therapy' and 'treatment' as well as a manual search and review of reference lists

**Quality assessment\*****Allocation sequence generation**

Computer-generated of random numbers or similar: 2 points

Not described or inadequate: 1

**Allocation concealment**

Central randomization: 3 points

Sealed envelopes or similar: 2

Not described or inadequate: 1

**Double blinding**

Identical placebo tablets or double dummy: 2 points

Double-blind, but method not described: 1

No double blinding or inadequate method: 0

**Description of protocol deviations**

Numbers and reasons described: 1

Not described: 0

**Efficacy of randomization**

Prognostic variables balanced, presented in tabular form: 2 points

Prognostic variables balanced and described in text: 1

No information reported or variables unbalanced: 0

\* The 10-point score is ranked high ( $\geq 6$  points) or low ( $\leq 5$  points) to define high and low levels of quality respectively.

the treatments assessed through phase III studies. The strength of evidence has been classified according to the recommendations of the National Cancer Institute, where a hierarchy is established considering the strength of study design and the strength of end-points<sup>9</sup> (Table 2).

## CURATIVE THERAPIES

### Surgery: resection and transplantation

There is no agreement on a common treatment strategy for patients with HCC worldwide, and several proposals have been published.<sup>4, 10</sup> The three major

curative therapies, resection, liver transplantation and percutaneous treatments, compete as first-line treatment option for small single HCC in patients with well-preserved liver function. Evidence of benefit from curative therapies is derived from numerous non-randomized cohort studies (3iiA, Table 2).

Surgery is the mainstay of HCC treatment. Resection and transplantation achieve the best outcomes in well-selected candidates (5-year survival of 60–70%), and are considered as the first option in patients with early tumours from an intention-to-treat perspective.<sup>12, 13</sup> Resection yields good results (5-year survival 60–70%) in candidates who present with single tumours and excellent liver functional reserve (3iiA). Japanese

Treatments assessed	Benefit (evidence)*	RCTs	
		1978–2002†	2002–2005
<b>Surgical treatments</b>			
Surgical resection	Increase survival (3iiA)	0	1
Liver transplantation	Increase survival (3iiA)	0	0
<b>Loco-regional treatments</b>			
Percutaneous treatments (PEI/RF)	Increase survival (3iiA)	5	6
Embolization/chemoembolization	Increase survival (1iiA)	17	2
Lipiodolization/arterial chemotherapy	Treatment response (3iiDiii)	10	1
Internal radiation (I <sup>131</sup> , Y <sup>90</sup> , others)	Treatment response (3iiDiii)	3	0
<b>Systemic treatments</b>			
<b>Hormonal compounds</b>			
Tamoxifen	No survival benefit (1iA)	8	4
Anti-androgens		1	
Others		2	1
Systemic chemotherapy	No survival benefit (1iiA)	9	1
Immunotherapy	No survival benefit (1iiA)	4	0
Other treatments	No survival benefit (1iiA)	2	
<b>Total</b>		<b>61</b>	<b>16</b>

**Table 2.** Evidence-based benefits of treatments according to the strength of study design and of end-points

Update summary of randomized controlled trials (RCTs) published between 1975 and 2005 assessing primary treatments of hepatocellular carcinoma (HCC).

\* Classification of evidence adapted from NCI: <http://www.cancer.gov>. Study design: randomized controlled trial, meta-analysis = 1 (double-blinded, 1i; non-blinded, 1ii); non-randomized controlled trials = 2; case series = 3 (population-based 3i, non-population-based, consecutive 3ii, non-population based, non-consecutive 3iii); end-point: survival (A), cause-specific mortality (B), quality of life (C), indirect surrogates (D), disease-free survival (Di), progression-free survival (Dii), tumour response (Diii).

† Adapted from Llovet and Bruix.<sup>7</sup>

PEI, percutaneous ethanol injection; RF, radiofrequency ablation.

authors use the indocyanine green clearance to identify the best candidates, whilst portal pressure and bilirubin are the parameters used in Europe.<sup>12</sup> Tumour recurrence complicates 70% of cases at 5 years, and no adjuvant therapy has unquestionably proven to prevent this complication through RCTs<sup>14, 15</sup> (1iiDiii).

