

Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial

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Summary

Background There is no standard treatment for unresectable hepatocellular carcinoma. Arterial embolisation is widely used, but evidence of survival benefits is lacking.

Methods We did a randomised controlled trial in patients with unresectable hepatocellular carcinoma not suitable for curative treatment, of Child-Pugh class A or B and Okuda stage I or II, to assess the survival benefits of regularly repeated arterial embolisation (gelatin sponge) or chemoembolisation (gelatin sponge plus doxorubicin) compared with conservative treatment. 903 patients were assessed, and 112 (12%) patients were finally included in the study. The primary endpoint was survival. Analyses were by intention to treat.

Findings The trial was stopped when the ninth sequential inspection showed that chemoembolisation had survival benefits compared with conservative treatment (hazard ratio of death 0.47 [95% CI 0.25–0.91], $p=0.025$). 25 of 37 patients assigned embolisation, 21 of 40 assigned chemoembolisation, and 25 of 35 assigned conservative treatment died. Survival probabilities at 1 year and 2 years were 75% and 50% for embolisation; 82% and 63% for chemoembolisation, and 63% and 27% for control (chemoembolisation vs control $p=0.009$). Chemoembolisation induced objective responses sustained for at least 6 months in 35% (14) of cases, and was associated with a significantly lower rate of portal-vein invasion than conservative treatment. Treatment allocation was the only variable independently related to survival (odds ratio 0.45 [95% CI 0.25–0.81], $p=0.02$).

Interpretation Chemoembolisation improved survival of stringently selected patients with unresectable hepatocellular carcinoma.

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Introduction

The incidence of hepatocellular carcinoma is increasing worldwide.¹ Curative therapies, such as resection, liver transplantation, or percutaneous treatments, benefit only 25% of patients and are the only chance to improve life expectancy.^{2–5} Despite the implementation of surveillance programmes for early hepatocellular carcinoma, most tumours are diagnosed at advanced stages, for which no standard therapy has been established.^{2–5} Arterial embolisation induces objective responses in 16–55% of patients and lowers the rate of tumour progression. However, six randomised trials have found no survival benefits in comparisons of this therapy with or without chemotherapy (doxorubicin, cisplatin) versus conservative management or suboptimum treatments.^{6–11} Similarly, two systematic reviews of some of these trials showed discrepant results.^{12,13} The lack of survival benefits could be due to two factors. First, prognosis is related not only to the hepatocellular carcinoma itself, but also to the functional status of the underlying cirrhosis. Second, objective responses are not maintained with time. Accordingly, we hypothesised that very strict selection of candidates and a more aggressive retreatment schedule, aiming to prolong the initial antitumoral effect, might allow the identification of a treatment-related survival benefit and clarify the uncertainty about the usefulness of this therapy.

This sequential, multicentre, randomised controlled trial assessed the survival benefits of arterial embolisation or chemoembolisation in patients with unresectable hepatocellular carcinoma in comparison with conservative management. The three-group design would allow us to identify potential advantages from the type of embolisation applied.

Methods

Patients

The study included consecutive white patients who met the entry criteria and agreed to participate in the trial, recruited during a 4-year period in three centres in the area of Barcelona. Hepatocellular carcinoma was diagnosed, staged, and treated according to a previously reported schedule.² Patients with early tumours (single tumours measuring less than 5 cm or three nodules measuring less than 3 cm) are considered for radical therapies. Resection is indicated for patients with single tumours, absence of portal hypertension, and normal bilirubin concentrations. Patients with portal hypertension or abnormal bilirubin concentrations or three nodules of less than 3 cm in diameter are considered for transplantation. Percutaneous treatments are used when surgery is precluded. Patients with multinodular tumours enter randomised or phase II trials, assessing locoregional therapies or systemic agents. Finally, endstage patients defined by a performance status of 3 or more¹⁴ or an Okuda stage III¹⁵ receive symptomatic treatment.

