

Epirubicin-Lipiodol Chemotherapy versus ¹³¹Iodine-Lipiodol Radiotherapy in the Treatment of Unresectable Hepatocellular Carcinoma

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Background. Arterially administered iodized oil (Lipiodol) is selectively retained by hepatocellular carcinomas (HCCs), and has been used as a vehicle for delivery of therapeutic agents to these tumors. This study compared the efficacy of Lipiodol-targeted epirubicin chemotherapy with Lipiodol-¹³¹I radiotherapy.

Methods. Ninety-five patients with unresectable HCC confined to the liver were administered either Lipiodol-epirubicin emulsion (n = 69; 61 cirrhotics; Okuda tumor Stage I, 14; II, 37; III, 18; epirubicin dose, 75 mg/m²) or Lipiodol-¹³¹I (¹³¹I) (n = 26; 18 cirrhotics; Okuda tumor Stage I, 6; II, 19; III, 1; dose 750–1050 MBq). The last 28 patients (17 epirubicin, 11 ¹³¹I) were treated within a prospective randomized trial. Bolus drug or isotope was injected into the hepatic artery by transfemoral cannulation. Lipiodol and ¹³¹I uptake were gauged by 10th day computed tomography and 48-hour scintiscan. Treatments were repeated two-monthly when indicated.

Results. Tumor size at 2 months remained static or diminished partially in 21 of 38 epirubicin recipients (55%) and 15/22 ¹³¹I recipients (68%). Actuarial survival at 6, 12, and 24 months was 40%, 25%, and 6% with epirubicin, and 58%, 25%, and 0% with ¹³¹I; 30-day mortality was 11% and 15%, respectively. Comparison with historic controls indicated survival benefit in Stages I and II.

Similar findings were recorded in the 28 patients in the randomized trial.

Conclusions. Patients with unresectable HCC receiving Lipiodol-epirubicin or Lipiodol-¹³¹I show good tumor localization, acceptable toxicity, and comparable survival benefit at 6 and 12 months with either modality. *Cancer* 1995;76:2202–10.

Key words: iodized oil, hepatocellular carcinoma, epirubicin, chemotherapy, ¹³¹Iodine, radiotherapy.

Primary hepatocellular carcinoma (HCC) is a common malignancy worldwide, and a leading cause of cancer-related deaths in large parts of Africa and Southeast Asia.^{1,2} Surgical resection (and in selected cases, orthotopic liver transplantation) is the treatment of choice, but unfortunately, the overwhelming majority of patients present with advanced inoperable disease.³ Lipiodol (Lipiodol Ultra Fluid, Laboratoire Guerbet, Roissy Charles de Gaulle, France) is a radiologic contrast agent derived by iodination of poppyseed oil. When administered via the hepatic artery, it is retained by HCCs for prolonged periods of time.⁴ This unusual property of Lipiodol has been exploited therapeutically, using the oil as a vehicle for targeted intra-arterial delivery of cytotoxic drugs or radioisotopes to unresectable HCCs. Sufficient data now exist to indicate that such Lipiodol-targeted therapies may be administered with a reasonable degree of safety to patients, and that they offer more effective palliation than systemic or intra-arterial chemotherapy and external beam radiotherapy.^{5–7} Drugs that have been conjugated to Lipiodol include 5-fluorouracil,⁸ doxorubicin,^{5,8} epirubicin,^{9,10} cisplatin,¹¹ and SMANCS,¹² a lipophilic macromolecular derivative of neocarzinostatin. The principal radioisotope that has been conjugated to Lipiodol is ¹³¹Iodine.¹³

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Comparisons have been made between different chemotherapeutic regimens, but to date there are no published reports comparing Lipiodol-targeted chemotherapy with Lipiodol-targeted radiotherapy. This study attempts to assess the benefits of Lipiodol-targeted chemotherapy (epirubicin) and Lipiodol-targeted radiotherapy (^{131}I) in two comparable groups of patients at the same center.