Transplantation is the first choice for patients with small multinodular tumours (three nodules  $\leq 3$  cm) or those with advanced liver dysfunction<sup>12, 13</sup> (3iiA). Theoretically, transplantation may simultaneously cure the tumour and the underlying cirrhosis. The broad selection criteria applied two decades ago led to poor results in terms of recurrence (32–54%) and survival (5-year survival <40%), but allowed the identification of the best candidates for transplantation.<sup>14</sup> These are patients with single HCC  $\leq 5$  cm or up to three nodules  $\leq 3$  cm who in major Liver and Transplantation Units achieve

70% survival at 5 years with a recurrence rate below 15%.<sup>12, 13</sup> The major drawback of transplantation is the scarcity of donors. The enlargement of waiting time has led 20% of the candidates to drop-out before receiving the procedure, thus jeopardizing the outcome if analysed according to intention-to-treat. Adjuvant therapies whilst on the waiting list are used in most centres to prevent tumour progression. Robust data from RCT are lacking and thus, the potential benefits advocated for percutaneous ablation, chemoembolization or chemotherapy are derived from observational studies and cost-effective analyses (3iiDiii).

### Percutaneous treatments

Percutaneous ablation achieves complete responses in more than 80% of tumours smaller than 3 cm in

**Table 3.** Randomized controlled trials published in English as full papers between June 2002 and December 2005 assessing primary treatments of hepatocellular carcinoma

Reference	Treatment arms (no. patients)
Loco-regional treatments ( <i>n</i> = 10)	
Surgical resection ( <i>n</i> = 1)	
1. Huang <i>et al.</i> <sup>19</sup>	Resection (38) PEI (38)
Percutaneous treatments ( <i>n</i> = 6)	
2. Lin <i>et al.</i> <sup>20</sup>	RF (62) PEI (62) PAI (63)
3. Shiina <i>et al.</i> <sup>21</sup>	RF (118) PEI (114)
4. Lin <i>et al.</i> <sup>22</sup>	RF (52) PEI (52) PEI high dose (53)
5. Lencioni <i>et al.</i> <sup>23</sup>	RF (52) PEI (50)
6. Shibata <i>et al.</i> <sup>24</sup>	RF (36) Microwave coagulation (36)
7. Lin <i>et al.</i> <sup>25</sup>	Microwave coagulation + Shenqi mixture (36) Microwave (36)
Embolization/chemoembolization ( <i>n</i> = 2)	
8. Akamatsu <i>et al.</i> <sup>32</sup>	Embolization + PEI (12) PEI (14) Embolization + RF(10) RF (6)
9. Becker <i>et al.</i> <sup>33</sup>	TACE + PEI (29) TACE (29)
Lipiodolization ( <i>n</i> = 1)	
10. Homma <i>et al.</i> <sup>31</sup>	Lipiodol-Adriamycin (34) Lipiodol-Carboplatin (31)
Systemic treatments ( <i>n</i> = 6)	
11. Barbare <i>et al.</i> <sup>36</sup>	Tamoxifen (210) Placebo (210)
12. Chow <i>et al.</i> <sup>37</sup>	Tamoxifen 60 ng/day (76) Tamoxifen 120 mg/day (121) Placebo (132)
13. Trinchet <i>et al.</i> <sup>38</sup>	Tamoxifen (184) Leuprorelin/flutamide/tamoxifen (192)
14. Pan <i>et al.</i> <sup>39</sup>	Tamoxifen + octreotide (15) 5-Fu + mitomycin C (15)
15. Yuen <i>et al.</i> <sup>40</sup>	Long-acting octreotide (35) Placebo (35)
16. Yeo <i>et al.</i> <sup>41</sup>	Doxorubicin (94) Cisplatin/interferon- $\alpha$ 2b/ doxorubicin/fluorouracil (PIAF) (94)

PEI, Percutaneous ethanol injection; PAI, percutaneous acetic acid injection; RF, radio-frequency ablation; TACE, transarterial chemoembolization.

diameter, but in 50% of tumours of 3–5 cm in size<sup>16</sup> (1iiD). The best results obtained in series of HCC patients treated by percutaneous ethanol injection (PEI) or radiofrequency ablation (RF) provide 5-year survival rates of 40–70%.<sup>17, 18</sup> The best outcomes have been reported in Child–Pugh A patients with small single

tumours, commonly <2 cm in diameter.<sup>16</sup> Independent predictors of survival are initial complete response, Child–Pugh score, number or size of nodules, and base-line alpha-fetoprotein levels. Thus, Child–Pugh A patients with non-surgical small tumours – that are expected to achieve complete responses – are the ideal

