Randomized Controlled Trial for Hepatocellular Carcinoma with Portal Vein Thrombosis: Intra-arterial Iodine-131-Iodized Oil Versus Medical Support

Jean-Luc Raoul, Dominique Guyader, Jean-François Bretagne, Régis Duvauferrier, Patrick Bourguet, Djemal Bekhechi, Yves M. Deugnier and Michel Gosselin

Service de Radiologie, Hôpital Sud; Service d'Hépatogastroentérologie, Clinique des Maladies du Foie and Service de Médecine Nucléaire, Hôpital Pontchaillou, Centre Hospitalier Régional Universitaire 35033 Rennes Cédex, Cis Biointernational Saclay, France

Portal vein thrombosis is a poor prognostic factor in patients with hepatocellular carcinoma (HCC) and a contraindication for chemoembolization. Intra-arterial injection of ^{131}I-iodized oil which does not modify arterial flow, is feasible in this condition. The aim of this prospective randomized controlled trial was to compare the efficacy of treatment with radiolabeled oil (treated group) versus medical support (control group) in patients with stage I or II HCC (classification of Okuda) with portal vein thrombosis. **Methods:** Twenty-seven HCC patients (26 males, 1 female), aged 53–79 yr, with portal vein thrombosis were randomly assigned to Lipiocis® group (n = 14) or Control group (n = 13). Additional injections of radiolabeled oil were given 2, 5, 8 and 12 mo after initial therapy. Medical support treatment consisted of: tamoxifen (n = 5), 5 FU intravenously (n = 1), NSAIDs or corticosteroids (n = 5). Efficacy was evaluated according to survical rate (Kaplan-Meier method; log rank test), AFP serum values (measured at 2, 5, 8 and 12 mo) and angiography. **Results:** The two groups were comparable (Child's classification, Okuda's classification, liver function tests, location of the thrombus). Tolerance was excellent in the Treated group. The actuarial survival curves were significantly different ($p < 0.01$) between the two groups, the survival rates (CI 95%) at 3, 6 and 9 mo being 71% (48%–95%), 48% (12%–55%), 7% (1%–31%) for the Treated group; and 10% (1%–33%), 0% and 0% for the Control group. **Conclusion:** Intra-arterial hepatic injection of ^{131}I-labeled iodized oil is a safe and effective palliative treatment of HCC with portal vein thrombosis.

Key Words: hepatoma; portal vein thrombosis; radionuclide therapy; interventional radiology; iodine-131-labeled iodized oil

J Nucl Med 1994; 35:1782–1787

Advances in the treatment of hepatocellular carcinoma have been made in the past several years due (*1*) to the development of liver transplantation (*2*), the increasing use of intraarterial procedures, the advent of trans-percutaneous injection of hepatic tumors with alcohol (*3*) and the use of antiestrogens (*4*). The most important breakthrough, however, has been the development of intravascular procedures and in particular, the use of Lipiodol (Laboratories Guerbet, Aulnay sous Bois, France) as a carrier for therapeutic agents. Coupling Lipiodol with a chemotherapeutic agent (doxorubicin or cisplatinum) allows in situ chemotherapy (*5–8*). Internal radiation therapy (*9,10*) can be achieved as well by using ^{131}I-labeled Lipiodol (Lipiocis®, Cisbiointernational, Saclay, France). Intra-arterial infusions of emulsions composed of Lipiodol and anticancer agents are frequently associated with embolization, thereby increasing therapeutic efficacy, but increasing side effects.