Accordingly, this study included patients with untreated hepatocellular carcinoma not suitable for curative treatment. Diagnosis was confirmed by needle biopsy or by two coincidental imaging techniques associated with increased α -fetoprotein. Exclusion criteria were age older than 75 years, advanced liver disease (Child-Pugh class C),¹⁶ active gastrointestinal bleeding, encephalopathy, refractory ascites, presence of vascular invasion (including segmental portal obstruction), extrahepatic spread; portosystemic shunt, hepatofugal blood flow; any contraindication to an arterial procedure such as impaired clotting tests (platelet count below $50 \times 10^9/L$ or prothrombin activity below 50%), renal failure, severe atheromatosis; any contraindication to doxorubicin (serum bilirubin more than $85.5 \mu\text{mol/L}$, leucocyte count less than $3 \times 10^9/L$, cardiac ejection fraction less than 50%); or endstage tumoral disease.

Design and procedures

Patients who met these criteria and gave written informed consent entered the study, which was approved by the investigation and ethics committee of each hospital, according to the standards of the Declaration of Helsinki. Randomisation was centralised and stratified by centre. Patients were further stratified into four categories according to tumour stage (uninodular *vs* multinodular) and Okuda stage (I *vs* II). Randomisation was done with a computer-generated allocation and sealed envelopes to give, in equal proportions: patients receiving arterial embolisation with gelfoam; patients receiving arterial chemoembolisation with gelfoam and doxorubicin associated with lipiodol, and patients receiving symptomatic treatment. Double-blind and double-dummy techniques were discarded because the nature of the treatment and the associated side-effects meant they were not feasible.

Arterial embolisation was done at baseline, 2 months, and 6 months, then every 6 months thereafter. Delay between allocation and treatment was always less than a month. Treatment was discontinued if any exclusion criteria developed or at the patient's request. Progressive disease led to discontinuation of treatment if vascular invasion or extrahepatic spread developed. Embolisation was done by injection of a mixture of radiological contrast and gelfoam fragments until flow stagnation was achieved. Patients in the chemoembolisation group received an emulsion of doxorubicin (Pharmacia-UpJohn, Barcelona, Spain) at a dose adjusted to bilirubin concentrations ($<25.6 \mu\text{mol/L}$, 75 mg/m^2 ; 25.6 – $51.3 \mu\text{mol/L}$, 50 mg/m^2 ; 51.3 – $85.5 \mu\text{mol/L}$, 25 mg/m^2) and 10 mL lipiodol (Laboratoire Guerbert, Aulnay-sous-Bois, France) before mechanical obstruction. No antibiotic prophylaxis was given.

Patients in the conservative-treatment group did not receive suboptimum treatments. In these patients, liver decompensation (gastrointestinal bleeding, hepatic encephalopathy, ascites, bacterial infections) was treated as in patients with non-neoplastic liver disease. Non-steroidal anti-inflammatory agents were not used in treatment of pain, because they are known to induce renal failure in patients with decompensated liver disease.

Treatment response was assessed by contrast-enhanced spiral computed tomography at 6 months, before the third procedure. Its magnitude was defined according to the WHO criteria:¹⁷ complete response, no evidence of neoplastic disease; partial response, reduction in total tumour load of more than 50%; no change, reduction of less than 50% or increase of less than 25%; progressive disease: increase of equal to or more than 25%. Thus, objective responses accounted for complete and partial responses sustained for at least 6 months.

Patients were assessed every 3 months until death by clinical examination and biochemistry. Tumour burden, including presence of vascular invasion or extrahepatic spread, was assessed by ultrasonography and computed tomography every 6 months. Bone metastases were sought by scintigraphy if clinically suspected.

Statistical analysis

The primary endpoint was survival. Treatment response was a secondary endpoint. The study had a sequential design¹⁸ to allow the trial to be stopped if significant differences were detected. The sequential triangular test (PEST version 3.0) was used for the sequential inspection (every five deaths) and for the final analysis independently comparing the proportions of deaths in each treatment group with that in the control group. The assumptions were 2-year survival of 65% in the treatment groups and 40% in the control group (reference hazard ratio 0.47, allocation ratio 1), with a two-sided type I error of 5% and a power of 80% to detect an increase in survival. The maximum and mean numbers of events expected were 85 and 29 for comparisons between each treatment group and the control group. A positive z value indicates that treatment was better than control, and a negative value that treatment was worse. The slope of the upper boundary of the triangle was 0.26 (treatment significantly better than control, $p < 0.05$) and that of the lower boundary was 0.79 (treatment worse than or equal to control). The V statistic is proportional to the sample size. Both variables were calculated every sequential inspection. The study would be stopped when the plot line obtained crossed any boundary of the triangle.

