

A COMPARISON OF LIPIODOL CHEMOEMBOLIZATION AND CONSERVATIVE TREATMENT FOR UNRESECTABLE HEPATOCELLULAR CARCINOMA

GROUPE D'ETUDE ET DE TRAITEMENT DU CARCINOME HÉPATOCELLULAIRE*

Abstract Background. Chemoembolization with Lipiodol (iodized oil) is widely used to treat patients with unresectable hepatocellular carcinoma. Severe side effects have been reported, and improved survival has not been clearly demonstrated.

Methods. Patients with unresectable hepatocellular carcinoma who did not have severe liver disease and who met additional entry criteria were randomly assigned to receive either Lipiodol chemoembolization (70 mg of cisplatin, 10 ml of Lipiodol, and gelatin-sponge [Gelfoam] particles delivered through the hepatic artery) or conservative management involving treatment of complications and pain. Courses of treatment were to be given every two months for a maximum of four courses. The main end point was survival.

Results. The study was stopped in December 1992, after a sequential analysis showed the lack of the expected benefit from chemoembolization. As of October 1, 1994, 39 of the 50 patients assigned to chemoembolization and 40 of the 46 patients assigned to conservative management had died. Twenty-six patients assigned to chemoembolization received all four courses of treatment. There was no significant difference in survival between

the two groups, although there was a trend favoring the chemoembolization group (estimated relative risk of death in the control group, 1.4; 95 percent confidence interval, 0.9 to 2.2; $P=0.13$). The comparison of survival between the two groups was not substantially changed by adjustments for differences in base-line and prognostic characteristics (adjusted relative risk, 1.3; 95 percent confidence interval, 0.8 to 2.1; $P=0.31$). At one year, the estimated survival rates were 62 percent in the chemoembolization group (95 percent confidence interval, 48.6 to 75.4 percent) and 43.5 percent in the conservative-management group (95 percent confidence interval, 29.2 to 57.8 percent). In the chemoembolization group, tumor growth, as assessed by tumor size and serum alpha-fetoprotein concentration, was reduced and the incidence of portal obstruction was lower than in the conservative-management group. Liver failure occurred after 47 courses of treatment in 30 patients assigned to chemoembolization.

Conclusions. In a group of patients with unresectable hepatocellular carcinoma but without severe liver disease, Lipiodol chemoembolization reduced tumor growth, often caused acute liver failure, and did not significantly improve survival. (N Engl J Med 1995;332:1256-61.)

THE efficacy of therapies for hepatocellular carcinoma is poor.^{1,2} Hepatocellular carcinoma is a hypervascular tumor.³ Hepatic intraarterial injection of antitumor agents, performed to increase the local concentration of drugs and reduce systemic side effects,⁴ and intraarterial embolization, which causes ischemic necrosis of the tumor,⁵ have been used as palliative treatments, either alone or in combination (chemoembolization). Mixing anticancer drugs with Lipiodol, an iodized oily agent that remains selectively in tumors for long periods,⁶ may enhance the antitumor effect.^{7,8} Treatment combining intraarterial chemotherapy with Lipiodol and embolization, or Lipiodol chemoembolization, is considered the most effective of these methods on the basis of reports of a decrease in tumor size in nonrandomized trials.⁹⁻¹³ Although this method is widely used, severe side effects have been reported^{9,14,15} and improved survival, as suggested by case-control studies, has not been clearly demonstrated.

To test the hypothesis that Lipiodol chemoembolization would result in a 75 percent rate of survival after eight months, as compared with the 50 percent rate as-

sociated with conservative management, we compared four courses of Lipiodol chemoembolization with conservative treatment in patients who had unresectable hepatocellular carcinoma but not severe liver disease.

METHODS

Consecutive patients who met the entry criteria and who agreed to participate were included in this multicenter, sequential, randomized, open-label trial. The diagnosis of hepatocellular carcinoma was based on histologic or cytologic findings or on findings of cirrhosis, liver tumor, and a serum alpha-fetoprotein value exceeding 250 ng per milliliter. Patients were excluded if they had an indication for surgery, had been treated previously for hepatocellular carcinoma, had severe hepatic disease (defined as the presence of one of the following: encephalopathy, gastrointestinal hemorrhage in the past month, clinical ascites, a serum bilirubin concentration of at least 2.9 mg per deciliter [50 μmol per liter], or a serum albumin concentration below 30 g per liter), had vascular contraindications to Lipiodol chemoembolization (such as portal obstruction of at least three segmental branches), had contraindications to treatment with cisplatin, had a serum creatinine concentration of 120 μmol per liter (1.36 mg per deciliter) or higher, or had extrahepatic metastasis.