Another drawback exists in that this technique interrupts hepatic arterial flux for a few days and is therefore contraindicated in case of portal vein thrombosis. Therapeutic abstention therefore is most often advised. But some hepatocellular carcinoma patients with portal vein thrombosis have a good general condition, or a portal vein thrombosis not related to the cancer, or a previous porta-caval shunt; however these patients cannot undergo embolization due to the lack of portal vein patency. During the past several years we have developed an internal radiation therapy procedure allowing for an objective tumorous response in 40% of cases (*11*). Our technique does not modify arterial flux and, therefore, can be used in hepatocellular carcinoma with portal vein thrombosis. Then, taking into account these good preliminary results, we wanted to demonstrate the efficacy of this new therapy in terms of survival in a randomized controlled trial. The aim of this prospective, randomized trial was to compare the efficacy of this technique versus a symptomatic treatment.

Received Nov. 24, 1993; revision accepted May 27, 1994.

For correspondence or reprints contact: JL Raoul, Service d'Hépatogastroentérologie, Hôpital Pontchaillou, 35033 CHRU Rennes, France.

PATIENTS AND METHODS

This protocol was approved by the ethical committee of Pontchaillou Hospital. Enrollment began in September 1990 and was prematurely stopped in March 1992 for ethical reasons after an interim analysis.

Eligibility Criteria

Patients were included in the study if they presented with hepatocellular carcinoma stage I or II by the classification of Okuda et al. (*12*), associated with portal vein thrombosis, but free of extrahepatic metastases.

Diagnosis of HCC was made either on the basis of histologic or cytologic findings or on elevated serum alpha-1-feto-protein (AFP) levels (>500 ng/ml) associated with the presence of a liver mass.

Portal vein thrombosis was demonstrated by either angiography, duplex Doppler ultrasound examination or by a CT scan with bolus injection. Thrombi were identified on contrast-enhanced CT scans (*13*) by the presence of a low-attenuation intraluminal filling defect frequently associated with collateral venous pathways and alterations in hepatic attenuation. Patients were included if the thrombosis was located either in the portal trunk or in one of its two main branches.

Classification of Okuda et al. (*12*) is based on the presence of four parameters of poor prognosis: 1 = albumin level less than 30 g/liter; 2 = total bilirubin level greater than 30 mg/liter; 3 = ascites; and 4 = tumor size greater than 50% of total liver volume. By definition, patients with stage I disease have none of these signs, those with stage II disease have one or two, and those with stage III disease have more than two.

The severity of the underlying cirrhosis was determined using Child's classification. This classification is based upon five parameters: ascites, encephalopathy, prothrombin time, albumin level and bilirubin level. Each parameter is graded from 1 (best) to 3 (worse) points, the total ranging between 5 and 15 points. Class A corresponds to the less severe cirrhosis (5, 6 points), and Class B (7–9 points) and Class C (10–15 points) correspond to severe cirrhosis.

The detection of extrahepatic metastasis was limited to a chest x-ray and examination of the adrenal glands on CT scan or ultrasonography.

Patients were not included if a surgical treatment (resection or transplantation) could be undertaken despite portal vein thrombosis.

Treatments

In the Treated group, intra-arterial injection was performed after having confirmed portal vein thrombosis following splenic or superior mesenteric artery angiography. Three milliliters of ^{131}I-iodized oil (60 mCi) were then injected into the hepatic artery. After the therapeutic injection, the patients were isolated for 7 days for radioprotection of other patients and visitors. Visits were permitted during the last 3 days for short periods of time. Additional injections were planned 2, 5, 8 and 12 mo after the first injection and were canceled or postponed in case of poor performance status (Karnofsky index <60%) or occurrence of extrahepatic metastases.

Scintigraphy was performed on Day 5; planar scintiscans of the liver and the thorax (anterior and posterior views) were obtained over a 10-min period with a large-field-of-view gamma camera. Two biodistribution parameters were determined: the L/L+l ratio (L: liver, l: lungs) corresponding to the injected activity retained by the liver and the T/NT ratio which is the ratio of activities between tumorous and nontumorous area.

On Day 7, CT scans were performed to determine liver and tumor volumes.

The radiation doses were roughly estimated using the liver and tumor volumes and the two determined biodistribution parameters (L/L+l, T/NT); half-life was not determined and a value of 5 days was used in accordance with previously published data (*9*).