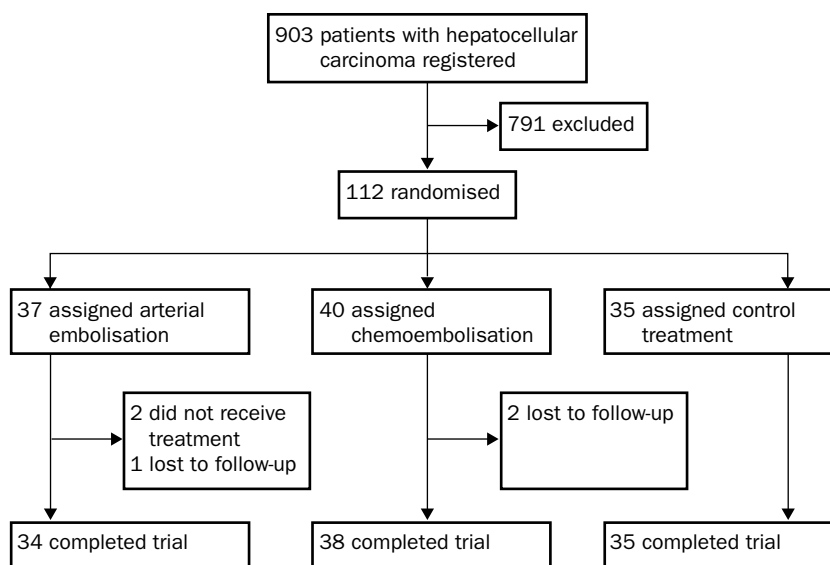


Figure 1: Trial profile

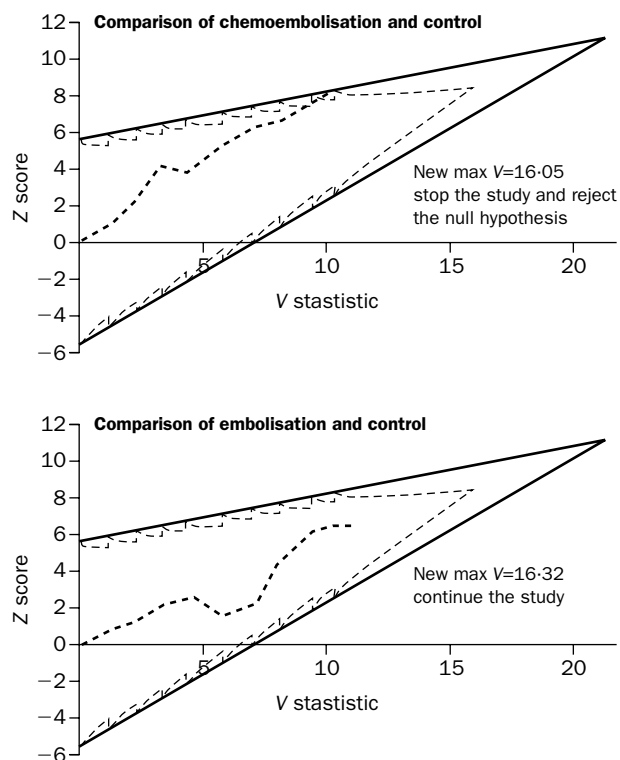


Figure 2: Design of sequential analyses of chemoembolisation vs control (upper) and embolisation vs control (lower)

A positive z value indicates that treatment was better than control, whereas a negative indicates the opposite. The slope of the upper boundary of the triangle was 0.26 (treatment better than control) and the lower boundary was 0.79 (treatment worse than or equal to control). The V statistic represents the sample size. After the ninth inspection, the upper triangular boundary was crossed, favouring chemoembolisation vs control, with a hazard ratio of death of 0.47 (95% CI 0.25–0.91, $p=0.025$; upper). Conversely in the lower diagram, comparing embolisation with control, the plot lines remain within the boundaries, indicating the need to recruit additional patients to achieve a valid conclusion.