Randomization

After providing written informed consent, prospective participants underwent arteriography. If no contraindications were identified, the patients were enrolled and underwent randomization. Randomization was stratified according to center and was carried out by telephone. The patients were assigned to one of two regimens: treatment, with one course of Lipiodol chemoembolization every two months for a total of four courses, with the first course given immediately after randomization; or conservative management, with standardized pain medications (acetaminophen or morphine, given in doses appropriate for the level of pain) and treatment of complications.

Chemoembolization

All participating radiologists had prior experience with Lipiodol chemoembolization. First, the superior mesenteric artery was injected to assess portal flow. When portal flow was adequate, the hepatic

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Supported by grants from Assistance Publique-Hôpitaux de Paris (87/1990), Société Nationale Française de Gastroentérologie, and Caisses d'Épargne d'Île-de-France.

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artery was catheterized. The tip of the catheter was placed distal to the gastroduodenal artery or in either the left or right branches of the hepatic artery. The emulsion consisted of 70 mg of cisplatin and 10 ml of Lipiodol (Lipiodol Ultrafluide, Laboratoire Guerbet, Aulnay-sous-Bois, France) and was prepared just before injection by mixing through a three-way stopcock from one syringe to another. With fluoroscopic guidance, the radiologists injected this mixture into the arteries that fed the tumors. The injection could be slowed or discontinued if retrograde flow occurred. Embolization was subsequently performed with gelatin-sponge (Gelfoam) particles. The goal was to decrease arterial flow without causing total obstruction. Particular care was taken to avoid reflux. After embolization, angiography was performed to determine the extent of vascular occlusion and to assess blood flow in other arterial vessels. Amoxicillin-clavulanic acid (3 g per day) and metronidazole (1.5 g per day) were administered intravenously for 24 hours before the procedure and continued for eight days either intravenously or, when possible, orally.

Follow-up

Serum alpha-fetoprotein was measured and an abdominal computed tomographic scan was obtained at the beginning of the study, every two months during the first year, and thereafter every four months. All computed tomographic scans were reviewed by two radiologists who were unaware of the patient's clinical data or treatment assignment. The average diameter of the largest nodule recorded during computed tomographic scanning before the study began was noted, and changes in the size of the tumor on subsequent scans were expressed as a percentage of the initial size of the nodule. Changes in the serum alpha-fetoprotein concentration were expressed as a percentage of the base-line levels. The extent of initial segmental portal obstruction was also assessed on hepatic arteriography.

Statistical Analysis

The main end point was survival. The study was conducted as a sequential trial to minimize the number of patients needed and obtain more rapid results. A triangular test design was used.¹⁶ The accumulated data were examined after approximately every 10 deaths. At each examination, the *z* and *V* statistics were calculated. A positive *z* value indicated that chemoembolization was superior to conservative management, and a negative value that chemoembolization was inferior. The *V* statistic approximately represents the sample size. Once the sequential values of *z* and *V* were calculated, they were plotted against one another and the plotted point was compared with the stopping boundary for the trial. The study was designed to have a type I error of 5 percent with a power of 90 percent to detect an increased survival benefit for chemoembolization after eight months as compared with conservative management. Since the survival rate after conservative management was assumed to be 50 percent, to be deemed a superior treatment, chemoembolization would have to yield a rate of 75 percent. With this approach, if the plotted point lies above the upper boundary of the triangle or below the lower boundary, the trial is stopped (upper boundary: chemoembolization 50 percent more effective than conservative management; lower boundary: less than a 50 percent difference in survival between the two treatments).

Comparisons between groups were on an intention-to-treat basis. Comparisons were made with the Wilcoxon test for continuous variables, Fisher's exact test for binary variables, and the chi-square test for categorical variables. Survival curves were estimated according to the Kaplan-Meier method¹⁷ and compared with use of the log-rank test.¹⁸ To determine factors predictive of death and to adjust the treatment comparison for base-line differences between the groups and for prognostic factors, the Cox model was used.¹⁹ The selection was based on the likelihood-ratio test. All variables having a *P* value in the univariate analysis of 5 percent or less were included in the model. SAS (SAS Institute, Cary, N.C.) and BMDP (BMDP Statistical Software, Los Angeles) software packages were used.