Materials and Methods

Patient Selection

From October, 1988, to June, 1993, all patients presenting with unresectable HCC at the University Departments of Surgery and Medicine, Royal Free Hospital were considered for inclusion in the study. Initial investigations for each patient included hematology, liver biochemistry, coagulation profile, viral hepatitis serology, and serum alpha fetoprotein (AFP). The lesions were staged in every instance by abdominal ultrasound and computed tomography (CT), chest X-ray and CT, and a radioisotope bone scan. Confirmation of the diagnosis was attempted by Tru-cut biopsy or needle aspiration cytology. On completion of the staging investigations, patients were invited to join the study only if they met the requirements listed in Table 1. Patients with evidence of extrahepatic spread of tumor within the abdomen or with distant metastases were excluded from the study. Resectability was determined at a joint consultation between physicians and surgeons. Patients with resectable lesions who declined surgery were not included. Very large tumor size, multifocal lesions involving both lobes, involvement of major vascular structures in or around the liver, extrahepatic tumor spread, and poor hepatic reserve due to concomitant cirrhosis were the most frequent reasons that tumors were unresectable. Abnormal liver function per se was not a contraindication, and patients included in the study ranged from Child-Pugh grades A to C.¹⁴ Patients with fulminant liver failure with uncorrected coagulopathy were not included; they were reconsidered

Table 2. Ninety-Five Patients Treated With Lipiodol-Epirubicin or Lipiodol ^{131}I : Demographic Characteristics, Nature and Severity of Underlying Liver Disease, and Tumor Stages

Characteristics	Lipiodol-epirubicin	Lipiodol ^{131}I
Total patients	69	26
Sex	54 male, 15 female	22 male, 4 female
Age (yrs) [range (median)]	20–81 (61)	20–75 (64)
Cirrhotics	61	18
Child-Pugh grades	A 27, B 27, C 7	A 13, B 5, C 0
Etiology of cirrhosis		
Hepatitis B virus	23	9
Hepatitis C virus	8	4
Alcohol	14	4
Cryptogenic cirrhosis	9	1
Other	8	0
Okuda tumor stage	I 14, II 37, III 18	I 6, II 19, III 1

at a later date if their liver function improved. Coagulation abnormalities were corrected as far as possible to reduce the risks of angiography. Obstruction of the main trunk of the portal vein, demonstrated on angiography or ultrasonography, was considered a contraindication for targeted arterial therapies. Only patients with a World Health Organization performance status of 0–3 were invited to participate in the study. Advanced age was not deemed to be a contraindication if the patient's general physical condition was satisfactory, with no serious concurrent medical problems. Tumor size, number, and stage were noted, but did not influence patient selection. Written informed consent was obtained from all patients who agreed to participate, and the study protocol was approved by the Royal Free Hospital Ethical Committee.

Patient Numbers and Characteristics

A total of 95 patients participated in the study—69 received Lipiodol-epirubicin and 26 received Lipiodol ^{131}I . Their age and sex, the nature of their underlying liver disease, and their tumor stages are shown in Table 2. The first 67 patients in the series were allocated to one arm or the other according to treatment availability and patient preference. On several occasions, consecutive patients were administered Lipiodol-epirubicin because ^{131}I was not available. The last 28 patients were prospectively randomized to receive one treatment or the other: 17 received epirubicin and 11 received ^{131}I . Choice of treatment for each of these patients was determined by drawing a computer-generated randomization slip from a sealed envelope. The epidemiologic characteristics of this subset of patients are shown in

Table 1. Criteria for Inclusion in the Trial of Lipiodol-Targeted Therapies for Unresectable Hepatocellular Carcinoma

Tumor confined to the liver
Tumor unresectable
Absence of fulminant liver failure or coagulopathy
Portal vein patency
Physical condition: WHO performance status of 0–3

WHO: World Health Organization.

Table 3. Twenty-eight Patients Treated With Lipiodol-Epirubicin or Lipiodol ¹³¹I in a Prospective Randomized Trial: Demographic Characteristics, Nature and Severity of Liver Disease, and Tumor Stages

Characteristics	Lipiodol-epirubicin	Lipiodol ¹³¹ I
Total patients	17	11
Sex	13 male, 4 female	9 male, 2 female
Age (yr) [range (median)]	35–73 (62)	20–75 (63)
Ethnicity		
White	6	7
Middle East	8	4
Far East	3	0
Cirrhotics	16	6
Child-Pugh grades	A 8, B 8, C 0	A 5, B 1, C 0
Etiology of cirrhosis		
Hepatitis B virus	5	1
Hepatitis C virus	4	4
Alcohol	4	1
Cryptogenic cirrhosis	2	0
Other	1	0
Okuda tumor stage	I 6, II 7, III 4	I 2, II 8, III 1