All analyses were by intention to treat. Comparisons among groups were done by ANOVA for continuous variables and the χ^2 test for categorical variables. Cumulative survival curves according to the Kaplan-Meier method were compared by the Mantel-Cox test. Stepwise forward Cox's regression analysis of survival was used to assess baseline predictors and the treatment effect simultaneously. Follow-up was closed at death or the last visit before Oct 1, 2000. Data for patients considered for radical therapies after treatment response were censored at the time of the procedure. Calculations were done with the SPSS package (version 10.0).

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

The study began on July 1, 1996, and was stopped on July 28, 2000, when the ninth sequential inspection detected significant differences in favour of chemoembolisation. 112 (12.4%) of the 903 patients diagnosed with hepatocellular carcinoma during this time met the entry criteria and agreed to take part (figure 1). Of the 791 excluded, 310 had early hepatocellular carcinoma and underwent curative therapy (resection or liver transplantation in 154, and percutaneous treatments in

	Embolisation (n=37)	Chemoembolisation (n=40)	Control (n=35)
Demography			
Age, years*	64 (62–67)	63 (61–66)	66 (64–68)
M/F	30 (81%)/ 7 (19%)	32 (80%)/ 8 (20%)	23 (66%)/ 12 (34%)
Cause of cirrhosis			
Hepatitis C virus	30 (81%)	33 (82%)	32 (91%)
Hepatitis B virus	2 (5%)	4 (10%)	1 (3%)
Alcohol	4 (11%)	3 (8%)	1 (3%)
Other	1 (3%)	..	1 (3%)
Tumour-related symptoms			
Ascites	9 (24%)	6 (15%)	11 (31%)
Abdominal pain	7 (19%)	3 (8%)	3 (9%)
Constitutional syndrome	1 (3%)	1 (2%)	4 (11%)
Biochemistry			
Serum bilirubin (mmol/L)*	22.2 (18.8–27.4)	20.5 (18.8–23.9)	25.6 (22.2–29.1)
Prothrombin activity (%)*	81 (75–87)	82 (77–87)	77 (71–83)
Serum albumin (g/L)*	35 (33–37)	35 (33–37)	35 (33–37)
γ -glutamyltranspeptidase (IU/L)*	113 (70–156)	112 (85–139)	101 (66–137)
Alkaline phosphatase (IU/L)*	233 (203–263)	220 (182–258)	257 (202–311)
Distribution of α-fetoprotein concentrations			
<10 mg/L	15	15	11
10–100 mg/L	9	18	16
>100 mg/L	13	7	8
Tumour stage			
Solitary†	9 (24%)	13 (32%)	8 (23%)
Multinodular	27 (73%)	26 (65%)	27 (77%)
Two nodules	6	7	8
More than two nodules	21	19	19
Diffuse	1 (3%)	1 (3%)	..
Disease characteristics			
Diameter main nodule (mm)*	52 (46–60)	49 (40–58)	44 (39–49)
Bilobar disease	18 (49%)	19 (47%)	18 (51%)
Child-Pugh class A/B ¹⁶	27/10	31/9	21/14
Okuda stage I/II ¹⁵	24/13	27/13	22/13
BCLC stage B/C ²	28/9	35/5	27/8
Performance status¹⁴			
0	28	35	27
1	7	4	4
2	2	1	4

Data are numbers of patients unless otherwise indicated. *Mean (95% CI).

†Solitary tumours with or without satellites.

Table 1: Baseline characteristics

156), 68 were older than 75 years, 46 had advanced liver disease, 29 had contraindications to embolisation or doxorubicin, 97 had vascular invasion or extrahepatic spread, 199 had endstage cancer, and 42 refused to take part. The patients included in the trial represent 37.7% of the 297 patients diagnosed at intermediate stages of hepatocellular carcinoma, who were the target population of the study.