Informed Consent

The study was conducted in accordance with the ethical standards set forth in the Declaration of Helsinki. Written informed consent was obtained from each patient. As required by French regulations,

the protocol was approved by one ethics committee in France (Hôpital Avicenne, Bobigny, France), as well as by ethics committees in Brussels, Belgium, and Montreal.

RESULTS

Sequential Analysis and Decision to Stop the Trial

The trial was begun on July 15, 1990. Twenty-four centers in three countries participated. Sequential analyses were performed after approximately every 10 deaths. Figure 1 shows the results of the fifth sequential analysis conducted on November 1, 1992. At that time, 92 patients were enrolled: 47 in the chemoembolization group and 45 in the conservative-management group. Forty-seven deaths had been reported: 20 in the chemoembolization group and 27 in the conservative-management group. Since the lower triangular boundary had been crossed (Fig. 1), the trial was stopped, and we concluded that there was less than a 50 percent increase in survival after eight months with chemoembolization as compared with conservative management ($P < 0.05$).

When entry was closed on December 1, 1992, 96 patients had been enrolled. During this period, 778 patients presented with hepatocellular carcinoma at the 24 centers, but 682 (88 percent) were excluded from the trial. The main reasons for exclusion were liver failure (205 patients, 30 percent), vascular contraindications (149 patients, 22 percent), indications for surgery (115 patients, 17 percent) or percutaneous alcohol injection (11 patients, 2 percent), extrahepatic metastasis (39 patients, 6 percent), and refusal by the patient to participate (93 patients, 14 percent). Seventy patients were excluded for various other reasons. Results are presented for the 96 patients who underwent ran-

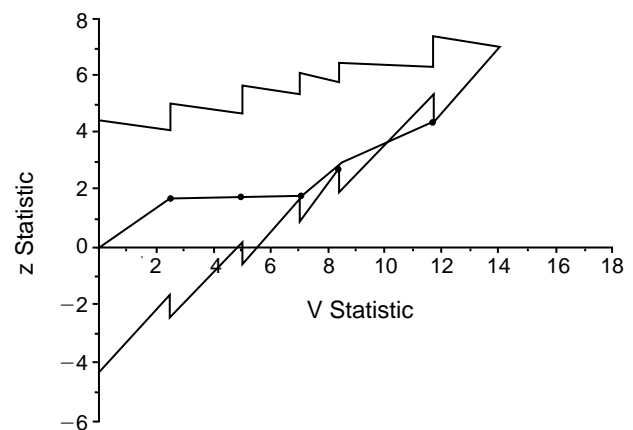


Figure 1. Design of the Triangular Test and the Results of the Fifth Sequential Analysis.

The five interim data sets resulted in five pairs of values for the *z* statistic, which approximately represents the effect of lipiodol chemoembolization on overall survival as compared with that of conservative management, and the *V* statistic, which approximately represents the sample size. The corresponding points were plotted on the graph as they became available and compared with the stopping boundary set out by the triangular test (see the text). At the fifth analysis, the lower triangular boundary was crossed, causing the trial to be stopped.

domization — 50 assigned to chemoembolization and 46 assigned to conservative management — and include follow-up through October 1, 1994. No patient was lost to follow-up, and 79 (82 percent) died.

Base-Line Characteristics

The diagnosis of hepatocellular carcinoma was based on histologic or cytologic findings in 79 patients and on findings of cirrhosis, liver tumor, and a serum alpha-fetoprotein concentration in excess of 250 ng per milliliter in 17 patients. The two groups were well balanced with respect to the main characteristics (Table 1). Cirrhosis was present in 87 patients (91 percent), all of whom had well-compensated liver function (Child-Pugh class A). The classification of Okuda et al.²⁰ was used to assess liver function and tumor volume; 90 percent of the patients had stage I disease (47 in the chemoembolization group and 39 in the conservative-management group), and 10 percent had stage II disease (3 in the chemoembolization group and 7 in the conservative-management group). More patients in the conservative-management group had multinodular and large tumors and segmental portal obstruction.