**Table 4.** Randomized controlled trials assessing percutaneous treatments as primary therapies in hepatocellular carcinoma

	No. patients	Aetiology HCV/HBV	Cirrhosis (child A/B)	Tumour size (≤2/>2 cm)	Complete necrosis (%)	1-year survival (%)			Local recurrence
						1 year	2 year	4 year	
Huang <i>et al.</i> <sup>19</sup>	76	35/35	78 (57/3)	45/31	nd				Overall recurrence rate
PEI	38					100	100	92	47%
Resection	38					97	91	88	39%
Lin <i>et al.</i> <sup>20</sup>	187	60/124	100 (138/49)	111/76					2 year
RF	62				96	93	81	nd	14%
PEI	62				88	88	66	nd	34%
PAI	63				92	90	67	nd	31%
Shiina <i>et al.</i> <sup>21</sup>	232	188/29	100 (170/62)	102/130					2 year
RF	118				100	97 (94*/99†)	91 (89*/93†)	74 (70*/77†)	2%
PEI	114				100	92 (93*/95†)	81 (78*/85†)	57 (48*/64†)	11%
Lin <i>et al.</i> <sup>22</sup>	157	46/109	100 (119/37)	47/110					2 year
RF	52				96	90	82	nd	18%
PEI	52				88	85	61	nd	45%
PEI high dose	53				92	88	63	nd	33%
Lencioni <i>et al.</i> <sup>23</sup>	102	42/15	100 (80/22)	nd‡					2-year LRFS
RF	52				91§	100	98	nd	4%
PEI	50				82§	96	88	nd	38%
Shibata <i>et al.</i> <sup>24</sup>	72	66/5	100 (40/32)	42/52					2 year
RF	36				96	nd	nd	nd	12%
Microwave coagulation	36				89	nd	nd	nd	24%

nd, Not described; LRFS, local recurrence-free survival; PEI, percutaneous ethanol injection; RF, radiofrequency ablation; PAI, percutaneous acetic acid injection; HCV, hepatitis C virus; HBV, hepatitis B virus.

\* Subgroup analysis: patients with multiple tumours.

† Subgroup analysis: patients with solitary tumour.

‡ Mean tumour size PEI (2.8 cm) RFA (2.8 cm).

§ Values after one RF session or one PEI cycle.

candidates to PEI and RF. Treatment of patients with larger tumours (3–5 cm), multiple tumours (three nodules <3 cm) and advanced liver failure (Child–Pugh B) is reasonable on individual basis. Although these treatments provide good results, they are unable to achieve response rates and outcomes comparable with surgical treatments, even when applied as the first option<sup>11</sup> (3iiA).

#### *Curative treatments: evidence obtained from new RCT 2002–2005*

Huang *et al.* published in 2005 the first RCT directly comparing resection and PEI in 76 patients with one to two tumours of <3 cm.<sup>19</sup> According to the authors, there were no statistically significant survival differ-

ences between groups, despite a 5-year survival rate of 82% for resection and 45% for PEI. Concerns regarding the power of the study (recruitment stopped at 76 patients of 120 estimated), allocation bias and methodological quality (quality score 5) and the selection of the target population (Child–Pugh B should be a contraindication for resection) preclude to achieve consistent conclusions. Nonetheless, we have to acknowledge that the Taiwanese group has pioneered this controversial area of research. Further trials comparing these two approaches are encouraged, particularly in tumours of <2 cm, which have been considered the main area of controversy between both treatments.<sup>14</sup> Beyond this size, the complete necrosis rate achieved by percutaneous ablation is still far from that obtained with resection.