37 patients were assigned arterial embolisation, 40 chemoembolisation, and 35 conservative management. Over-running lasted until Oct 1, 2000. The upper triangular boundary was crossed for the comparison of chemoembolisation and control (figure 2, upper), with a hazard ratio of death of 0.47 (95% CI 0.25–0.91, $p=0.025$), indicating that survival was significantly better in the chemoembolisation group than in the control group. Since there was a difference in bilirubin concentration between

	Embolisation (n=37)	Chemo- embolisation (n=40)	Control (n=35)	Total (n=112)
Deaths	25 (67%)	21 (52%)	25 (71%)	71 (63%)
Cause of death				
Tumour progression	20	14	23	57
Hepatic failure with stable disease	4	5	2	11
Other	1*	2†	0	3

*Neoplasm of lung. †Neoplasm of tongue and treatment-related death (septic shock).

Table 2: Causes of death

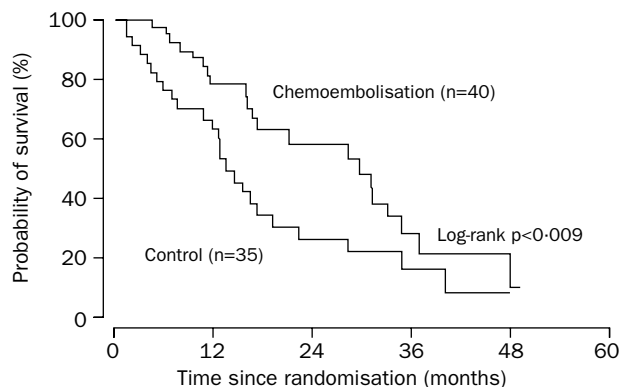
these treatment groups, we did a sequential analysis stratified by baseline bilirubin concentration, which showed a significant adjusted hazard ratio of death of 0.46 (0.24–0.89, $p=0.023$). The sequential inspection comparing embolisation and control at this timepoint showed an estimated hazard ratio of death adjusted for bilirubin concentration of 0.57 (0.31–1.04, $p=0.07$; figure 2, lower).

The only difference between the groups in baseline characteristics was in serum bilirubin (table 1).

Two patients in the embolisation group did not receive the treatment, but they were included in the intention-to-treat analysis. One died before treatment and the other had a transient ischaemic attack during catheterisation. Two patients who had objective responses were radically treated and their data were censored at the time of the new procedure: one patient in the embolisation group received percutaneous ethanol injection and one in the chemoembolisation group underwent transplantation. Three patients (one in the embolisation group, two in the chemoembolisation group) were lost to follow-up, and their data were censored at the time of the last visit.

At the time of the analysis, 71 (63%) patients had died (table 2). Mean follow-up was 21.7 months (95% CI 17.5–26.0) for the embolisation group, 21.2 months (17.3–25.1) for the chemoembolisation group, and 14.5 months (10.6–18.4) for the control group. The probabilities of survival at 1, 2, and 3 years were 75%, 50%, and 29% for the embolisation group (mean survival 25.3 months [95% CI 20.3–30.2]); 82%, 63%, and 29% for the chemoembolisation group (mean survival 28.7 months [23.6–33.7]); and 63%, 27%, and 17% for the control group (mean survival 17.9 months [13.1–22.7]). Survival was significantly better in the chemoembolisation group than in the control group ($p=0.009$; figure 3).

Serum bilirubin ($p=0.03$), constitutional syndrome (defined by weight loss, malaise, and anorexia) ($p=0.02$), treatment allocation ($p=0.02$), and treatment response ($p=0.0007$) were associated with better survival.



Patients at risk

Chemoembolisation	40	29	14	4	2
Control	35	19	7	3	0

Figure 3: Survival curves of the chemoembolisation and control groups

Treatment allocation was the sole baseline variable independently related to survival (odds ratio 0.45 [95% CI 0.25–0.81], $p=0.02$) in the Cox's regression model. Inclusion of treatment response identified this variable as an independent predictor (odds ratio 0.59 [0.44–0.81], $p=0.0007$) together with constitutional syndrome (0.46 [0.25–0.86], $p=0.04$). For patients who achieved objective responses sustained for at least 6 months, the probabilities of survival at 1, 2, and 3 years were 96%, 77%, and 47% ($p=0.002$ compared with patients with treatment failure, and $p=0.006$ *vs* control group). We noted no differences in intention-to-treat survival between non-responders and the control group (1-year survival 65% *vs* 63%; 2-year survival 41% *vs* 26%, $p=0.3$).

