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Nodular Hepatocellular Carcinoma

— Treatment with Intraarterial Injection of I-131 Lipiodol —

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Twenty four patients with hepatocellular carcinoma who refused surgery or had unresectable tumor ranging 2.5 to 8.0cm in size were treated with intrahepatic arterial injection of iodine-131-labeled iodized oil (I-131 Lipodol) in an attempt to achieve internal radiation of tumor. 555-2,220 MBq in 3-8 ml of I-131 Lipiodol was injected into the hepatic artery or proximal to the tumor feeding vessel depending on the tumor size. Tumor size reduction was observed in 88.9% of tumor smaller than 4.0cm in diameter, 65.5% between 4.1 to 6.0cm, and 25.0% of larger than 6.1cm, respectively. The tumor size reduction was corresponded to the gradual drop of serum AFP levels, decreased uptake on gallium-67 scintigraphy, and devascularization on follow-up angiography. Tumors having significant A-V shunts revealed further tumor growth. Adverse reactions from the treatment include fever, mild abdominal pain, nausea and elevation of transaminases. These have been mild and well-tolerated by the patients. This method was able to provied long term local control without complications related to thyroid, lung, GI tract and bone marrow.

Key Words: *Liver neoplasms, therapy. Iodine and iodine compounds, radioactive. Liver neoplasms, radionuclide studies. Radionuclides, therapeutic.*

INTRODUCTION

Hepatocellular carcinoma(HCC) is one of the most common malignant neoplasms in the far East and its prognosis with conventional treatment is extremely poor with an average survival of six months (Okuda, 1986). Although the tumor is small in size, surgical resection is often not indicated because of preexisting advanced cirrhosis, multifocality, or site of the lesions. For the treatment of unresectable HCCs, systemic chemotherapy, and ligation of hepatic artery were used. Order et al (1985) reported on a preliminary study of isotopic immunoglobulin therapy for primary liver cancer using systemic administration of 50 and 100mCi of I-131-antiferritin. However, the systemic administration had yield a lack of specific tumor localization, high radiation dose to normal liver and bone marrow depression.

Nakakuma et al (1979) and Iwai et al (1984) found that an oily contrast medium, used for contrast lymphangiogram, injected through the end of the ligated hepatic artery was selectively retained in HCC. Following these reports, Lipiodol (Laboratorie, Guerbet, France) has been utilized in the therapy as well as in the detection of small HCCs when it has been mixed with chemotherapeutic agents (Konno et al., 1984; Ohishi et al., 1985; Takayasu et al., 1987; Sasaki et al., 1987). As Lipiodol contains stable iodine of 127, labeling of Lipiodol with radioactive I-131 can be achieved

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by a simple exchange method (Park et al., 1986; Yoo et al. 1986). Biodistribution and in vivo kinetics of intrahepatic I-131 Lipiodol infused into the hepatic artery revealed a high-tumor to non-tumor ratio and a longer effective half life in the vascular HCC than in the non-tumor adjacent hepatic tissues (Nakajo et al., 1983; Raoul et al., 1988; Kim et al., 1989). Thus, the therapeutic trial of internal radio-therapy with this agent has been investigated by several researchers (Park et al., 1986; Yoo et al., 1988; Yoo et al., 1989; Kobayashi et al., 1986; Nakajo et al., 1988).

The purpose of this study is to assess the efficacy of arterial infusion of I-131 Lipiodol in patients with HCCs which were unresectable or in patients who refused surgical resection, using sequential determination of serum AFP and radiologic imaging studies.

PATIENTS AND METHODS

Patients

A total of twenty four patients with HCC who refused surgery or had unresectable tumor were treated with intrahepatic I-131 Lipiodol infusion from Feb. 1986 to Feb. 1989. The final diagnosis of HCC was made by aspiration cytology, elevated AFP with abnormal diagnostic images and surgical biopsy in 17, 5 and 2, respectively. The masses ranged in size from 2.5cm to 8.0cm. Eighteen patients (75%) had preexisting liver cirrhosis, confirmed by peritoneoscopy in 2, laparotomy in 2, and imaging studies in 14 cases. The patients ages were from 35 to 75 years and the mean was 53 years. The criteria for patient selection for the therapeutic protocol were as following: (1) patients who refused surgery or whose HCCs were unresectable due to multiplicity, deep location of tumor and vessel invasions. (2) hypervascular HCC on arteriogram. (3) superselective or hepatic arterial injection possible. (4) no clinical or radiologic evidence of extrahepatic metastatic disease. Patients with allergy to iodine, severe chronic lung or renal disease and main portal vein involvement by the tumor were excluded from the study. Seven patiebra were at stage I disease, twelve at stage II, and five at stage III, according to the Okuda's classification (1985). In 7 patients with stage I disease, four were inoperable due to deep location of tumor and three rejected surgical treatment. Seven patients (three in stage II, four in stage III) had portal vein thrombus in the second or third order branch and five patients (three in stage II, two in stage I) had significant A-V shunt of tumor.