Table 3. Histologic confirmation of the diagnosis was available in 63 of the 69 epirubicin recipients (15 out of 17 in the randomized trial group) and in 23 out of 26 patients who received ¹³¹I (10 out of 11 in the randomized trial group). The rest were diagnosed as having HCC on the basis of tumor circulation visualized at angiography, and a raised AFP level. Of the 69 epirubicin recipients, 52 were Caucasian and 17 were of Asian or African origin. In the ¹³¹I group, 21 out of 26 were Caucasian and the rest of Asian origin. The detailed ethnic breakdown of the two randomized groups is shown in Table 3. Seventy-nine of the 95 patients had underlying cirrhosis, and the severity of their disease was graded according to Pugh's modification of Child's criteria.¹⁴ Two patients had recurrent HCC after previous resection (one received epirubicin; the other received ¹³¹I in the randomized trial). Fifteen of the 28 patients in the randomized study had multifocal lesions on CT scans. All tumors were staged according to Okuda's staging criteria.³ Of the 28 patients in the randomized trial, 23 were symptomatic at presentation. Symptoms included abdominal pain or discomfort,¹² weight loss,⁸ anorexia and nausea,¹⁰ presence of a palpable abdominal lump,⁴ fever,² lassitude,⁴ ascites,³ and jaundice.²

Administration of Treatment

Lipiodol-epirubicin and Lipiodol-¹³¹I were administered during hepatic angiography. The dosage of epirubicin was calculated at 75 mg/m². In the event of im-

paired liver function, the dose was reduced by 25% if the serum bilirubin was greater than 30 μmol/l, and by 50% if the serum bilirubin was greater than 100 μmol/l. The desired amount of epirubicin (4'-epi-doxorubicin available as Pharmorubicin, Farmitalia Carlo Erba, Hertfordshire, England) was dissolved in 5–10 ml of sodium meglumine diatrizoate (Urografin 290, Schering AG, Burgess Hill, Sussex, England) and added to 10 ml Lipiodol Ultra Fluid. A stable colloidal emulsion of epirubicin and Lipiodol was created by agitation in a Pulsatron ultrasonic agitator for 5 minutes. These procedures were performed with aseptic precautions in the hospital's Pharmacy unit less than 6 hours before injection. The preparation was further agitated vigorously before injection. Doses administered ranged from 40 to 120 mg (median, 80 mg).

Patients scheduled to receive Lipiodol-¹³¹I underwent prior ⁹⁹Tc colloid liver scintigraphy to allow comparison with subsequent scintiscans for ¹³¹I uptake. Lipiodol-¹³¹I (CIS Bioindustries, Salay, France) was supplied for each individual patient on order, as a 2 ml vial with an activity of 15–40 mCi (550–1480 MBq). This was diluted to a total volume of 12 ml with ordinary Lipiodol, using two sterile 20 ml syringes and a luer lock three-way tap. Tumor size was not a consideration in determining dosage in either group. No premedication with potassium iodide was necessary as the contrast media administered during prior screening investigations provided adequate thyroid blockade. Dosage administered at a single session ranged from 220–1315 MBq (median, 820 MBq).

At angiography, the hepatic artery was cannulated under fluoroscopic control via the transfemoral approach, using the Seldinger technique. The drug/isotope was injected over a period of 1 minute, and the line flushed with 20 ml of normal saline after injection. Appropriate radiation protection measures were taken by the medical staff at all times.

Follow-Up and Assessment

Patients were closely observed in the first 12 hours after treatment, particularly to exclude groin hematoma or vascular injury. Thereafter, they were assessed daily to chart the progression of their symptoms and clinical condition. Their full blood count, serum electrolytes, blood urea, serum creatinine, liver function tests, serum albumin, and coagulation profile were checked on alternate days during the hospital stay. A CT scan of the liver was performed in all cases 7–10 days after treatment to assess Lipiodol retention by the tumors.

