Selective Internal Radiation Therapy with Intra-arterial Iodine-131-Lipiodol in Inoperable Hepatocellular Carcinoma

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From August 1990 to June 1993, 26 patients with inoperable hepatocellular carcinoma were treated with intra-arterial iodine-131-Lipiodol (^{131}I-L). **Methods:** Iodine-131-Lipiodol was given through either an implantable arterial port (9 patients) or during hepatic angiography (17 patients). All 26 patients had multiple lesions, 3 had involved resection margin after surgical resection and 1 had diffuse infiltrative lesions. The median size of the largest tumor among 22 patients with a measurable lesion was 4.5 cm (2–9.5 cm). The end points are tumor response in terms of tumor size, change in serum alpha-fetoprotein level, toxicity of treatment and overall survival. **Results:** Twenty-three patients received a single treatment of 1.11–2.22 GBq (30–60 mCi) ^{131}I-L. Three patients received 2.22–4.44 GBq (60–120 mCi) ^{131}I-L in three fractions. Considering both radiological regression and reduction in serum alpha-fetoprotein level as objective response criteria, the overall response rate was 52% (13 out of 25 patients with evaluable disease). Ten out of 15 patients who had raised alpha-fetoprotein levels had more than 50% reduction and 8 patients had more than 90% reduction in alpha-fetoprotein level. Since analysis, 19 patients have died and 7 remain alive, giving a minimum median survival of 6 mo (range 1.2–16.6 mo), with 4 surviving more than 1 yr calculated from the day of treatment. There was only one patient who had late deterioration of liver function compatible with radiation hepatitis. There was no bone marrow toxicity documented in any patients. **Conclusion:** Treatment with intra-arterial ^{131}I-L was well tolerated in patients with inoperable hepatocellular carcinoma and produced an objective response of 52% with median survival of 6 mo. A fractionated dose of ^{131}I-L was feasible and the radiation dose could be escalated safely.

Key Words: hepatocellular carcinoma; iodine-131-lipiodol; selective internal radiation

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Hepatocellular carcinoma (HCC) is the most frequently occurring malignant tumor in the liver. It is the seventh most common form of cancer in males and the ninth in females worldwide. Its occurrence is even more common in Hong Kong, where HCC is the second most common cancer in males and the seventh most common in females. It accounts for 8.5% of all newly diagnosed cases of malignancy and 12.5% of all cancer deaths (*1*). Most patients present late and <10% are cured with surgical resection. Treatment of inoperable HCC with systemic cytotoxic chemotherapy has not been shown to improve survival. Since the liver has a dual blood supply and hepatic tumors derive blood mainly from the hepatic artery, intra-arterial treatments offer opportunities of selectively targeting the tumor. Intra-arterial treatment can be in the form of regional chemotherapy, chemoembolization or selective internal radiation (SIR).

Lipiodol (Laboratoire Guerbet, France) is a poppy seed oil containing 38% iodine by weight. It was first used as an x-ray contrast medium for hepatic angiography and has been shown to be cleared less rapidly from HCC cells than normal liver tissue, when injected into the hepatic artery (*2,3*). Because of this property, it is commonly used as a drug carrier in chemoembolization and other regional targeted treatment.

The iodine moiety of Lipiodol can be changed to radioactive ^{131}I through an atom-atom exchange reaction. By infusing the converted radioactive (^{131}I-L) intra-arterially, a therapeutic dose of radiation can be delivered to the tumor (*4*). Since ^{131}I-L is both a gamma- and beta-ray emitter, its flow can easily be detected by a gamma camera and accurate dosimetry can be obtained. In the study by Park et al., it was shown that HCC tissue would receive, on average, 8 times the radiation dose received by the normal liver (239 cGy per mCi to tumor and 31 cGy per mCi to normal tissue in a 4-cm tumor) (*5*). Hence it is possible for a 4-cm tumor to receive a dose of more than 10,000 cGy by giving about 1.48 GBq (40 mCi) of ^{131}I-L while the dose to normal liver is still kept at a tolerable level. Furthermore, radioactivity detected in the peripheral tissue is relatively small so that systemic toxicity is minimal.

For tumors larger than 5 cm, a large dose of ^{131}I-L (>1.85 GBq) is required to deliver an adequate dose in a single fraction. This is technically difficult because of radi-

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ation protection and the volume of ^{131}I-L may be too large for the tumor to hold. Therefore, the prescribed dose of ^{131}I-L may be fractionated and delivered throughout an extended period of time. This can also expose the tumor to a more uniform dose of internal irradiation over a longer period of time.