Survival

As of October 1, 1994, 39 patients assigned to chemoembolization had died and 40 patients assigned to conservative management had died. The causes of

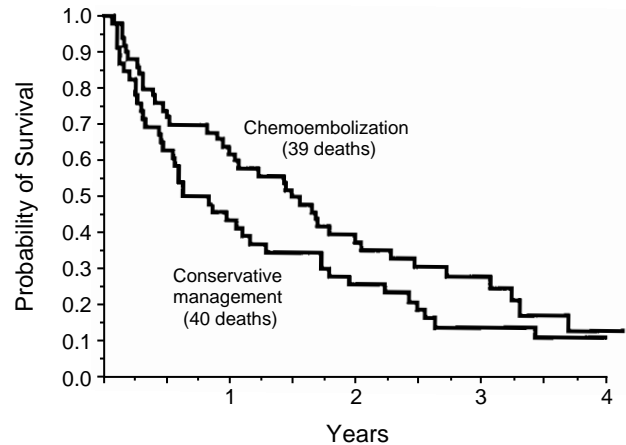


Figure 2. Kaplan-Meier Estimates of Survival in 50 Patients Assigned to Lipiodol Chemoembolization and 46 Patients Assigned to Conservative Management ($P=0.13$ by the Log-Rank Test).

death — mainly, liver failure, gastrointestinal hemorrhage, and spontaneous bacterial peritonitis — did not differ between the two groups. There was no significant improvement in survival in the chemoembolization group as compared with the conservative-management group (relative risk of death in the latter group, 1.4; 95 percent confidence interval, 0.9 to 2.2; $P=0.13$ by the log-rank test) (Fig. 2). At eight months, the estimated survival rate was 70 percent (95 percent confidence interval, 57.3 to 82.7 percent) in the chemoembolization group and 50 percent (95 percent confidence interval, 35.6 to 64.4 percent) in the conservative-management group; at one year, the estimated survival rates were 62 percent (95 percent confidence interval, 48.6 to 75.4 percent) and 43.5 percent (95 percent confidence interval, 29.2 to 57.8 percent), respectively; and at two years they were 37.8 percent (95 percent confidence interval, 24.3 to 51.3 percent) and 26 percent (95 percent confidence interval, 13.3 to 38.7 percent), respectively. The difference in survival between the groups was also adjusted for the following base-line variables, which were either unbalanced or prognostic as assessed by the log-rank test: Karnofsky score ($P=0.004$), ascites demonstrated by ultrasonography ($P<0.001$), serum bilirubin concentration ($P<0.001$), serum albumin concentration ($P=0.004$), tumor type ($P=0.02$), tumor mass ($P<0.001$), segmental portal obstruction ($P<0.001$), and serum alpha-fetoprotein concentration ($P=0.009$). With the use of the Cox model, the adjusted estimated risk of death remained unchanged, with a relative risk of 1.3 (95 percent confidence interval, 0.8 to 2.1) in the conservative-management group as compared with the chemoembolization group ($P=0.31$ by the likelihood-ratio test).

Tumor Growth

Fifteen patients died within two months of randomization (seven in the chemoembolization group and eight in the conservative-management group). In the

Table 1. Base-Line Characteristics of the 96 Patients Studied, According to Treatment Group.*

CHARACTERISTIC	CHEMOEMBOLIZATION (N = 50)	CONSERVATIVE MANAGEMENT (N = 46)
Age — yr	63	65
Range	43–74	34–75
Male sex — no. (%)	48 (96)	44 (96)
Cirrhosis — no. (%)	46 (92)	41 (89)
Main cause of cirrhosis — no. (%)		
Alcohol	35 (76)	30 (73)
Hepatitis B virus	2 (4)	3 (7)
Hepatitis C virus	4 (9)	4 (10)
Primary hemochromatosis	5 (11)	4 (10)
Esophageal varices — no. (%)	24 (48)	20 (43)
Serum bilirubin — $\mu\text{mol/liter}^\dagger$	26 \pm 23	24 \pm 16
Serum albumin — g/liter	37 \pm 7	38 \pm 8
Prothrombin activity — %	73 \pm 14	75 \pm 16
Serum alpha-fetoprotein — ng/ml	23	92
Range	2–33,400	2–28,260
Histologic confirmation of diagnosis — no. (%)	39 (78)	40 (87)
Tumor mass — no. (%)		
Uninodular, <3 cm in diameter	8 (16)	3 (7)
Uninodular, 3–5 cm in diameter	12 (24)	4 (9)
Uninodular, >5 cm in diameter	5 (10)	7 (15)
Multinodular	19 (38)	26 (57)
Diffuse	6 (12)	6 (13)
Tumor volume $\geq 50\%$ of liver volume — no. (%)	3 (6)	7 (15)
Segmental portal obstruction — no. (%)	1 (2)	6 (13)
Tumor capsule — no. (%) \ddagger	8 (16)	10 (22)