The mean numbers of treatment sessions were 3.08 (95% CI 2.4–3.5; range 0–7) for embolisation and 2.8 (2.3–3.2; 1–8) for chemoembolisation ($p=0.5$). Treatment was discontinued in 60 (78%) patients (table 3). Assessment of response was possible in 102 patients who survived for at least 5 months. 30 achieved objective responses sustained for 6 months (one complete response, 29 partial responses), 16 after embolisation and 14 after chemoembolisation (embolisation *vs* control, $p=0.001$; chemoembolisation *vs* control, $p=0.004$). Chemoembolisation significantly lowered the probability of portal-vein invasion (17% *vs* 58% at 2 years in controls, $p=0.005$). No differences were identified in the probability of developing functional liver impairment or extrahepatic spread.

	Embolisation (n=37)	Chemoembolisation (n=40)	Both groups (n=77)
Reason			
Tumour progression (portal thrombosis, extrahepatic spread, or performance status >2)	15	9	24
Liver failure without tumour progression	3	2	5
Technical problems (arterial hepatic obstruction, collateral or hepatofugal blood flow, low ejection fraction)	3	8	11
Adverse events (leucopenia, ischaemic biliary stricture, transient ischaemic attack, allergic dermatitis)	1	4	5
Patient's decision	2	4	6
Death on treatment	4	3	7
Other (lung cancer, percutaneous ethanol injection)	2	0	2
Treatment discontinuation	29 (78%)	31 (77%)	60 (78%)
Active treatment at end of follow-up	8 (22%)	9 (23%)	17 (22%)

*There were no significant differences between groups.

Table 3: Reasons for treatment discontinuation among patients who received embolisation*

There was one treatment-related death in the chemoembolisation group at day 17 caused by septic shock due to *Escherichia coli*. Treatment-related complications affected 18 patients: seven of the embolisation group (cholecystitis, two; and ischaemic hepatitis, liver abscess, pulmonary thromboembolism, liver failure, and gastrointestinal haemorrhage in one each), and 11 in the chemoembolisation group (cholecystitis and leucopenia, two each; and ischaemic biliary stricture, hepatic infarct, spontaneous bacterial peritonitis, *Staphylococcus aureus* bacteraemia, septic shock, allergic dermatitis, and severe alopecia in one each).

Discussion

There is no standard therapy for patients with unresectable hepatocellular carcinoma.²⁻⁵ Six randomised trials of arterial embolisation, with or without chemotherapy, have shown a strong antitumoral effect, but none detected survival benefits in comparison with conservative management or suboptimum treatments.⁶⁻¹¹ Two systematic reviews justified additional studies to define the efficacy of this technique unequivocally,^{12,13} and our study offers relevant data by showing that chemoembolisation with gelfoam and doxorubicin improves survival in selected candidates with unresectable hepatocellular carcinoma. The trial was stopped because sequential inspection showed that chemoembolisation improved survival. Treatment allocation and the response to treatment were identified as prognostic predictors, further confirming the benefits of therapy.

The benefits in survival can be ascribed both to the restrictive selection of candidates and to the relevant response to treatment and its maintenance. Only 12% of the patients diagnosed with hepatocellular carcinoma (37% of those at intermediate to advanced stages) met the inclusion criteria and agreed to take part. This selected target population excluded most patients who have factors associated with treatment intolerance or failure,¹⁹⁻²¹ such as tumour-related symptoms, diffuse neoplasm, renal failure, Child-Pugh C class disease, or portal or segmental thrombosis. However, most of our patients showed preserved liver function (70% Child-Pugh class A¹⁶) and intermediate tumoral stage² (81%). These data suggest that we recruited the individuals in whom the benefits of treatment may become apparent, and that we excluded those with the worst prognosis, who would die early during follow-up. We recorded some treatment-related morbidity, but this necessitated discontinuation of treatment in less than 10% of cases. By contrast, in a previous study toxic effects leading to liver failure were observed in half of the patients.⁹ The strict selection applied precludes the generalisation of our results to all unresectable tumours and highlights the need for selective recruitment to obtain survival advantages.