With such a background, a phase II study using intra-arterial ^{131}I-L in treatment of inoperable hepatocellular carcinoma was initiated in 1990 with the objective of documenting the efficacy and toxicity of ^{131}I-L treatment.

PATIENTS AND METHODS

Patients

From August 1990 to June 1993, 26 patients with inoperable HCC were entered into the study. Included were 22 males and 4 females aged from 29 to 72 yr (median age 53.5 yr). The median Karnofsky Score was 90% (range 80%–100%). The diagnosis of HCC was based on either histology or raised alpha-fetoprotein (AFP) level of more than 500 ng/ml together with characteristic features on computerized tomography (CT) or ultrasonogram (US) and angiographic evidence of HCC. In all cases, the tumor was inoperable because of either extensive disease or severe cirrhosis. Previous treatment such as surgery, chemotherapy or chemoembolization did not exclude patients from entering into the trial.

The pre-entry investigations included complete blood picture, clotting profiles, renal and liver function tests, serum AFP level, hepatitis B surface antigen, chest radiograph, CT scan and US of the abdomen and hepatic angiography (HAG). Biopsy was optional. Patients younger than 75 yr, with a good Karnofsky performance score of >70%, adequate liver function with total bilirubin <50 μmole/liter, measurable lesion radiologically (<10 cm in diameter for the largest lesion) or with raised AFP level, after providing written consent were entered into the study. Patients were excluded from the study if they had thyroid disease or other serious medical conditions, extrahepatic disease or major vascular involvement by tumor including the main portal vein, main hepatic artery, hepatic veins and inferior vena cava on preoperative investigation. Patients having arterial anomaly on HAG were also excluded from the study.

Methods

Labeling of Lipiodol was done in our radioisotope laboratory by an atom-atom exchange reaction based on the work of Madsen et al. (*5*). Labeling efficacy was verified by chromatography. The volume of ^{131}I-L was <5 ml. Suitable patients first received Lugol's iodine solution (2 drops 3 times a day for at least 1 wk before treatment and 4 wk after treatment) to block thyroid uptake of radioactive iodide ions formed during cellular degradation of ^{131}I-L. On the day of treatment, the patient was subjected to selective hepatic artery cannulation under fluoroscopic control with the Seldinger technique. The prescribed dose of ^{131}I-L was then slowly given into the hepatic artery. Patients diagnosed to have inoperable disease during laparotomy would have an implantable Port-A-Catheter (Pharmacia Deltec Inc., St. Paul, MN) inserted into the gastroduodenal artery for ^{131}I-L treatment through the port at a later date.

The dose of ^{131}I-L was determined according to the size of the tumor and aimed to deliver no less than 10,000 cGy to the tumor. The absorbed dose determination was based on a study by Madsen et al. (*5*). Patients having tumors <6 cm would receive one treatment through HAG. For tumors between 6 and 10 cm, an arterial port was placed through laparotomy and the dose of ^{131}I-L would be given through the port in the gamma camera suite and in fractions as follows: 50% of the prescribed dose was given on day 1, 25% on the day after one biological half-life of ^{131}I-L (usually about 3–5 days) and 25% on the day after two half-lives. The biological half-life of ^{131}I-L was determined by a diagnostic dose of 1 mCi of ^{131}I-L through the port which was done 1 wk before the therapeutic dose. After the treatment, patients were nursed in an isolation ward and were discharged when the activity of the radioisotope was below 0.37 GBq (10 mCi) which was about 2–3 wk after treatment. Handling of all radioactive materials and patients receiving radioisotope treatment concurred with local rules and code of practice on radiation safety in Hong Kong Government Hospitals (*6*). Repeat treatment could be given for recurrent disease after ^{131}I-L treatment if patient's condition and liver function permitted.

Monitoring Response and Toxicity to ^{131}I-L Treatment

Patients who had raised AFP had the blood taken for AFP on the day before treatment and on alternate days until discharge and weekly thereafter. CT was used to document response 2 mo after treatment. For monitoring toxicity, blood counts and liver function tests were performed at the same time for each blood sample taken for AFP measurement. Other symptoms were also recorded daily in the hospital and on each follow-up 2–4 wk after discharge. Toxicity was graded according to the WHO classification (*7*).