*Plus-minus values are means \pm SD.

\dagger To convert values for bilirubin to milligrams per deciliter, divide by 17.1.

\ddagger Assessed by computed tomography.

Table 2. Maximal Changes in Tumor Size and Serum Alpha-Fetoprotein Concentrations and Occurrence of Portal Obstruction in the 81 Patients Who Survived More Than Two Months after Randomization.*

CHARACTERISTIC	CHEMOEMBOLIZATION	CONSERVATIVE	P VALUE
	(N = 43)	MANAGEMENT (N = 38)	
	<i>no. (%)</i>		
Tumor size			0.001†
Decreased >50%	7 (16)	2 (5)	
Decreased 25–50%	16 (37)	3 (8)	
Stable	16 (37)	14 (37)	
Increased ≥25%	4 (9)	19 (50)	
Serum alpha-fetoprotein			0.001†
Decreased >50%	10 (23)	3 (8)	
Decreased 25–50%	4 (9)	1 (3)	
Stable	25 (58)	15 (39)	
Increased ≥25%	4 (9)	19 (50)	
Portal obstruction			0.02‡
Yes	3 (7)	10 (26)	
No	40 (93)	28 (74)	

*Because of rounding, not all numbers total 100 percent.

†For the comparison of three groups (decreased vs. stable vs. increased) by the chi-square test with 2 df.

‡By Fisher's exact test.

other 81 patients, tumor growth, as assessed by tumor size and the serum alpha-fetoprotein concentration, was reduced in the chemoembolization group as compared with the conservative-management group (Table 2). The incidence of portal obstruction was lower in the chemoembolization group (one segmental and two truncal obstructions occurring more than eight months after enrollment in three patients) than in the conservative-management group (seven segmental and three truncal obstructions occurring less than eight months after enrollment in four patients and after more than eight months in six patients). There was no difference between groups in the occurrence of extrahepatic metastasis.

Outcome and Complications of Chemoembolization

Among the 50 patients assigned to chemoembolization, 49 received at least one course of chemoembolization and 26 received all four of the planned courses. The patient who was not treated had a hepatic-artery dissection during arteriography before treatment was begun. The reasons for stopping treatment early in 23 patients were death (13 patients), arterial obstruction (5), proximal arterioportal fistula (1), extrahepatic metastasis (1), and refusal by the patient to continue (3).

In the chemoembolization group, a temperature of 38°C or above, abdominal pain, or vomiting was noted in 86 percent of the courses in 47 patients (Table 3). These symptoms lasted a mean (\pm SD) of 2.5 \pm 2.1 days (range, 1 to 10). Liver failure, defined as the presence of encephalopathy, ascites, or an increase in the serum bilirubin concentration of 0.9 mg per deciliter (15 μ mol per liter) or more, occurred after 47 courses of treatment in 30 patients. Gastrointestinal hemorrhage was caused by esophagitis (two patients), duodenal ulcer (one patient), and antral ulcerations (one patient). One

patient with diffuse hepatocellular carcinoma and cirrhosis graded as Child–Pugh class A died of liver failure 10 days after the second course of treatment. Death was considered a complication of treatment because this patient's liver function was judged to be well compensated before treatment and acute liver failure occurred immediately after treatment. In the six other patients who were treated and who died within two months after randomization, death was not as clearly related to the treatment.

Other complications of chemoembolization included dysuria, hiccups, and inguinal hematoma in two patients each and worsened diabetes, a decrease in the platelet count to below 70,000 per cubic millimeter, and a decrease in the serum sodium concentration to below 125 mmol per liter in one patient each. The average period of hospitalization was 6.6 days (range, 2 to 24) for each course of treatment. The mean (\pm SD) number of days of hospitalization per patient during the first eight months of the study (or until death) was significantly higher in the chemoembolization group than in the conservative-management group (29 \pm 16 days vs. 13 \pm 14 days, $P < 0.001$ by the Wilcoxon test).