The survival probabilities obtained with chemoembolisation are the best so far reported in controlled investigations, whereas those in the embolisation and control groups accord with those of previous studies.^{6-11,22} Treatment should affect survival by inducing and maintaining objective responses. Patients in the two treatment groups received similar numbers of sessions and had similar rates of treatment-related complications, treatment withdrawal, and objective responses sustained for at least 6 months (around 40%). However, only chemoembolisation induced a lower rate of vascular invasion, and deaths in this group were less frequently ascribed to tumour progression. Accordingly, we believe the improved survival can be ascribed to treatment-related

effects. Unfortunately, because the trial was stopped early, we cannot undertake a proper analysis or test the rejection of the null hypothesis in the embolisation group.

It could be argued that survival benefits are biased by an imbalance among the groups in determinant prognostic variables, such as bilirubin concentrations or the tumour burden. Although baseline bilirubin concentrations were substantially lower in the chemoembolisation group than in the control group, this variable did not reach independent prognostic significance in the regression analysis. Furthermore, the sequential design with adjustment for bilirubin concentrations did not affect the final result. The difference in the tumour burden could also call into question the benefits of chemoembolisation. However, we stratified the patients before randomisation by Okuda stage (I *vs* II) and by tumour stage (single *vs* multinodular), which should prevent an important imbalance due to tumour load.

Until now, patients who met our entry criteria were left untreated because of the lack of effective options, or were considered for inclusion in randomised controlled trials that ideally should have a no-treatment group.²⁻⁵ A meta-analysis of randomised controlled trials of arterial embolisation for hepatocellular carcinoma that includes our data with those previously published may show a significant difference rather than the previous non-significant trend. However, such an assessment will have to be carefully done to control for heterogeneity in both selection of patients and treatment technique. In addition, it should assess the effect of a sustained response to treatment since we identified this follow-up variable as the most powerful predictor of outcome. A meta-analysis of individual data may overcome these limitations, but it requires the unification of all studies into a single database to homogenise data and outputs for any conclusion to be drawn. While we wait for these confirmatory studies and from now on, chemoembolisation should become the standard approach for a selected group of candidates (unresectable intermediate hepatocellular carcinoma and preserved liver function).

Other members of the Barcelona-Clinic Liver Cancer Group
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Contributors

J M Llovet was coordinator at Hospital Clínic and was involved in study design, analysis, collection, and interpretation of data, statistical analysis, and writing of the report. M I Real, X Montaña, C Ayuso, J Muchart, R Vilana, L Bianchi, J R Ayuso, T Caralt, C Brú, and M Solé were responsible for diagnosis, staging, treatment, and assessment of response. R Planas was coordinator at Hospital Germans Trias i Pujol and R Solà was coordinator at Hospital del Mar; both contributed to collection and interpretation of data. S Coll and M Sala were involved in collection and interpretation of data. J Aponte and C Acosta were involved in statistical analysis. J Rodés contributed to study design, analysis, interpretation of data, and writing of the report. J Bruix was the principal investigator and was involved in study design, analysis, interpretation of data, and writing of the report.

Conflict of interest statement

None declared.

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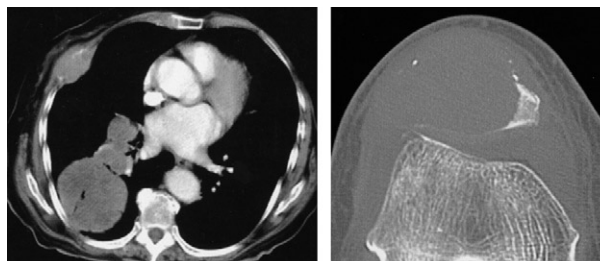
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Clinical picture

Patellar metastasis

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A 73-year-old woman presented with right-sided chest pain and a painful, swollen right knee. She was a life-long smoker with a previous history of breast cancer. On examination, we found digital clubbing and an exquisitely tender right knee. Thoracic computed tomography showed an 8.5 cm mass in the right lower lobe with a metastatic deposit in the right fourth rib, anteriorly (figure, left). Computed tomography of the knee showed destruction of the patella (figure, right). The relative avascularity of sesamoid bones is believed to account for the rarity of patellar metastases.



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