Objective Response Definition

Complete response (CR) is defined as the disappearance of all known lesions on radiological ground and normalization of the AFP level for at least 4 wk. Partial response (PR) is a decrease of 50% or more in the maximum diameter of the largest tumor nodule and/or more than 50% decrease of AFP levesl for at least 4 wk. There should be no new appearance of lesions or progression of lesions. No change (NC) is defined as less than a 50% decrease or not more than 25% increase in the maximum diameter of the largest tumor nodule. Progressive disease (PD) is defined as more than a 25% increase in the maximum diameter of the largest tumor nodule or one of the measurable lesions, or the appearance of new lesions.

Survival Analysis

Survival duration was calculated from the first day of ^{131}I-L treatment. Actuarial survival curve was plotted by the Kaplan-Meier method.

RESULTS

Of the 26 patients in the study, 10 had definitive surgical resection as the first treatment which later recurred locally before ^{131}I-L treatment. Six patients had cytoreduction surgery and residual disease treated with ^{131}I-L. Eight patients had inoperable HCC with no previous treatment. Two patients had inoperable HCC which failed treatment with intra-arterial oily chemoembolization.

Nine patients had a port-a-catheter inserted during laparotomy and subsequent ^{131}I-L given through the port. These patients were originally intended either for resection or cytoreduction. Twenty-two patients had radiologically evaluable disease. Twenty-six patients had multinodular tumors. Considering the largest measurable lesion, median tumor size was 4.1 cm in diameter (range 2–9 cm). Accord-

TABLE 1
Patient Characteristics and Response

Patient no.	Sex/age	Previous treatment	Largest tumor (cm)	Okuda staging classification	^{131}I-L dose (GBq)	Change in AFP (%)	Overall response	Survival (mo)
1	M/36	OT	4.2	II	1.85 + 2.96*	−94.1	PR	10.97
2	F/65	Nil	9	II	3.7 + 3.7*	−97	PR	6.27
3	M/60	Nil	9	II	2.22 + 2.22*	−39.4	PR	3.4
4	M/35	CE	9.5	II	4.44	−6.7	PD	2.3
5	M/55	OT	2.3	I	1.48		NC	12.9
6	F/71	OT	margin	I	1.11		CR	16.57†
7	M/50	OT	3.5	I	1.48	−79.8	PR	13.53
8	M/57	OT	9	II	1.85 + 1.21*		PD	1.97
9	M/4l	OT	6	II	1.85		NC	4.07
10	M/50	CE	5.4	II	1.85	−100	PR	13.97†
11	F/48	OT	margin	I	1.85		inevaluable	7.13
12	M/54	Nil	6	II	1.85		PR	5.4
13	M/45	OT	2	I	1.85	−56.5	PR	11.03
14	F/52	OT	3	I	1.85		PD	7.3
15	M/29	OT	5.4	II	1.85	rising	PD	2.07
16	M/67	OT	3	I	1.85	−98.6	NC	8.57
17	M/44	OT	6	II	1.85	rising	PD	2.53
18	M/60	Nil	4.5	II	1.85	−95.7	PR	12.17†
19	M/60	Nil	3	I	1.85		PD	1.2
20	M/53	OT	2.3	I	1.85		NC	10†
21	M/32	OT	2.5	I	1.85		NC	9.3†
22	M/58	Nil	4	II	1.85	−99.7	PR	3.6
23	M/70	OT	margin	I	1.85	rising	PD	4
24	M/72	Nil	diffuse	II	1.85	−95.5	PR	2.3†
25	M/62	OT	2	I	1.85		CR	4.2†
26	M/52	Nil	4	II	1.85	100	PR	3.47

*Two courses of ^{131}I-L treatment given.
†Patients are still alive.
OT = resection of HCC; CE = chemoembolisation; CR = complete response; PR = partial response; NC = no change; and PD = progressive disease; Nil = no previous treatment.

ing to Okuda's staging classification, there were 12 Stage I, 14 Stage II and no Stage III patients. Four patients who had evaluable lesions on laparotomy only, either because of diffuse disease or resection margin involvement, were evaluated for toxicity and survival. Fifteen patients had raised AFP levels with a median level of 5465 ng/ml (range 79–131, 450 ng/ml). Patient characteristics and treatment results are shown in Table 1.