Deviations from the Protocol

Two patients assigned to conservative management each received three courses of chemoembolization. One patient requested this treatment after randomization, and the other was inadvertently treated because of a mistake in transmitting the treatment assignment. These patients were analyzed as part of the conservative-management group and survived 7 and 29 months, respectively. Analysis of the data after the exclusion of these two patients did not change the survival results. One patient assigned to chemoembolization received only one course of treatment because of

Table 3. Complications of 148 Courses of Lipiodol Chemoembolization in the 50 Patients Assigned to Such Treatment.

COMPLICATION	NO. OF COMPLICATIONS (%)	NO. OF PATIENTS WITH EACH COMPLICATION (%)*
Abdominal pain	82 (55)	40 (80)
Vomiting	85 (57)	40 (80)
Temperature $\geq 38^\circ\text{C}$	73 (49)	38 (76)
Death	1 (1)	1 (2)
Ascites	6 (4)	5 (10)
Encephalopathy	1 (1)	1 (2)
Gastrointestinal hemorrhage	4 (3)	4 (8)
Cholecystitis	2 (1)	2 (4)
Serum AST or ALT activity $\geq 5 \times$ upper limit of normal 3 days after treatment†	46 (31)	27 (54)
Increase in serum bilirubin of ≥ 0.9 mg/dl‡	47 (32)	29 (58)
Other complications§	12 (8)	9 (18)

*Occurrence of the complication after at least one course.

†AST denotes aspartate aminotransferase, and ALT alanine aminotransferase.

‡Difference between the base-line value and the value measured three days after treatment.

§Other complications consisted of dysuria (2 patients), hiccups (2), inguinal hematoma (2), worsened diabetes (1), a decrease in the platelet count to below 70,000 per cubic millimeter (1), and a decrease in the serum sodium concentration to below 125 mmol per liter (1).

arterial obstruction and thereafter received percutaneous alcohol injection.

DISCUSSION

Using a sequential design, we did not demonstrate a survival benefit for repeated Lipiodol chemoembolization in patients with unresectable hepatocellular carcinoma but without severe liver disease. Nonetheless, there was a trend toward increased survival, with an estimated relative risk of death of 1.4 in the conservative-management group (95 percent confidence interval, 0.9 to 2.2) as compared with the chemoembolization group. Since imbalances in base-line and prognostic characteristics between the groups could have favored the chemoembolization group, adjustments were made with a Cox model. After this analysis, the relative risk of death in the conservative-management group as compared with the chemoembolization group was estimated to be 1.3 (95 percent confidence interval, 0.8 to 2.1).

Lipiodol chemoembolization has numerous side effects, requires hospitalization, and is expensive.^{9,14,15} Since it did not markedly improve survival, we do not believe its use can be recommended. Death was the main reason treatment was discontinued before four courses had been completed, emphasizing the frequency of treatment failure.

Consensus is lacking about the most suitable method of chemoembolization. The use of Lipiodol and Gelfoam particles is the most generally accepted method. As compared with Gelfoam particles, Gelfoam powder may cause more harm to areas of the liver without tumor, especially in patients with cirrhosis.^{21,22} The use of chemotherapy is also controversial. Cisplatin has been suggested to be more effective than doxorubicin,^{23,24} particularly in one randomized trial.⁸ We used a lower dose of cisplatin (70 mg) than have other studies^{8,25} in order to reduce the side effects of the medication, especially renal toxicity. Our prior experience suggested that patients with alcoholic cirrhosis are highly susceptible to the toxic effects of cisplatin.

In our study, tumor size decreased in more than half the patients who received chemoembolization and was stable in most other patients in this group. This finding is consistent with those of previous nonrandomized studies.^{9,12,25-27} In contrast, tumor size increased in half the patients assigned to conservative management. The pattern of findings for the serum alpha-fetoprotein concentration was similar. The incidence of portal obstruction was higher in the conservative-management group than the chemoembolization group.