In the Control group, no specific treatment was systematically given, but a general practitioner was free to prescribe tamoxifen (20–40 mg/day), NSAIDs, corticosteroids or antalgic drugs at any time to his patient.

Randomization Procedure

Once inclusion criteria had been fulfilled, written informed consent was obtained from the patients. They were then randomly assigned to either observation (Control group) or intra-arterial radioiodinated oil therapy (Treated group).

Statistical Analysis

Survival from the day of randomization was the only end point of this study. AFP serum values (2, 5, 8 and 12 mo after the first injection) and portal vein thrombosis on angiography (Treated group) were recorded but these parameters were considered to be of secondary importance in this study. The response was considered as partial for a decrease in AFP serum values greater than 50%, and as complete when AFP values returned to normal. Tumor size (on CT scans) was not considered a good criteria in this study because only treated patients had an intrahepatic injection of Lipiodol which allowed for a good tumor size determination. It would then be very difficult to compare tumor size evolution in both groups; moreover in most patients the tumor was diffuse or multinodular and it was quite impossible to precisely draw their limits.

It was estimated that a minimum of 28 patients per group would be necessary to demonstrate a 6-mo survival improvement of 35% (from 15% to 50%), with a type I error probability of 5% and a type II error probability of 10%.

The two groups were compared by the Mann-Whitney nonparametric test. Probability values <0.05 were considered statistically significant. Survival curves were estimated by the Kaplan-Meier method. The 95% confidence intervals (CI 95%) were calculated by Rothman's method and survival curves were compared by using the log-rank test.

A first analysis was carried on after the twenty-seventh inclusion. The results were so statistically significant that we decided to stop the study.

Patients

A total of 27 patients were entered in the trial. They were aged from 53 to 79 yr, and 26 males and 1 female were included. Half of them were in good hepatic condition (Class A in Child's classification); cirrhosis was mainly related to alcohol abuse.

RESULTS

Among the 27 patients, 14 were assigned to the Treated group and 13 to the Control group. Patient characteristics are shown in Table 1. There were no significant differences between the two groups. AFP serum levels tended to be higher than 500 ng/ml more often in the control group and more often tumor involved both lobes in the Treated group (these patients had a CT scan enhanced by Lipiodol injec-

TABLE 1
Patient Characteristics and Pretreatment Laboratory Findings in the Two Groups*

	Control group (n = 13)	Treated group (n = 14)
Age (yr)	67.6 ± 6.7	65.4 ± 6.5
Cirrhosis (yes/no)	13/0	14/0
Etiology		
Alcohol	11	11
Genetic hemochromatosis	0	1
B virus	2	2
Childs' classification (A/B/C)	6/7/0	8/6/0
Points	6.8 ± 1.6	6.3 ± 1.2
Prothrombin (%)	80 ± 16	86 ± 13
Albumin (g/liter)	36.2 ± 5.1	37 ± 5.2
Bilirubin (μmole/liter)	39.3 ± 41.3	21.6 ± 9.0
AFP		
>500 ng/ml (n)	9	5
Range	5–129400	3–16820
Okuda's stage 1/2 (n)	5/8	3/11
Location of tumor (n) both lobes/right/left lobe	7/4/2	12/1/1
Location of thrombosis (n) trunk/right/left branch	10/1/2	10/1/3

*Results expressed as mean ± s.d. or as number of patients.

tion), but these differences were not statistically significant.

In the Treated group, 5 patients received one therapeutic injection, 4 had two injections, 3 had three injections, 1 had four injections and 1 had five injections. The estimated cumulated radiation doses ranged from 10 to 100 Gy (43 ± 29 Gy). In the Control group, 5 patients were treated with the antiestrogen drug tamoxifen, 1 received an intravenous bolus of 5-fluorouracil and 5 received NSAIDs, corticosteroids or antalgic drugs.