Lipiodol-¹³¹I recipients were nursed and monitored in a radiation-shielded room for the first 48–72 hours after treatment. Contact of patients with medical staff

and family members was kept to a minimum. Patients were transferred to ordinary wards or discharged from the hospital only after the residual activity was measured at <800 MBq, as per the recommendations of the British National Radiological Protection Board.¹⁵ In addition to the posttreatment CT scan, all Lipiodol-¹³¹I recipients underwent gamma scintigraphy or a liver single photon emission computerized tomography 24–48 hours after treatment to assess uptake of radioactivity by the tumor. This was repeated once again within the next 20 days. Gamma scintigraphy was performed with a Scintrex 480S Digicamera fitted with a high energy collimator. Planar anterior and posterior images of the liver and thorax were obtained for analysis. On these images, regions of interest were drawn around the tumor, the liver, and the lungs, and total activity measured in each region. Six patients in the prospective study underwent single photon emission computerized tomography, which provides three-dimensional data and allows exclusion of activity from the surrounding tissues. These scans were performed on an IGE Gemini 700 camera fitted with a 400 KeV parallel-hole high resolution collimator, linked to a Saturn Nuclear Medicine computer for data storage and image analysis. IGE software was used for image reconstruction and dosimetry. The posttherapy scintiscan images were also compared with pretreatment ⁹⁹Tc colloid scan images to assess if ¹³¹I uptake had occurred through the entire tumor.

Patients were seen in the outpatient clinic 8 weeks after their treatment, with a fresh CT scan, and at similar intervals thereafter. The maximum tumor dimensions were compared with pretreatment scans to assess response. Tumor response, as determined by two observations 8 weeks apart, was graded as follows: (1) complete response; disappearance of all known disease; (2) partial response, 50% or more decrease in tumor load; no appearance of new lesions or progression of any lesion; (3) no change, less than 50% decrease in total tumor load; no progression of any lesion; (4), progressive disease, increase in size of one or more lesions or appearance of new lesions. To obtain a simple measure of the palliative effect achieved, patients on the randomized controlled study were asked at follow-up appointments to grade the symptomatic relief accorded by the treatment as "good," "moderate," or "poor."

Further sessions of the same therapy were offered to the patient if appreciable tumor response or symptomatic relief had been obtained from the first session, the treatment had been well tolerated, and the patient's overall condition and liver function were deemed satisfactory. A total of 133 treatments were administered to the 69 epirubicin recipients (range, 1–4 treatments per patient; mean treatment sessions per patient, 1.9). The

Table 4. Tumor Responses Achieved by the Two Treatment Modalities

	Epirubicin	¹³¹ I
Complete response	0 (0)*	0 (0)
Partial response	3 (3)	7 (2)
No change	18 (4)	8 (4)
Progressive disease	17 (4)	7 (3)
Total	38 (11)	22 (9)

* Values in parentheses represent patients in the prospectively randomized groups.

26 ¹³¹I recipients received 43 treatments (range 1–3 treatments; mean, 1.7 treatments).

Survival of patients was calculated up to either (1) death (2) loss to follow-up (3) administration of other treatments, or (4) conclusion of the study in December, 1993.

Statistical analysis was performed on a mainframe computer using the software program SAS (Statistical Analysis System) Version 5 (©SAS Institute Inc., Cary, North Carolina, 1985).

Results

Effectiveness of Localization

Assessment on computed tomography scans. Sixty-six of 69 epirubicin recipients underwent a CT scan 7–10 days after therapy (3 patients who suffered early posttreatment mortality could not be evaluated). All evaluated patients showed selective localization of Lipiodol in the tumor(s), compared with the rest of the liver. All images were assessed by the same consultant radiologist, and the degree of Lipiodol retention by the tumor was judged to be satisfactory in every patient.

Radiation dosimetry. Uptake of Lipiodol ¹³¹I, as assessed on gamma camera imaging or on single photon emission computerized tomography, revealed selective localization in all cases. 'Area of interest' calculations in 15 patients revealed a mean tumor:liver ratio of 9:1. The mean (± standard deviation) cumulative radiation dose to the tumor was calculated at 34.7 (±32.4) Gy. Mean cumulative doses to nontumor liver parenchyma and to the lungs were 3.3 (±1.5) Gy and 4.4 (±2.3) Gy, respectively.

Tumor Response

Diminution in size. The changes in tumor size after treatment are documented in Table 4. Overall, 21 of 38 (55%) evaluable epirubicin recipients and 15 out of 22 (68%) ¹³¹I recipients demonstrated a slowing of their

disease process (partial response or no change). Within the randomized study, the relative proportions were similar—7 of 11 (64%) with epirubicin and 6 of 9 (67%) with ^{131}I .

Alpha fetoprotein levels. Among patients receiving epirubicin, 43 had a raised serum AFP level before receiving therapy. A persistent decrease in AFP was documented in four patients. In the ^{131}I group, 22 had a raised serum AFP at presentation, and a decrease was documented in 2 patients.