Three patients who had relatively large tumors (9–9.5 cm) were given a fractionated dose of ^{131}I-L ranging from 2.22 to 4.44 GBq. The rest of the patients received a single fraction treatment of a median dose of 1.85 GBq (range 1.11–1.22 GBq). Four patients had repeated treatment because of recurrent disease or a rising AFP level. The maximum total dose of ^{131}I-L given was 7.4 GBq in one patient delivered on two occasions 4 mo apart.

The treatment was generally well tolerated. There was no complication relating to angiography. All patients were completely ambulatory after the treatment with an average hospital stay of 2 wk for single fraction treatment. Liver enzyme levels had no significant change after the treatment. Deterioration of liver function usually occurred during the terminal phase of the disease and was attributed to recurrent disease rather than radiation hepatitis. However, there was one patient with a very protracted course of deteriorating liver function over 5 mo with controlled local disease. The patient remained in good general condition despite deep jaundice and high liver enzyme levels. This may have been due to radiation hepatitis since there was no bone marrow toxicity documented.

All patients except one were evaluated for response either radiologically and/or by change in AFP levels. There were 2 CR (8%), 11 PR (44%), 5 NC (20%) and 7 PD (28%). The overall response rate was 52%. The first CR patient was a 71-yr-old female with cytoreduction surgery which left behind microscopic disease whose lesions were not measurable radiologically. This patient is now surviving without any evidence of disease for more than 16 mo. The second CR patient was a 62-yr-old male with two previous resections for recurrent HCC whose lesion regressed completely after treatment. Both patients had no raised AFP for the treatment response to be monitored. Of 15 patients with raised AFP levels, 10 had more than 50% reduction in AFP levels. Eight of these 10 patients had more than 90% reduction in AFP levels. Two patients had an AFP reduc-

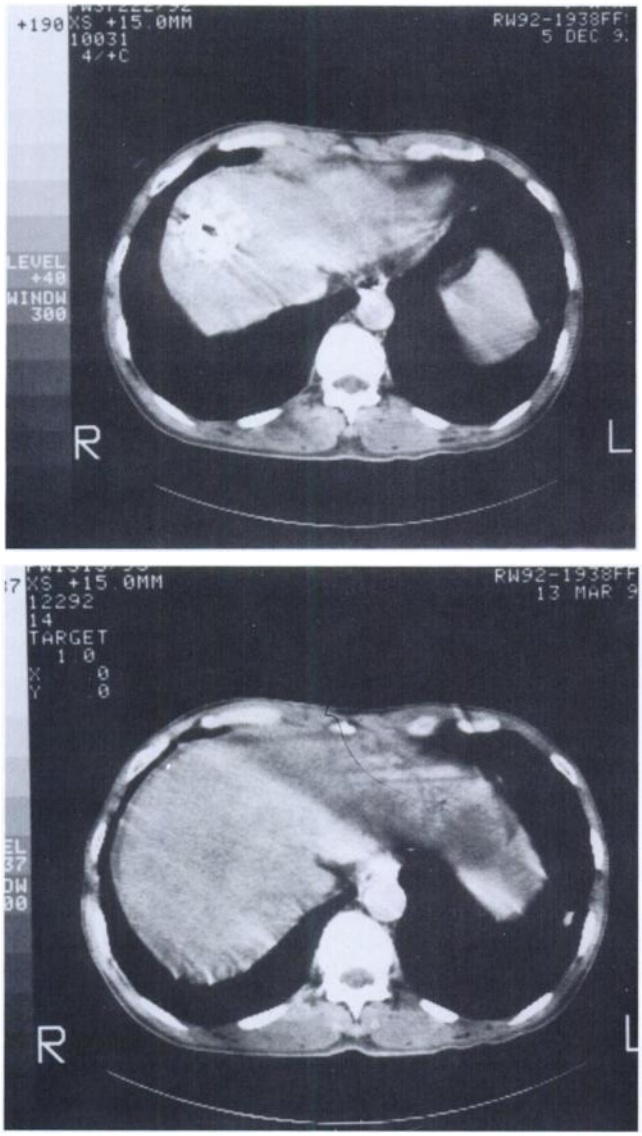

FIGURE 1. (A) CT scan of the liver of Patient 18 with a 4.5 cm HCC in the right lobe before ^{131}I-L treatment. (B) CT scan of the liver of the same patient performed 2 mo after a 1.85-GBq ^{131}I-L treatment. The AFP decreased to less than 5% of the pre-treatment level.

tion of less than 50%. Only three patients had no response with an increase in AFP level after treatment.