Survival

Nine months after the end of the inclusion period, all patients in the Control group were deceased. In the Treated group, one patient was still alive after a follow-up of more than 80 wk. Median survival duration was 8 wk in the Control group and 24 wk in the Treated group.

The survival rate, as expressed by a survival curve (Fig. 1), calculated according to the Kaplan-Meier method, was significantly higher (Chi 2 = 10.5; $p < 0.01$) in the Treated group as compared to the Control group. The 3-mo survival rates were equal to 10% (CI 95%: 1%–33%) and 71% (CI 95%: 48%–95%), and the 6-mo survival rates to 0% and 48% (CI 95%: 12%–55%) for the Control and Treated group, respectively. The 1-yr survival rate for the Treated group was equal to 7% (CI 95%: 1%–31%).

Response Rate

In the Treated group, AFP levels were monitored in only five patients because in the other nine, four died before the second injection and five had AFP serum levels below 20 ng/ml before treatment. Among these five, a partial response was observed in two, AFP serum levels remained stable in two others and one patient had increased values. The response rate was 40%. In the Control group, AFP serum levels were monitored in only two patients showing a dramatic increase.

Evolution of the portal vein thrombosis was angiographically monitored in nine patients in the Treated group. The thrombosis remained stable in five cases, decreased in two cases of troncular thrombosis and disappeared in two cases: one with thrombosis of the portal trunck and one with thrombosis of the right vein. The response rate was 44%. In one case, the patient had an enlarged multinodular liver and the thrombosis could be related to compression of the portal trunk by the tumors; on the first angiography the portal vein was never seen and collateral venous pathways were numerous; on the second angiography the portal

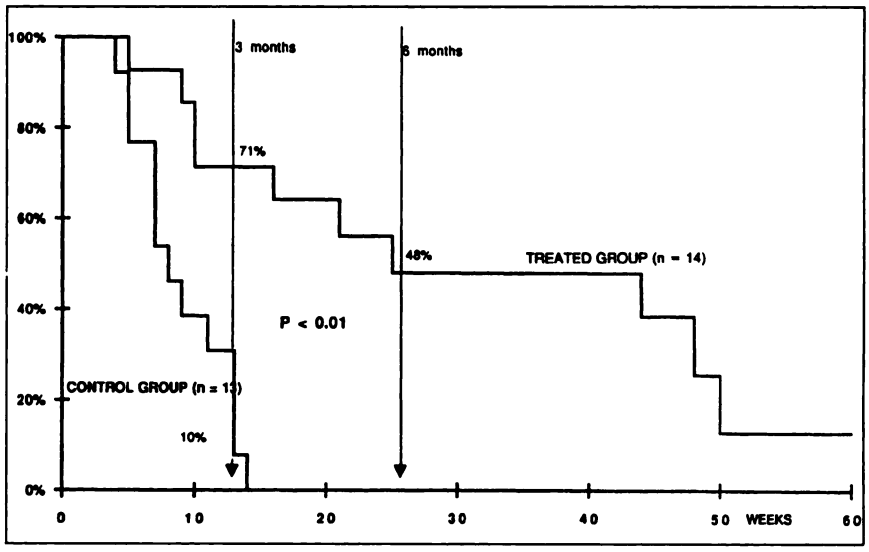

FIGURE 1. Comparison of survival rates (Kaplan-Meier method) between Treated and Control groups. The survival rate is significantly higher ($p < 0.01$) in the Treated group versus the Control group.