Palliation of symptoms. In the prospective randomized groups, 14 of 17 epirubicin recipients and 9 of 11 ^{131}I recipients were symptomatic at presentation. The palliative effects achieved were graded by the patients themselves as follows: epirubicin—'good' 8, 'moderate' 2, 'poor' 3, and 1 was difficult to assess; ^{131}I —'good' 5, 'moderate' 1, 'poor' 3. Thus 10 of 14 patients treated with epirubicin and 6 of 9 patients treated with ^{131}I felt they had received good or moderate palliation of symptoms.

Treatment-Related Morbidity and Mortality

Fulminant hepatic failure was the principal cause of death within 30 days of either form of treatment. Seven of 69 epirubicin recipients developed this complication, with 5 deaths. In the ^{131}I group, 4 out of 26 patients developed this complication and died from it. In the epirubicin group, there were three other mortalities, two from sudden tumor rupture and one from a perforated peptic ulcer. The overall 30-day mortality was 12% with epirubicin and 15% with ^{131}I . It should be clarified that 6 of these 12 deaths occurred after the second session of treatment. All but one patient had cirrhosis of Child-Pugh grade B or C and Stage II or III tumor. In some of the patients, it was difficult to determine whether the liver failure had been precipitated by the treatment or by tumor progression and underlying cirrhosis.

Technical complications arising from the angiographic procedure were rare. One patient developed hepatic arterial dissection after cannulation. The procedure was abandoned but repeated successfully 2 weeks later.

The other complications arising from the two treatments are listed in Table 5. Statistical comparison of the incidence of complications in the two groups (Chi square test with Yates' correction or Fisher's exact test if the numbers were small) revealed that pyrexia was significantly more common in the patients receiving epirubicin ($P = 0.001$ for the entire cohort and $P = 0.003$ for the randomized subset). Pyrexia is known to occur after systemic epirubicin therapy, and is probably a consequence of tumor necrosis. Among the nonrandom-

ized patients, there was also a significantly higher incidence of anemia ($P = 0.007$), leukopenia ($P = 0.017$), and thrombocytopenia ($P = 0.009$) after epirubicin therapy. However, these complications related to bone marrow suppression were generally transient and self-limited. Two patients with leukopenia required supportive therapy. With either therapy, a rise in serum bilirubin and transaminases, which returned to normal within 10 days, was frequently noted. Some patients suffered an aching discomfort in the right hypochondrium, probably secondary to tumor necrosis. The chest infections recorded in some instances may have been pneumonitis secondary to localization of small amounts of Lipiodol in the lungs. The alopecia was partial and reversible.

Survival

Of 69 Lipiodol-epirubicin recipients, 13 (5 Stage I, 8 Stage II) were excluded from survival analysis (2 were lost to follow-up within 2 months of receiving therapy, 4 underwent hepatic resection, 3 underwent liver transplantation, and 4 received other forms of treatment). Fifty-six patients were evaluated. Fifty-three were followed for a minimum of 1 year (or to death), and the last three were alive at 6, 6, and 8 months after therapy. At the conclusion of the study, 49 of the 56 were dead, 46 from tumor-related causes and 3 from unrelated causes. Seven patients were alive at the end point of the study having survived 6, 6, 8, 12, 14, 21, and 36 months.

Of 26 Lipiodol- ^{131}I recipients, 1 was lost to follow-up soon after treatment and was excluded from the analysis. Twenty-five patients were evaluated—20 were followed for at least 1 year (or to death), 4 were followed for 6 months, and one was lost to follow-up after 2 months. Seventeen of the 25 evaluated were dead at the end of the study, all from tumor-related causes. Six were alive (6-, 6-, 6-, 6-, 12-, and 19-month survivals), and 2 had been lost to follow-up at 2 and 16 months, respectively.

The actuarial survival according to tumor stage in the two treatment groups is depicted in Figures 1 and 2. Survival at 6, 12, and 24 months was 40%, 25%, and 6% with epirubicin, and 58%, 25%, and 0% with ^{131}I . Kaplan-Meier curves for the two subsets of patients in the prospective randomized trial are depicted in Figure 3. No statistically significant differences in survival were found between the two groups, either in the overall study or in the prospectively randomized trial.