Table 5. Clinical characteristics of randomized controlled trials of systemic treatments, arterial chemotherapy and combined treatments

	No. patients	Etiology HCV/HBV/ alcohol (%)	Percent with cirrhosis (% with child A)	Performance status (0/1-2)	Objective response	Portal thrombosis (%)	Survival
Barbare <i>et al.</i> <sup>36</sup>							
Tamoxifen (20 mg/day)	210	14/6/73	90 (48)	22/78	NA	41	1 year (23%)
Placebo	210	11/6/78	87 (50)	15/85		37	(20%) 3 month
Chow <i>et al.</i> <sup>37</sup>							
Tamoxifen (60 mg/day)	74	NA	NA/55				41%
Tamoxifen (120 mg/day)	121		NA/38	21/68	NA	NA	35%
Placebo	132		NA/40	24/69			44%
Trinchet <sup>38</sup>							
Leuprorelin (3.75 mg/month s.c.) + flutamide (750 mg/day p.o.) + tamoxifen (30 mg/day)	192	19/3/72	90 (62)		NA	21	1 year 23%
Tamoxifen (30 mg/day)	184	13/10/74	93 (68)	NA	NA	15	28%
Pan <i>et al.</i> <sup>39</sup>							
Tamoxifen (40 mg/day) + octreotide (0.6 mg/day)	15	NA	NA		CR: 26%	NA	1 year 64%
5-FU (1 g b.i.w) i.v. + MMC (20-30 mg q.w.) i.v.	15				PR: 46%		21%
Yuen <i>et al.</i> <sup>40</sup>					CR: 0%		
Short-acting octreotide (250 µg b.i.d s.c. × 2 week) followed by long-acting octreotide (30 mg s.c. Q14W × 6 doses)	35	NA/86/NA	71 (51)	NA	CR: 0%	48.6	Median survival 1.9 month
Placebo	35		86 (34)		CR: 12.5%	60	1.9 month
Yeo <i>et al.</i> <sup>41</sup>							
Gisplatin/interferon-α2b/ doxorubicin/fluorouracil†	94	4/82	44 (78)	92.5/7.5	CR: 0%	54	Median survival 8.7 month
Doxorubicin‡	94	8/80	48 (82)	87/13	PR 20%	43	6.8 month
Homma <i>et al.</i> <sup>31</sup>					CR: 0%	NA	1 year 40%
Intrahepatic arterial infusion doxorubicin (20 mg/m <sup>2</sup> )-lipiodol	34	76/12/NA	85 (56)	NA	PR 22.6%	NA	60%
Carboplatin (150 mg/m <sup>2</sup> )-lipiodol	31	71/19/NA	81 (52)		CR: 6.5%		
Akamatsu <i>et al.</i> <sup>32</sup>					PR: 22.6%		1 year

Table 5. Continued

	No. patients	Etiology HCV/HBV/alcohol (%)	Percent with cirrhosis (% with child A)	Performance status (0/1-2)	Objective response	Portal thrombosis (%)	Survival
TAES + percutaneous (PEI, RF)	22	92-70/10/NA	50-77 (70-58)	NA	NA	NA	95
Percutaneous (PEI, RF)	20	83-64/17-14/NA	50 (86)				82
Becker <i>et al.</i> <sup>33</sup>							1 year
TACE¶ + PEI	27	30/57	92 (63)	NA	0%	22.2	62
TACE	25	32/55	88 (88)		0%	32	63
Lin <sup>25</sup>			Karnofsky				1 year
Shenqi mixture 20 mL t.i.d × 1 month + microwave coagulation	36	NA	64-5	CR: 8%; PR: 66%		NA	83
Microwave coagulation	36	NA	66	CR: 3%; PR: 53%			67

CR, Complete response; PR, partial response; NA, not available; HCV, hepatitis C virus; HBV, hepatitis B virus; PEI, percutaneous ethanol injection; RF, radiofrequency ablation; TACE, transarterial chemoembolization; TAE, transarterial embolization; 5-FU, 5-fluorouracil; MMC, mitomycin.

† Cisplatin 20 mg/m<sup>2</sup> on days 1 through 4, interferon- $\alpha$ 2b 5 MU/m<sup>2</sup> on days 1 through 4, doxorubicin 40 mg/m<sup>2</sup> on day 1, 5-FU 400 mg/m<sup>2</sup> on days 1 through 4 every 3 weeks for up to six cycles.

‡ Doxorubicin 60 mg/m<sup>2</sup> on day 1 every 3 weeks for up to six cycles.

§ Gelfoam.

¶ Mitomycin/Gelfoam.