TABLE 2
Characteristics of Included Patients

	Treated group						Control group				
No.	Age	LV (ml)	TV (ml)	N inj	Do	Survival (wk)	No.	Age	LV (ml)	TV (ml)	Survival (wk)
1	64	3000	2500	1	10 Gy	D(5)	3	60	1800	900	D(11)
2	66	3000	1700	2	22 Gy	D(25)	4	57	1200	300	D(7)
5	64	1800	400	3	90 Gy	D(44)	7	74	1800	1200	D(11)
6	53	3200	1700	5	58 Gy	D(48)	8	64	1500	600	D(6)
9	55	1500	500	3	87 Gy	A(82)	10	77	2000	1200	D(5)
11	58	3000	2600	4	40 Gy	D(50)	13	73	1400	1000	D(7)
12	67	1200	200	1	40 Gy	D(9)	14	73	1500	450	D(9)
16	79	1000	450	1	36 Gy	D(10)	15	72	1500	200	D(13)
18	68	1400	600	2	28 Gy	D(21)	17	67	1800	600	D(5)
21	71	1800	1000	2	36 Gy	D(38)	19	72	3000	2000	D(14)
22	64	1200	150	3	100 Gy	D(38)	20	79	1500	500	D(4)
23	74	2000	1200	1	17 Gy	D(16)	24	65	1800	600	D(13)
26	69	1800	1000	1	19 Gy	D(10)	25	78	2000	400	D(11)
27	69	1800	750	2	26 Gy	D(24)					

LV = liver volume; TV = tumor volume; N inj = number of injections; Do = estimated cumulated dosimetry; D = dead; and A = alive.

trunk was clearly seen and collateral veins had disappeared. In the second case, the thrombosis was located in the right portal branch and was supposed to be of tumorous origin because it was close to the main tumor and retaining Lipiodol after its injection. After the third injection, this right branch was clearly defined without intraluminal thrombus and the tumor itself had decreased in size.

Tolerance in the Treated Group

Clinical tolerance was estimated as excellent in all cases, but asthenia was frequently observed during 2 wk following time of injection.

One patient presented 3 wk after the third injection with fever and an extensive interstitial pneumonia. An allergic pneumonia due to Lipiodol was suspected as metastatic disease was excluded by the long-term efficacy of antibiotics and corticosteroid treatment.

No side effects related to the use of NSAIDs, corticosteroids, tamoxifen or 5-Fluorouracil was described in the Control group.

DISCUSSION

Lipiodol injected into the hepatic artery has been demonstrated to remain selectively in hepatocellular carcinoma. This selective tumor targeting by Lipiodol permits a more accurate diagnosis by enhancing the tumor CT scan's density, allowing the detection of minute tumors (*14*). The study of ^{131}I-labeled Lipiodol biodistribution (*9*) shows that it is retained essentially within the liver and lungs, liver uptake being predominant, exceeding 75% of the injected dose, with an effective half-life of approximately 5 days. In addition, the ratio between tumorous and nontumorous hepatic areas is high, exceeding 5.3, confirming the preferential uptake of Lipiodol within the tumor. Treatment using a high dose of radiolabeled Lipiodol has been shown to be well tolerated in a phase I trial (*10*). Moreover, this good tolerance was confirmed in a phase II trial including 50 patients with HCC (*11*) and associated with an objective tumor response in 40% of cases.

Portal vein thrombosis in HCC is an important prognostic factor in patients having a poor prognosis whether receiving systemic (*15*) or intra-arterial (*16*) chemotherapy, or a nonspecific treatment (*17*). In these series, the 1-yr survival rates were poor, ranging from 8% (*16,17*) to 18% (*15*). Moreover, such patients are unsuitable for transarterial embolization, and therefore treatment is limited either to palliative therapy or to intra-arterial injection of a Lipiodol and chemotherapeutic agent emulsion.

As it does not modify the hepatic arterial flux, an intra-arterial injection of ^{131}I-iodized oil could be proposed in such patients. Moreover, the therapeutic effect of ^{131}I-iodized oil is derived solely from a radiative and not an ischemic effect such as is the case with chemoembolization. This procedure could then be proposed in patients with HCC and portal thrombosis without modification of its efficacy. Portal vein tumorous thrombi have been found to be arterially vascularized (*18*), and ^{131}I-iodized oil has been detected in these thrombi following intra-arterial injection of ^{131}I-iodized oil (*14*). A biodistribution study showed that ^{131}I-iodized oil was retained within the tumor thrombi (*14*), and thus one might expect ^{131}I-iodized oil to act upon the thrombus itself.