Prognostic Factors Influencing Survival

The influence of age, severity of underlying cirrhosis (Child-Pugh grades A, B or C), tumor stage (Okuda I, II

Table 5. Morbidity Related to Treatment of Unresectable Hepatocellular Carcinomas With Lipiodol Epirubicin and Lipiodol¹³¹I

Morbidity	Lipiodol-epirubicin		Lipiodol ¹³¹ I	
	n = 69	[n = 17]	n = 26	[n = 11]
Pyrexia	53 (84%)	[15 (88%)]	10 (38%)	[3 (27%)]
Raised serum bilirubin/transaminases	29 (42%)	[3 (18%)]	7 (27%)	[2 (18%)]
Anorexia, nausea, or vomiting	8 (12%)	[4 (23%)]	1 (4%)	[1 (9%)]
Abdominal pain	6 (9%)	[2 (12%)]	1 (4%)	[1 (9%)]
Anemia	19 (28%)	[1]	0	
Thrombocytopenia	15 (22%)	[0]	0	
Leukopenia	13 (19%)	[3 (18%)]	0	
Chest infection	4	[4 (23%)]	2	
Alopecia	4	[1]	0	
Ascites	2	[2]	1	
Peptic ulceration	2	[2]	0	
Variceal bleeding	1	[1]	0	

Values in brackets [] (represent data from the prospectively randomized groups).

or III), and degree of tumor response at 2 months (partial response, no change, or progressive disease) on survival was assessed using the Cox proportional hazards model. Univariate analysis revealed significant associations between survival and the Child-Pugh grade of cirrhosis (risk ratio, 1.41 for every increase in grade of cirrhosis; $P = 0.012$), the Okuda tumor stage (risk ratio, 2.79 for every increase in tumor stage; $P = 0.0001$), and the degree of tumor response (risk ratio, 2.75 for every decrease in the degree of response; $P = 0.0002$). Multivariate analysis revealed that grade of cirrhosis did not contribute significantly to the prognostic information after allowing for tumor stage, but tumor stage had a strong prognostic significance (risk ratio, 2.15 for every increase in tumor stage; $P = 0.027$). The degree of tumor response as judged on a CT scan at 2 months correlated

significantly with further survival (risk ratio, 3.35 for every decrease in the degree of response; $P = 0.0001$).

No significant association was found between the administered dosage of therapeutic agent (mg of epirubicin or MBq of ¹³¹I) and tumor response. However, among ¹³¹I recipients, tumor response correlated with the amount of activity retained by the tumor. Patients with progressive disease had a significantly lower mean tumor radiation dose than those with no change or partial recovery ($P < 0.05$; pooled estimate of variance).

Discussion

The majority of reports on the use of Lipiodol-targeted therapies have come from the Far East. The European experience provides a useful counterpoint, reflecting a

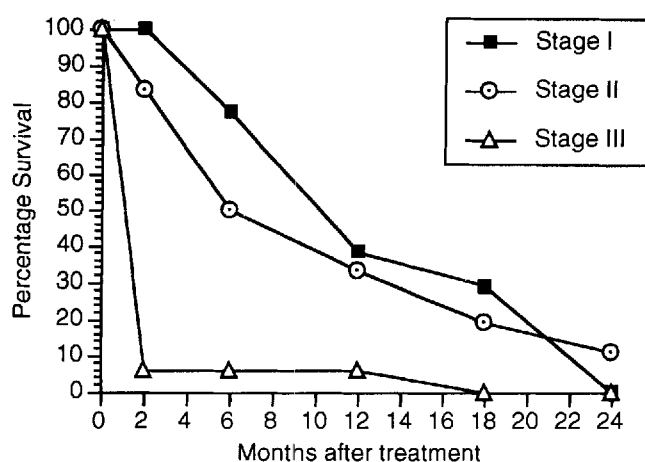


Figure 1. Actuarial survival after treatment of unresectable HCC with Lipiodol epirubicin.

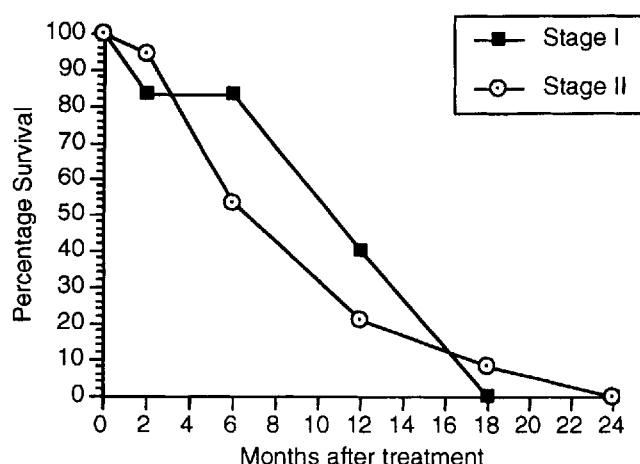


Figure 2. Actuarial survival after treatment of unresectable HCC with ¹³¹I Lipiodol.