Twenty-two patients had radiologically evaluable disease. One patient with CR and three with PR were documented by CT. Twelve patients had stable disease and the remainder had progressive disease. CT performed both before and after treatment of one patient who achieved PR after 1.85 GBq (50 mCi) of ^{131}I-L is shown in Figure 1. A gamma scan after ^{131}I-L treatment of the same patient is shown in Figure 2. Although the majority of patients had stable disease as assessed radiologically, the AFP level decreased gradually after treatment (Fig. 3).

Nineteen patients had died and seven were alive at the time of analysis, giving a minimum median survival of 6 mo (range 1.2–16.6 mo). The seven surviving patients had a median follow-up at 10 mo (2.3–16.6 mo). The Kaplan

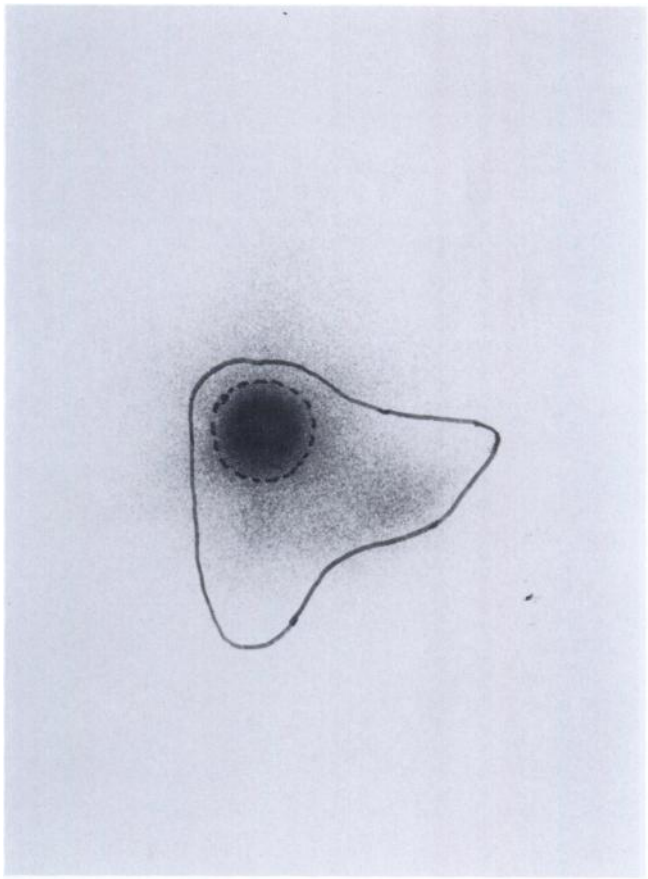

FIGURE 2. Anterior view of the gamma camera picture after ^{131}I-L treatment of the same patient in Figure 1.

Meier actuarial survival curve of all patients is plotted in Figure 4. There was 50% survival at 7 mo after treatment.

DISCUSSION

HCC is a chemotherapy-resistant tumor. External radiotherapy is not a treatment of choice because tolerance of normal liver to whole-liver irradiation is only about 3000 cGy (*9*) (which is not tumoricidal) and the nontumorous liver tolerance is expected to be even lower in a cirrhotic liver. In order to make radiotherapy feasible, there are two

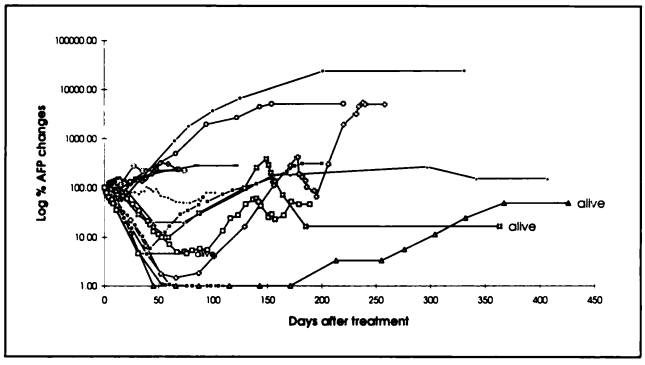

FIGURE 3. Plotting log % AFP level changes against time after treatment (15 patients).