In this study we have employed a standard activity of 60 mCi by injection. We have previously demonstrated that the calculated radiation dose was not correlated with survival which could be related to the difficulty in determining the biodistribution and CT scan parameters. In patients with huge tumors and portal vein thrombosis, the exact determination of these parameters was hardly feasible. After a therapeutic injection, scintigraphic study was not performed at Day 1 for radioprotection of the staff and

conducted only at Day 5. Patients were discharged at Day 7 and the half-life could not be determined; we used a value of 5 days corresponding to our mean value as determined on scintigraphic (*9,11*) and on urinary elimination studies (unpublished data). Moreover, a fixed dose of 60 mCi seemed to be the best compromise between efficacy and tolerance in term of hospitalization length.

Our results show that in patients with HCC and portal vein thrombosis, treatment by ^{131}I-iodized oil is well tolerated and efficient.

As previously shown in patients with HCC free of portal thrombosis, tolerance was excellent in this study. Such a good tolerance was expected since the procedure does not modify hepatic arterial flux. Most patients experienced asthenia for 1 to 3 wk as has been described following chemoembolization, and this asthenia was more severe after the first injection as compared to the following injections. We observed a case of interstitial pneumonia 3 wk after the third therapeutic injection. We have previously described a similar case (*11*) following ^{131}I-iodized oil injection, and another case has been described after injection of ^{131}I-iodized oil mixed with a chemotherapeutic agent (*19*). The clinical and radiological signs were similar to those observed in lymphatic invasion of the pulmonary bed, but the symptoms responded well to corticosteroids. Whether such an allergic reaction represents a contraindication for further injections of ^{131}I-iodized oil or not remains to be seen.

The main efficacy criterion was survival. A significant difference between survival from the two groups was observed. The survival curves diverge rapidly, the 6-mo survival rate being 0% in the Control group versus 43% (CI 95%: 12%–55%) in the Treated group. These results prompted us to stop inclusions. The significant difference in the survival curves between the two groups could be related to the efficacy of the treatment or to a bias in randomization. There were no significant differences between the two groups; bilirubin levels and AFP levels were slightly (but not significantly) more elevated in the Control group but this was related to one patient in each case. The main prognostic factors (Child's and Okuda's classifications) did not differ between the two groups or show a tendency to be worse in the Treated group (Okuda's stage). The survival in the control group was lower than expected in our study design. This could be due to the low number of included patients. In most cases the literature shows that portal thrombosis was located in a branch of the portal vein contrary to that observed in both our groups. In fact, our patients had frequently huge tumors explaining the severity of the thrombosis itself but also the severity of their evolution. Moreover, on one hand, the low number of included patients diminishes somewhat the potency and the relevance of our conclusion, but on the other hand, five patients in the Control group were treated by tamoxifen, a drug demonstrated as potentially efficient in increasing survival in HCC (*4*). Other potential efficacy criteria such as AFP serum levels and portal vein thrombosis were assessed only in the Treated group with an objective response observed in about 40% of the treated patients. This value is quite similar to what we had observed in our phase II trial (*11*).