**Table 6.** Assessment of the quality of the design of randomized controlled trials according to the modified scale of Jadad

Reference	Allocation generation	Allocation concealment	Double-blinded	Adequate follow-up	Efficacy of randomization	Quality score*
Chow <i>et al.</i> <sup>37</sup>	1	3	2	1	1	8
Trinchet <sup>38</sup>	2	3	0	1	2	8
Becker <i>et al.</i> <sup>33</sup>	1	3	0	1	2	7
Lin <i>et al.</i> <sup>20</sup>	2	1	0	1	2	6
Shiina <i>et al.</i> <sup>21</sup>	2	1	0	1	2	6
Lin <i>et al.</i> <sup>22</sup>	2	1	0	1	2	6
Lencioni <i>et al.</i> <sup>23</sup>	2	1	0	1	2	6
Yuen <i>et al.</i> <sup>40</sup>	2	2	0	0	2	6
Shibata <i>et al.</i> <sup>24</sup>	1	2	0	0	2	5
Yeo <i>et al.</i> <sup>41</sup>	1	1	0	1	2	5
Huang <i>et al.</i> <sup>19</sup>	1	1	0	1	2	5
Barbare <i>et al.</i> <sup>36</sup>	1	1	0	1	2	5
Homma <i>et al.</i> <sup>31</sup>	1	1	0	0	2	4
Akamatsu <i>et al.</i> <sup>32</sup>	1	2	0	0	0	3
Pan <i>et al.</i> <sup>39</sup>	1	1	0	0	0	2
Lin <i>et al.</i> <sup>25</sup>	1	1	0	0	0	2

Studies are sorted according to the quality score.

\* Trials rated  $\geq 6$  were considered of high quality.

To our knowledge, at least two RCTs are currently underway in China.

The Barcelona 2000 Consensus conference recommended comparing different percutaneous approaches in the setting of well-designed RCTs.<sup>6</sup> Six new RCTs including 822 patients were identified, four comparing PEI or percutaneous acetic acid injection (PAI) vs. RF,<sup>20–23</sup> one comparing microwave coagulation vs. RF<sup>24</sup> and another comparing microwave coagulation associated with Chinese herbs in early HCC patients<sup>25</sup> (Tables 3–4). The four high-quality studies had either survival<sup>21, 23</sup> or local recurrence as primary endpoint<sup>20, 22</sup> (Table 6). Survival advantages favouring RF vs. PEI were identified in the study by Shiina *et al.*<sup>21</sup> including 232 Japanese patients (4-year survival 74% vs. 57%,  $P = 0.02$ ). Conversely, no differences in survival were reported in the European RCT conducted by Lencioni *et al.*<sup>23</sup> (2-year survival rates of 98% for RF vs. 88% for PEI, ns). Two additional RCTs from Lin *et al.* reported survival advantages in the subgroup analysis of tumours larger than 2 cm favouring RF compared with either PEI or PAI.<sup>20, 22</sup> Therefore, the characteristics and data provided so far do not provide enough evidence to support survival benefits coming from RF, and further research is needed (1iiA).

A more consistent message has been delivered regarding the impact of RF on the local control of

HCC. The actuarial probability of local recurrence was significantly lower in the RF arm compared with either PEI arm or PAI arm in all four studies (2 year local recurrence rate: 2–18% vs. 11–45%), either assessed as primary or secondary end-point<sup>20–23</sup> (1iiD). It has been speculated that ethanol diffusion is blocked either by the intratumoral fibrotic septa and/or the tumour capsule. This undermines the curative capacity of this technique, particularly in tumours larger than 2 cm. The energy generated by RF ablation, in contrast, induces coagulative necrosis of the tumour producing a ‘safety ring’ of non-tumoral tissue, which might eliminate small undetected satellites.

Consistent with previous studies, RF requires fewer treatment sessions to achieve comparable antitumoral effects. Complete response rates were of 96–100% for RF vs. 86–89% for PEI. As it was described in one RCT,<sup>20</sup> the main drawback of RF is its higher rates of adverse events compared with PEI.