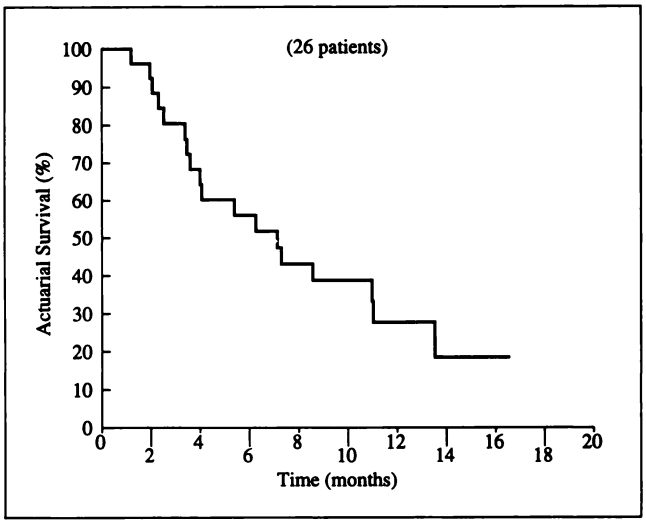

FIGURE 4. Actuarial survival curve in 26 patients.

approaches: (1) conformal radiotherapy with radiosensitizers (*10*) or (2) unsealed radioisotopes administered either systemically or regionally. These methods aim to increase the radiation dose to the liver tumor while keeping the dose to the nontumorous liver within safe limits. Systemic administration of ^{131}I-antiferritin has been reported to be useful when combined with external radiotherapy in treatment of inoperable HCC (*11,12*). Regional intra-arterial administration of radiolabeled ^{131}I-Lipiodol (*4*) or ^{90}Y microspheres (*13*) reported the first time that internal irradiation as a single modality could deliver a tumoricidal dose of radiation to a hepatic tumor without jeopardizing nontumorous liver tissue.

In a Korean study, 24 HCC patients were treated with ^{131}I-L and reported tumor reduction, based on radiological ground, in 89% of the patients having a small tumor (<4 cm in diameter) and in 65% patients with a tumor between 4 and 6 cm. All patients who responded were accompanied by a reduction of serum AFP levels. The dose of ^{131}I-L ranged from 0.55 to 2.22 GBq (15–60 mCi) (*14*). French multicenter trials using ^{131}I-L to treat 63 HCC patients produced an objective response in 40% of patients with minimal toxicity while keeping the radiation dose to normal liver below 2000 cGy (*15*). The latter study also considered a reduction of AFP a response criterion. Both trials included patients without previous treatment. In our present study, we confirmed similar findings in terms of tumor response, a decrease in AFP level and minimal toxicity. The lower response rate may be due to previous surgery or chemotherapy in 18 of our patients. The total response rate as documented by radiological method was low (4/22, 18%) despite a favorable decrease in AFP levels. Of 22 patients studied, 12 (54.5%) had a stable or less than partial response, possibly due to a CT scan performed too early or the use of US for disease evaluation. We have also noted similar findings when treating large HCC with ^{90}Y microspheres; radiological regression commonly occurred after 4 mo.

In the present study, a fractionated dose of ^{131}I-L was given to three patients who had large tumors and an implanted arterial port. The idea is to give a higher dose over an extended duration rather than a single-dose injection. This is justified only if an arterial port is available for repeated injection. The time between the two fractions was the biological half-life of ^{131}I-L which was determined well before the therapeutic dose with a 1-mCi diagnostic dose of ^{131}I-L. Through such means, we have further escalated the ^{131}I-L dose to more than 3.7 GBq (100 mCi) given in three fractions, which is feasible and safe. The dosimetric study and the correlation with treatment outcome will be published separately.

Repeat treatment was done in four patients and their total dose of ^{131}I-L was more than 3.7 GBq. With such a dose of radiation, there was no significant toxicity documented. All the patients had concurrent cirrhosis and there was no decompensation of liver function after treatment except in one patient who received a total of 4.81 GBq of ^{131}I-L.

In the present study, we treated four patients with tumors larger than 6 cm with a fractionated dose of ^{131}I-L through an arterial port. Three out of the four showed a partial response in reduction in AFP levels. This may be an alternative way to use a larger dose of ^{131}I-L to treat larger tumors without increasing the radiation hazard to surgical personnel. The tumor can also receive a more uniform dose over an extended period of time than in a single treatment. The dosimetric study with fractionated ^{131}I-L will be published separately. However, with the availability of ^{90}Y microspheres, we are now treating large HCC (>5 cm) with ^{90}Y which is a more powerful radioisotope.