To the best of our knowledge, no randomized controlled trial has yet been performed in HCC patients and portal vein thrombosis. This is due to the poor prognosis of these patients and to the poor efficacy or tolerance of the proposed treatments. Hepatic resection with removal of portal vein tumor thrombi was reported in 13 Japanese patients, 8 of whom had cirrhotic livers (*20*). Two patients died early after surgery, four died between 4 mo to 2 yr later and seven were still alive 5 to 44 mo later. Such an aggressive policy should be considered only in patients with a good hepatic reserve function even though the procedure may allow for ensuing arterial embolization. In the same series, nine patients with HCC and tumor thrombi went untreated and died 15–126 days after detection of the thrombus, as observed similarly in our Control group. Necrosis of tumor thrombus was also described on resected specimens after chemoembolization using doxorubicin (*21*). Three cases of portal vein repermeation were described (*22*) after one, four and five courses of intra-arterial Lipiodol and doxorubicin. In one patient, chemoembolization was even performed after recanalization of the portal vein. Livraghi et al. (*23*) used echoguided percutaneous alcohol injections in portal thrombosis in four patients with HCC. In one patient, complete thrombus necrosis was achieved and confirmed during ulterior liver transplantation. In another patient, biopsies of the thrombus yielded necrotic material only, and in the other two patients, progression of the thrombus was stopped. Nevertheless, these techniques are difficult, and their success often depends upon the skill and experience of the physician. Moreover, their efficacy has to be demonstrated on larger series of patients.

In contrast, not only is intra-arterial injection of ^{131}I-iodized oil tolerated, but it is highly feasible, as was shown in our previous phase II trial (*11*). From a technical standpoint, only the selective catheterization of the hepatic artery is required. Some authors (*24*) have performed supraselective catheterization of the artery vascularizing the tumor, but in our opinion this is not necessary since in most cases HCC is multinodular due to intrahepatic metastasis or to multicentric tumorigenesis. In the Korean study, subsegmental injection of ^{131}I-labeled iodized oil (*24*) was followed a few months later by recurrence in areas not perfused in several patients. Injection via the hepatic artery is certainly easier and more logical, allowing for treatment of the main tumor and minute "daughter" nodules. Efficacy is excellent with the histological demonstration, in one resected specimen (*25*), of achievement of complete necrosis.

This prospective, randomized and controlled study conducted in HCC patients with portal vein thrombosis has compared intra-arterial injection of ^{131}I-iodized oil to symptomatic treatment (including tamoxifen in 5 of 13 patients). It was prematurely stopped due to evidence of significant

efficacy in the Treated group. In conclusion, intra-arterial injection of ^{131}I-iodized oil in HCC patients with portal vein thrombosis significantly increases survival rate, is technically feasible and is well tolerated. Nevertheless, although improved by ^{131}I-iodized oil, the prognosis of HCC complicated with portal vein thrombosis remains poor.