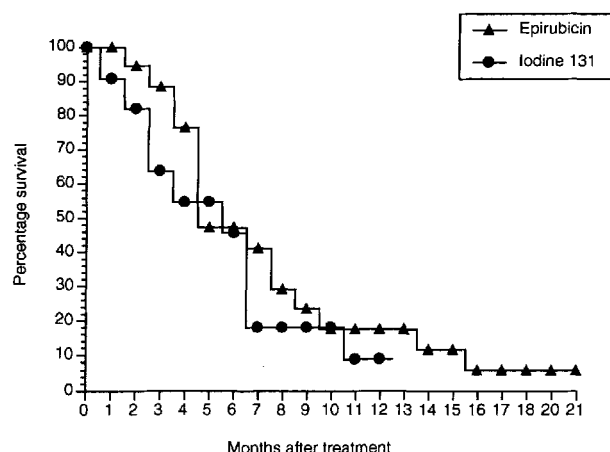


Figure 3. Kaplan-Meier curve depicting survival following treatment of unresectable HCC with Lipiodol epirubicin ($n = 17$) or Lipiodol ^{131}I ($n = 11$) in a prospective randomized trial.

different population of patients, possibly a different natural history of the disease, and at times, a different treatment philosophy. This study involves a large patient cohort treated at a single Western center, and is also one of the first attempts to compare Lipiodol-targeted chemotherapy with Lipiodol-targeted radiotherapy.

Choice of Patients, Therapeutic Agents, and Dosage

Patients with Okuda Stage III disease suffered a very high incidence of complications with either treatment, without any appreciable improvement in survival. It would be reasonable to conclude that this subgroup of patients should not be offered Lipiodol-targeted intra-arterial therapies.

Of the numerous cytotoxic drugs that have been used in combination with Lipiodol, epirubicin was chosen because of its documented efficacy against HCC and its acceptable range of toxicity. Quantitation of drug localization in the tumor remains a difficult problem. Assessments of Lipiodol uptake from CT scans have their limitations, and are at best semiquantitative.¹⁶ The available parenteral preparations of epirubicin are lipophobic, which led to initial concerns that the drug may separate from the Lipiodol *in vivo*. A bio-distribution study of radio-labeled doxorubicin administered via the hepatic artery has since confirmed that administration with Lipiodol increases the intratumoral concentration of the drug.¹⁷ Nevertheless, development of lipophilic drug formulations is likely to ensure more efficient delivery.

Embolization was not part of the therapeutic protocol in this study, but there now is evidence that although it does not add to the morbidity or mortality,

embolization of the tumor immediately after the injection of the drug-Lipiodol conjugate may enhance intratumoral drug concentrations¹⁷ and add to the survival benefit.^{18,19}

Among available radioisotopes, ^{131}I can be conjugated to Lipiodol with relative ease. As it is a beta and gamma emitter, its localization can be accurately assessed by gamma scintigraphy, whereas the beta radiation exerts the therapeutic effect. The doses of radiation used in this study have been conservative, and a preliminary report from another center suggests that higher doses may be administered safely and more often, and may achieve better responses.²⁰ Dosage may also be calculated on the basis of tumor size, and the extent to which it takes up a tracer dose of isotope.²¹ There are data to suggest that portal vein occlusion need not necessarily be considered a contraindication for these treatments, especially if they are not combined with embolization.²²

Tumor Responses

The arrest or diminution in tumor size at 2 months obtained in nearly two-thirds of the patients treated with either modality is encouraging, given the overall grim prognosis of untreated HCC. Tumor response at 2 months also proved to be a good indicator of further survival. Though tumor response in ^{131}I recipients was found to be improved if a higher dose of radiation was retained by the tumor, this did not always correlate with the amount of activity administered. Dose/activity ratios ranged from 0.2–16.1, with a mean of 4.1 ± 4.3 standard deviation (tumor radiation dose measured in cGy, administered activity measured in MBq). It was therefore difficult to predict before administration of therapy what the tumor response would be in a given patient. Alpha fetoprotein levels have been reported to correlate well with tumor progression or regression.⁹ In this study, however, a sustained decrease in AFP was recorded only in a very small number of patients, and no correlation could be found between posttreatment AFP levels and tumor response or survival. The reasons for this are not apparent.