In view of the fact that most of our patients had recurrent multifocal disease, the 50% survival at 7 mo is not unexpected. The median survival was 6 mo but seven patients are still alive with a median follow-up time of 10 mo. This may represent a prolongation in survival already when compared with our previous study of 340 patients with HCC. In that study, the median survival for selected patients with inoperable HCC treated with chemotherapy was only 18 wk (*16*). Nonetheless, we have shown that with selective internal irradiation using ^{131}I-L, it is possible to deliver an adequate tumoricidal dose of radiation to HCC which is feasible and safe. Systemic toxicities are usually minimal with regional administration and far less than cytotoxic chemotherapy.

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EDITORIAL

Iodine-131-Lipiodol for Hepatocellular Carcinoma: The Benefits of Targeting

Primary hepatocellular carcinoma is one of the most common malignant tumors in the world. It is responsible for an estimated 1 million deaths annually (*1*). HCC is especially prevalent in Southeast Asia, Japan (where it ranks second only to stomach cancer as a cause of death) and sub-Saharan Africa (*2*). The incidence in some Chinese provinces exceeds 75 cases per 100,000 people per year (*3*), and in males in Mozambique, the incidence is as high as 113 cases per 100,000 people per year (*4*). The disease is endemic in some African populations: a study of autopsies performed on the East African Bantu revealed evidence of HCC in four of every five people (*5*). By contrast, there is a low incidence in Northern Europe (around 2 per 100,000 people annually), but it is increasing in the United Kingdom (*6*), Scandinavia (*7*) and the United States, where the incidence in some states multiplied threefold in the past 20 yr (*8*). I remember discussing HCC with a research fellow from Nigeria, and asking him whether they had much HCC. He replied "three of my fellow medical students have died of HCC—is that a lot?"

HCC nearly always arises on the basis of underlying cirrhosis. For many years it has been appreciated that this is especially the case where the cirrhosis followed infection with the hepatitis B virus. The prevalence of HCC in the third world is associated with chronic hepatitis B infection, often transmitted from mother to child. We now appreciate that the majority of other cases arise following infection with hepatitis C.

The tumor often presents late, which, with underlying cirrhosis, makes surgery difficult or impossible in many patients. The median survival of patients with unresectable HCC may be as low as 3.5–7.5 wk.

In this issue, Leung et al. (*9*) report on HCC treatment using Lipiodol as a means of delivering targeted ^{131}I to the tumor. Lipiodol (iodized oil fluid injection (BP); ethiodized oil injection (USP)) is a lipid derived from the iodination of poppy seed oil and contains 475 mg of iodine per ml (38% by weight). It has been used for many years as a radiological contrast medium (its first recorded use as an angiographic medium was in 1923, when Sicard and Forestier injected the iodized oil into the antecubital vein of a patient to observe flow through the heart and pulmonary arteries (*10*)). In 1979, Nakakuma et al. injected Lipiodol into the hepatic end of the ligated hepatic artery and demonstrated its selective retention in foci of hepatocellular carcinoma (*11*). Lipiodol-enhanced arteriography is particularly effective in demonstrating the small "daughter" nodules often found in association with the main tumor mass of HCC (*12–14*). In technologically advanced countries this has become a part of the standard investigation of patients with suspected HCC, with CT being performed about 10 days after intra-arterial Lipiodol, when HCC may be clearly seen (*15*).

In 1985, Ohishi et al. (*16*) reported the results of treating HCC with Lipiodol carrying a chemotherapeutic agent (mitomycin C or Adriamycin) administered via the hepatic artery, and followed by embolization of the artery with Gelfoam particles. They reported reductions in tumor size, decreases in alpha-feto-protein (AFP) levels and survival rates of 89% at 6 mo and 69% at 1 yr in a population apparently selected only on the basis of being inoperable by virtue of cirrhosis or tumor size. In 1986, Kobayashi et al. (*17*) reported a further series of 41 patients treated in this way, but also on 7 patients treated with Lipiodol in which some of the iodine had been replaced by ^{131}I using exchange labeling. The Lipiodol was administered into one of the two main hepatic arteries, and all the patients showed a decrease in AFP levels and a reduction in tumor size. In one patient who died of liver failure 2 mo after therapy,

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