REFERENCES

1. Dusheiko GM, Hobbs KE, Dick R, Burroughs AK. Treatment of small hepatocellular carcinoma. *Lancet* 1992;340:285–288.
2. Iwatsuki S, Starzl TE, Sheahan DG, Yokoyama I, Demetris AJ, Todo S, et al. Hepatic resection versus transplantation for hepatocellular carcinoma. *Ann Surg* 1991;214:221–229.
3. Livraghi T, Festi D, Monti F, Salmi A, Vettori C. US-guided percutaneous alcohol injection of small hepatic and abdominal tumors. *Radiology* 1986; 161:309–312.
4. Farinati F, De Maria N, Fornasiero A, et al. Prospective controlled trial with antiestrogen drug tamoxifen in patients with unresectable hepatocellular carcinoma. *Dig Dis Sci* 1992;37:659–662.
5. Takayasu K, Shima Y, Muramatsu Y, et al. Hepatocellular carcinoma: treatment with arterial iodized oil with and without chemotherapeutic agents. *Radiology* 1987;162:345–351.
6. Lin DY, Liaw YF, Lee TY, Lai CM. Hepatic arterial embolization in patients with unresectable hepatocellular carcinoma. A randomized controlled trial. *Gastroenterology* 1988;94:453–456.
7. Kasugai H, Kojima J, Tatsuta M, et al. Treatment of hepatocellular carcinoma by transcatheter arterial embolization combined with intraarterial infusion of a mixture of cisplatin and ethiodized oil. *Gastroenterology* 1989; 97:965–971.
8. Nakamura H, Hashimoto T, Oi H, Sawada S. Transcatheter oily chemoembolization of hepatocellular carcinoma. *Radiology* 1989;170:783–786.
9. Raoul JL, Bourguet P, Bretagne JF, et al. Hepatic artery injection of ^{131}I-Lipiodol. Part I: biodistribution study results in patients with hepatocellular carcinoma and liver metastases. *Radiology* 1988;168;541–545.
10. Bretagne JF, Raoul JL, Bourguet P, et al. Hepatic artery injection of ^{131}I-Lipiodol. Part II: preliminary results of therapeutic use in patients with hepatocellular carcinoma and liver metastases. *Radiology* 1988;168:547–550.
11. Raoul JL, Bretagne JF, Caucanas JP, et al. Internal radiation therapy for hepatocellular carcinoma. Results of a French multicenter phase II trial of transarterial injection of iodine-131-labeled Lipiodol. *Cancer* 1992;69:346–352.
12. Okuda K, Ohtsuki T, Obata H, et al. Natural history of hepatocellular carcinoma and prognosis in relation to treatment: study of 850 patients. *Cancer* 1985;56:918–928.
13. Mathieu D, Vasile N, Grenier P. Portal thrombosis: dynamic CT features and course. *Radiology* 1985;154:737–741.
14. Raoul JL, Duvauferrier R, Bretagne JF, et al. Usefulness of hepatic artery injection of Lipiodol and ^{131}I-Lipiodol before the therapeutic decision in hepatocellular carcinoma. *Scand J Gastroenterol* 1993;28:217–223.
15. Okada S, Okazaki N, Nose H, Yoshimori M, Aoki K. Prognostic factors in patients with hepatocellular carcinoma receiving systemic chemotherapy. *Hepatology* 1992;16:112–117.
16. Akashi Y, Koreeda S, Enomoto S, et al. Prognosis of unresectable hepatocellular carcinoma: an evaluation based on multivariable analysis of 90 cases. *Hepatology* 1991;14:262–268.
17. Calvet X, Bruix J, Gines P, et al. Prognostic factors of hepatocellular carcinoma in the west: a multivariate analysis in 206 patients. *Hepatology* 1990;12:753–760.
18. Nakashima T, Kojiro M, eds. *Hepatocellular carcinoma. An atlas of its pathology*. Tokyo: Springer-Verlag; 1987.
19. Ueda E, Hirota S, Ogasawara M, et al. A case of interstitial pneumonia after hepatic arterial infusion of Lipiodol: anticancer agent drug emulsion for hepatocellular carcinoma. *Rinsho Hoshasen* 1990;35:967–970.
20. Kumada K, Ozawa K, Okamoto R, et al. Hepatic resection for advanced hepatocellular carcinoma with removal of portal vein tumor thrombi. *Surgery* 1990;108:821–827.
21. Takayasu K, Shima Y, Muramatsu Y, et al. Hepatocellular carcinoma: treatment with intraarterial iodized oil with and without chemotherapeutic agents. *Radiology* 1987;162:345–351.
22. Dehry S, Bessis L, Attallah R, Ajavon Y, Eisele G, Roche A. Reperméabilisation portale après chimiothérapie lipiodolée intraartérielle au cours d'un carcinome hépatocellulaire. A propos de 3 cas. *Gastroentérol Clin Biol* 1990;14:893–895.
23. Livraghi T, Grigioni W, Mazziotti A, Sangali G, Vettori C. Percutaneous alcohol injection of portal thrombosis in hepatocellular carcinoma: a new possible treatment. *Tumori* 1990;76:394–397.
24. Yoo HS, Lee JT, Kim KW, et al. Nodular hepatocellular carcinoma. Treatment with subsegmental intraarterial injection of iodine-131-labeled oil. *Cancer* 1991;68:1878–1874.
25. Novell R, Hilson A, Hobbs K. Ablation of recurrent primary liver cancer using ^{131}I-Lipiodol. *Postgrad Med J* 1991;67:393–395.