## PALLIATIVE THERAPIES

### Arterial embolization and other loco-regional treatments

Arterial embolization is the most widely used primary treatment for unresectable HCC RF.<sup>4, 26</sup> In early stages,

it may not be indicated as first-line option, as an outcome review from Japan reported worse results than surgery or percutaneous ablation.<sup>11</sup> Obstruction of hepatic artery induces extensive necrosis in large vascularized HCC. Embolization agents – usually gelatin or microspheres – may be administered together with selective intra-arterial chemotherapy mixed with lipiodol (chemoembolization). Doxorubicin, mitomycin and cisplatin are the commonly used antitumoral drugs.<sup>26</sup> Arterial embolization achieves partial responses in 15–55% of patients,<sup>4, 26</sup> and significantly delays tumour progression and vascular invasion<sup>27, 28</sup> (1iiDii).

A systematic review of RCTs published from 1978 to 2002 identified seven RCTs including a total of 516 patients comparing embolization vs. conservative management, five of which assessing chemoembolization with doxorubicin or cisplatin.<sup>7</sup> Survival benefits were obtained in two studies,<sup>27, 28</sup> one of which identifies treatment response as an independent predictor of survival.<sup>27</sup> Meta-analysis showed a beneficial survival effect of embolization/chemoembolization in comparison with the control group (1iiA). Overall, this effect may be considered modest, as is expected to occur in advanced neoplasms. Survival benefits were not identified with embolization alone, but the number of individuals analysed is still low. There is no good evidence for the best chemotherapeutic agent and the optimal re-treatment strategy. The two positive RCTs applied three to four treatments per year, using doxorubicin and cisplatinum respectively<sup>27, 28</sup> (1iiA).

The benefits of chemoembolization should not be offset by treatment-induced liver failure. The best candidates are patients with preserved liver function and asymptomatic multinodular tumours without vascular invasion or extrahepatic spread,<sup>4, 26</sup> while patients with liver decompensation or hepatic failure (Child-Pugh's B-C), should be excluded as the ischaemic insult can lead to severe adverse events.<sup>26, 29</sup> The heterogeneity in the selection of the 'ideal candidates' may result in opposite results, and thus should be taken into account when designing and analysing RCTs.

None of the other loco-regional therapies have resulted in a proven advantage in terms of survival. Some strategies provide objective response rates above 20%, as is the case of internal radiation with <sup>131</sup>I-labelled Lipiodol or Y-90, or arterial lipiodolization.<sup>4, 26, 30</sup> These treatments deserve further analysis,

as the RCT available until now either are not powered to identify survival advantages or include another potentially active control arm, precluding to identify advantages if present (1iiDiii).

#### *Loco-regional treatments: evidence obtained from new RCT 2002–2005*

Three small RCT assessing either chemoembolization in combination with percutaneous ablation or lipiodolization have been published in this period.<sup>31–33</sup> A German study reported no survival differences between a combination of chemoembolization and PEI vs. chemoembolization alone in 58 patients.<sup>32</sup> Therapy using reservoir intra-arterial infusion has been employed in patients with advanced HCC with disappointing results. A low-quality study assessing lipiodolization with carboplatin (150 mg/m<sup>2</sup>) compared with doxorubicin (20 mg/m<sup>2</sup>)<sup>33</sup> in 65 Chinese patients, showed significant survival benefits favouring the carboplatin arm (16.9 vs. 12.1 months,  $P = 0.0257$ ). Further studies are required to confirm these data.

#### **Systemic treatments**

Hormonal compounds and conventional external beam radiation have not shown survival benefits. A meta-analysis of seven RCTs comparing tamoxifen vs. conservative management, comprising 898 patients, showed neither antitumoral effect nor survival benefit of tamoxifen (1iA).<sup>7</sup> Thus, this treatment is discouraged in advanced HCC. Systemic chemotherapy has been tested in nine RCT.<sup>7</sup> The most active agents *in vitro* and *in vivo* are doxorubicin and cisplatin.<sup>7, 34</sup> Systemic doxorubicin has been tested in more than 1000 patients within clinical trials and provides partial responses in around 10% of cases, without any evidence of survival advantages (1iiA).<sup>7, 35</sup> The encouraging results of initial trials with interferon and octreotide have not been reproduced by others.

#### *Systemic treatments: evidence from new RCT 2002–2005*

Six randomized studies assessing tamoxifen and anti-androgen therapy<sup>36–39</sup> (4), octreotide<sup>40</sup> (1) and systemic chemotherapy – PIAF<sup>41</sup> (1) were published during the last 3 years (Table 5).