Case-control studies have reported that chemoembolization may markedly increase survival in hepatocellular carcinoma.^{9,10,12,13,28} The type of controls selected in these studies, however, is open to question. The beneficial effect suggested in one study could be related to the very low survival rate in the control group (0 percent at one year, in contrast with 43 percent in our

study).¹² In a randomized trial comparing chemoembolization and conservative management, survival was not significantly improved in the group treated with doxorubicin and Gelfoam powder.²⁹

We found that Lipiodol chemoembolization significantly inhibited tumor growth. This benefit may have been offset by worsened liver function, particularly in patients with cirrhosis. Prognostic factors for survival were related to growth of the tumor, as well as to signs of severe chronic liver disease, such as abnormal serum bilirubin and serum albumin concentrations, as previously shown.³⁰⁻³² Liver failure is a frequent cause of death in patients with cirrhosis and hepatocellular carcinoma.^{20,33-35} Despite the exclusion of patients with overt liver failure, three fifths of the patients had at least one episode of liver decompensation within a few days of treatment, and one patient died. It is possible that Lipiodol chemoembolization may be beneficial in a more select group of patients, but factors predictive of a response to this treatment, without the development of side effects, have yet to be determined.^{36,37}

We are indebted to Professor Daniel Dhumeaux for help in initiating the study and to Professor Alain Roche for technical advice.

APPENDIX

The following investigators participated in the Groupe d'Etude et de Traitement du Carcinome Hépatocellulaire: *Centre Hospitalier Universitaire, Angers, France* — F. Oberti, O. Ruget, P. Calès, and C. Caron-Poitreau; *Hôpital Jean Verdier, Bondy, France* — J.C. Trinchet, A. Abou Rached, Y. Ajavon, and M. Beaugrand; *Hôpital du Haut Lévéque, Pessac, France* — F. Dumas, P. Couzigou, and J. Drouillard; *Hôpital Saint André, Bordeaux, France* — C. Balabaud and P. Grelet; *Hôpital Saint Luc et Cliniques Universitaires de Mont-Godinne, Brussels, Belgium* — A. Guebel, M. Mélange, J. Pringot, and B. Van Beers; *Hôpital Beaujon, Clichy, France* — A. Hadengue, V. Vilgrain, and S. Erlinger; *Hôpital Henri Mondor, Créteil, France* — C. Duvoix, D. Mathieu, and D. Dhumeaux; *Hôpital Albert Michallon, Grenoble, France* — J.P. Zarski and S. Dalsoglio; *Hôpital Edouard Herriot, Lyons, France* — F. Mion, P.J. Valette, and P. Paliard; *Centre Hospitalier Lyon Sud, Pierre Bénite, France* — S. Claudel-Bonvoisin, J.C. Emery, and L. Descos; *Hôpital Saint-Luc, Montreal* — M. Dagenais, M.P. Dufresne, R. Lapointe, and P.M. Huet; *Centre Hospitalier Universitaire, Vandoeuvre-les-Nancy, France* — V. Bas, D. Regent, C. Bazin, and M.A. Bigard; *Hôpital Guillaume et Renée Laënnec, Nantes, France* — B. Hummeau, A. Bury, M. Le Rhun, F. Lerat, H. Gibaud, R. Rymer, and L. Le Bodic; *Hôtel Dieu, Nantes, France* — C. Masliah, B. Pouliquen, and D. Perrin; *Hôpital Saint Louis, Paris* — C. Chastang; *Hôpital Saint Antoine, Paris* — O. Chazouillères, A. Loria, R. Poupon, A. Pauwels, N. Mostefa-Kara, V.G. Lévy, P. Balladur, J.P. Deutsch, and J.M. Tubiana; *Hôpital Necker, Paris* — S. Pol and P. Berthelot; *Hôpital de la Salpêtrière, Paris* — D. Valla, J.C. Bousquet, and P. Opolon; *Centre Hospitalier, Pontoise, France* — M. Bouvry; *Centre Hospitalier Delafontaine, Saint Denis, France* — H. Labadie; *Centre Hospitalier Général, Saint-Nazaire, France* — T. Martin; *Centre Hospitalier Universitaire, Strasbourg, France* — J.P. Bronowicki and D. Vetter; *Clinique de l'Orangerie, Strasbourg, France* — J.J. Wenger; and *Centre Hospitalier Universitaire, Toulouse, France* — L. Buscaill, J. Frexinos, and F. Joffre.

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