Quality of life is a major criterion in determining choice of palliative therapies. Though the majority of reports on the use of Lipiodol-targeted treatments have commented scantily on this aspect, the existing data suggest that these therapies offer effective palliation.²³ Our experience with the patients within the randomized trial indicates that both modalities offer satisfactory palliation of symptoms in a majority of patients.

Survival Benefit Offered by Lipiodol-Targeted Therapies

For ethical reasons, it was not possible in this study to have a control group of patients who were not offered any treatment at all. The question of whether these therapies offer a survival benefit can therefore be answered only by comparing with historic controls, despite the flaws inherent in such comparisons. The natural history of HCC differs in different parts of the world, and a recent and geographically close parallel to our clinical situation may be found in the 30 untreated patients reported by Vetter et al.²⁴ from France. Comparison with this group indicated a survival benefit with either treatment in Stage I and Stage II disease at 6 and 12 months (at 6 months, for patients with Stage I disease, the survival figures were as follows: Vetter's untreated patients, 25%; epirubicin, 77%; ¹³¹I, 83%; and for Stage II disease: untreated, 14%; epirubicin, 50%; ¹³¹I, 53%. At 1 year, for patients with Stage I disease, the survival figures were: Vetter's untreated patients, 12%; epirubicin, 38%; ¹³¹I, 40%; and for Stage II disease: untreated, 0%; epirubicin, 33%; ¹³¹I, 21%).

Lipiodol Chemotherapy versus Lipiodol Radiotherapy

No major differences emerged between the two therapies in terms of palliative effect, survival benefit, and procedure-related mortality. The median hospital stay was 6 days in both groups studied prospectively. Patients who received chemotherapy had a significantly higher incidence of pyrexia, but this usually responded to Paracetamol, and settled within the first week. Epirubicin also caused marrow suppression and abnormalities in hematologic indices in a significant number of recipients, but this again was transient and generally did not require supportive measures. The incidence of isolated individual complications was higher in the chemotherapy group, though not statistically significant. Radiotherapy requires greater infrastructure and a dedicated clinical unit. The recipients must remain in isolation for 48–72 hours, and staff must adopt appropriate precautions. A comparison of the financial costs involved can be properly made after Lipiodol-¹³¹I becomes commercially available for unrestricted purchase.

Strategies for Improving Survival: Prospects for Future Clinical Studies

The poor prognosis associated with an advanced tumor stage at the time of treatment emphasizes the need for early diagnosis of these tumors. Regular screening of all

cirrhotics with ultrasonography and serum AFP measurements may help detect HCCs at an earlier stage in a large proportion of patients,²⁵ and significantly improve their prognosis.

Further therapeutic trials with larger patient numbers, possibly on a prospective multicenter basis, may provide more information on the relative merits of these therapies, and also diminish the potential for Type II statistical errors. Apart from epirubicin, good results have been reported with other agents such as cisplatin^{11,26} and doxorubicin,^{5,8} and prospective comparisons among available regimens would be useful, with particular emphasis on lipophilic formulations. Comparisons are also indicated among the available radioisotopes, including ⁹⁰Yttrium and ¹²⁵Iodine. Consideration should be given to administering as high a cumulative radiation dose to the tumor as is safely possible.

As data become available on other relatively new therapeutic options such as alcohol injection,^{27,28} laser ablation,²⁹ and cryoprobes,³⁰ the indications for Lipiodol-targeted therapies in unresectable HCC may become better defined in terms of tumor size, number, location, and stage. It may be possible to combine Lipiodol-targeted therapies with some of the newer modalities, and further improve the results obtained.³¹ The use of these treatments may even extend to lesions that at present are treated surgically. In at least one study, transcatheter oily chemo-embolization has yielded results comparable to resection or transplantation for Okuda Stage I and II HCCs.³² Finally, Lipiodol-targeted therapies are now being tried as preoperative adjuncts to resection and orthotopic liver transplantation for HCC, and the long term results of these studies are awaited.

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