### Hormone analogues

Despite the fact that a previous meta-analysis showed no impact of tamoxifen in survival/quality of life in patients with advanced HCC, three large RCTs were reported assessing tamoxifen in 1125 patients,<sup>36–38</sup> all of them with negative results in terms of survival outcome (Table 5). One additional poorly designed study assessed the combination of tamoxifen and octreotide in 30 patients.<sup>39</sup> One study was double-blinded,<sup>37</sup> and two showed a high quality score (Table 6).<sup>37, 38</sup> Two French studies<sup>36, 38</sup> included cirrhotic patients (72–78%) mainly due to alcohol-related liver disease. Portal vein thrombosis accounted for 15–41% of patients.<sup>38</sup> Several reasons were stated to pursue with these three negative trials: to evaluate tamoxifen in a large number of patients, in the setting of non-viral cirrhosis,<sup>36</sup> to use high-dose tamoxifen speculating on a therapeutic effect of tamoxifen independent of oestrogen receptors,<sup>37</sup> to combine anti-oestrogenic and anti-androgenic effects.<sup>38</sup> In the study using high-dose tamoxifen vs. placebo,<sup>37</sup> there was a significantly higher risk of death in the tamoxifen 120 mg group compared with the placebo group (hazard ratio, 1.39; 95% CI, 1.07–1.81). In the study assessing the effect of anti-androgens in combination with tamoxifen compared with tamoxifen alone,<sup>38</sup> the tumour growth was faster in the combined treated group. A single trial assessing long-acting octreotide vs. placebo did not identify differences in efficacy in 70 patients with advanced HCC.<sup>40</sup>

### Systemic chemotherapy

The group of Hong Kong reported one of the first and large RCT comparing combination chemotherapy [cisplatin/interferon- $\alpha$ 2b/doxorubicin/fluorouracil (PIAF)]<sup>41</sup> with single-agent chemotherapy (doxorubicin). Objective response rates were of 20.9% for the PIAF regime and 10.5% for doxorubicin. The median survival of the PIAF and doxorubicin groups was 8.67 and 6.83 months, respectively, without differences between groups. PIAF was associated with a significantly higher rate of myelotoxicity compared with doxorubicin. Treatment-related mortality was 9% in the PIAF regimen arm as a result of HBV re-activation and liver failure.

During this period of time, three relevant phase III studies have been finished with negative results in the treatment of advanced HCC, and reported in abstract form so far. The largest RCT ever conducted in HCC

compared seocalcitol – a vitamin-D like antiproliferative molecule – vs. placebo in 746 patients showing no differences in overall survival (9.6 months seocalcitol vs. 9.2 months placebo).<sup>42</sup> Nilotrexed, an inhibitor of thymidylate synthase, was compared with systemic doxorubicin in 446 patients with negative results (median survival 5 months vs. 7.5 months respectively).<sup>43</sup> Finally, negative results were also reported with a tubulin inhibitor (T-67, from Tularik) in a large multicentre RCT.<sup>44</sup>

### FUTURE PROSPECTS

With the improvement in the knowledge of the molecular pathogenesis of HCC, new drugs targeting molecular signalling pathways have jumped into the clinical arena. The excitement resulting from the survival benefits obtained with these drugs in patients with lung cancer (erlotinib and bevacizumab), breast cancer (trastuzumab and bevacizumab), renal cancer (sorafenib), gastrointestinal stromal tumours (imatinib) and liver metastases (cetuximab and bevacizumab) provides a hope for patients suffering HCC. Nowadays, RCTs testing tyrosine kinase inhibitors and anti-angiogenic agents are currently in phase III in HCC patients, worldwide. Phase II studies are also conducted to disclose whether epidermal growth factor receptor inhibitors, PDGF receptor inhibitors, and antibodies against VEGF among others have a role in the treatment of this neoplasm. More far from the bedside are the results of gene therapy in HCC patients with advanced tumours, which have been awaited during the last years.

### ADDENDUM

During the review process of the present manuscript, a new RCT from Livraghi *et al.* appeared published in MEDLINE. Treatment with stem cell differentiation stage factors of intermediate-advanced hepatocellular carcinoma: an open-randomized clinical trial. *Oncol Res* 2005;15(7–8): 399–408.

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