Method of Administration

Radioiodination of Lipiodol (I-131 Lipiodol) was achieved by using a simple exchange method (Park et al. 1986) at Reactor isotope department, Korea Advanced Energy Research Institute. The therapeutic dose of 15-60mCi of I-131 Lipiodol (555-2,220 MBq in 3-8 ml) was injected once into the right hepatic artery(RHA), left hepatic artery(LHA) or proximal to the tumor feeding artery (superselective) through 5 or 7 French catheter. Dose and volume to be injected was determined on CT measurement of size to deliver 10,000cGy and injection was made at a rate of 10-20 ml/hr either manually or via an automatic injection syringe. After completion of I-131 Lipiodol infusion, immediate plain x-ray film on liver was obtained to observe the homogeneous distribution of injected volume. Lugol's solution was prescribed for the patients to block the thyroid the day before infusion and for 3 days afterwards. Patients were isolated for three days to 1 week in a private room for radiation protection.

Initial and Follow-up Studies

Baseline studies before treatment included hematolog'c tests, serum AFP, and liver function tests(LFTs), and the size of the tumor was measured by ultrasonography(US), and/or computed tomography(CT). Ga-67 scan and angiography were performed for the evaluation of the tumor uptake activity and vascularity.

Follow-up studies were performed with measurements of AFP and LFTs (one month interval) and study with CT, and/or US (every two month interval), Ga-67 scan and angiography (three to six months after treatment) and followed for 6 to 34 months.

RESULTS

During the follow-up period of 6 to 34 months, 16 of 24 patients (66.7%) revealed size reduction of the tumor after treatment.

Decrease in AFP levels was achieved in 9 out of 10 patients whose serum AFP levels were higher than 400ng/ml, during the follow-up period. In 12 patients, post treatment angiography at the time of 3 to 18 months revealed a decrease in tumor size and devascularization without collateral vessels in the tumor area. Gallium-67 scan also revealed decreased uptake or cold defect in comparison with preembolization of gallium activity.

A reduction in tumor size of less than 25 percent was observed in 8 of the 24 patients (33.3%). In 3 pa-

tients the tumor size decreased more than 50 percent. HCC's less than 4cm in size were most prominent in tumor size reduction after treatment followed by those of 4.1 to 6.0cm in size. Masses larger than 6.1cm were least affected by this treatment (Table 1).

8 patients revealed further tumor growth or portal vein thrombus within 6 months. 5 of 8 patients whose tumor became larger revealed rapid clearance of intratumoral I-131 Lipiodol due to significant A-V shunts, and another 3 cases revealed inhomogeneous distribution of I-131 Lipiodol in the tumor due to inadequate injection of I-131 Lipiodol.

The patients were observed for possible side effects, but neither symptoms nor changes in the vital signs developed after infusion of radioactive iodized oil. Patients complained of slight pain in the area of the liver during infusion, and temporary abdominal pain and mild fever developed within a few days after infusion. These have been transient, mild and well tolerated by the patients. Liver function tests revealed a transitory elevation of serum SGOT and SGPT levels which returned to normal levels after a few days. There were no abnormal changes in the bilirubin, alkaline phosphatase or BUN levels (Table 2).

Among 16 patients with reduced tumor size two revealed extrahepatic metastatic lymphadenopathy; one in the retroperitoneum, the other in the mediastinum, and three developed another tumor masses in the other site of liver over 6 months after treatment. 3 patients (stage III) expired in spite of significant size reduction due to aggravation of underlying cirrhosis within 6 months. 12 patients are still alive more than 1 year since intial treatment. They did not show complications related to radioactive iodine such as hypothyroidism and bone marrow suppression

ILLUSTRATIVE CASE

A 56-year-old man (patient 1) was admitted with right upper abdominal pain. CT examination revealed a 6cm sized low density mass in the right anterior segment of liver (Fig. 1a), and Ga-67 scan showed hot uptake within the tumor (Fig. 1b). Aspiration cytology confirmed the diagnosis of hepatocellular carcinoma and angiography revealed a hypervascular mass (Fig. 1c). No duaghter tumor or venous invasion was identified on US and angiography. Patient refused the surgical resection of tumor. 8 ml of Lipiodol labeled with 1,850 MBq (50mCi) of I-131 activity was infused into the right anterior superior hepatic artery with five French catheter. Gamma camera image disclosed

Table 1. Tumor Size Reduction Rate

Size of Tumor	Size Reduction			Reduction cases	Reduction rate (%)
	>50%	26-49%	<25%		
less than 4cm	1/9	3/9	4/9	8/9	88.9
4.1-6.0cm	2/11	2/11	3/11	7/11	65.5
6.1-8.0cm	0/4	0/4	1/4	1/4	25.0

Table 2. Adverse Reactions to Treatment with Intrahepatic I-131 Lipiodol

	No. of patients	Percent
Moderate fever*	12	50.0
Abdominal pain*	6	25.0
Dyspnea	1	4.2
Pleural effusion	0	0
Elevation of SGOT* (>200 IU above base line level)	2	8.3
Elevation of serum bilirubin* (>3.0mg/dℓabove base line level)	1	4.2
Elevation of alkaline phsophatase	0	0
Anemia	0	0
Leukopenia (<300m²)	0	0
Thrombocytopenia (≦5×10/m²)	0	0

*during hospitalization

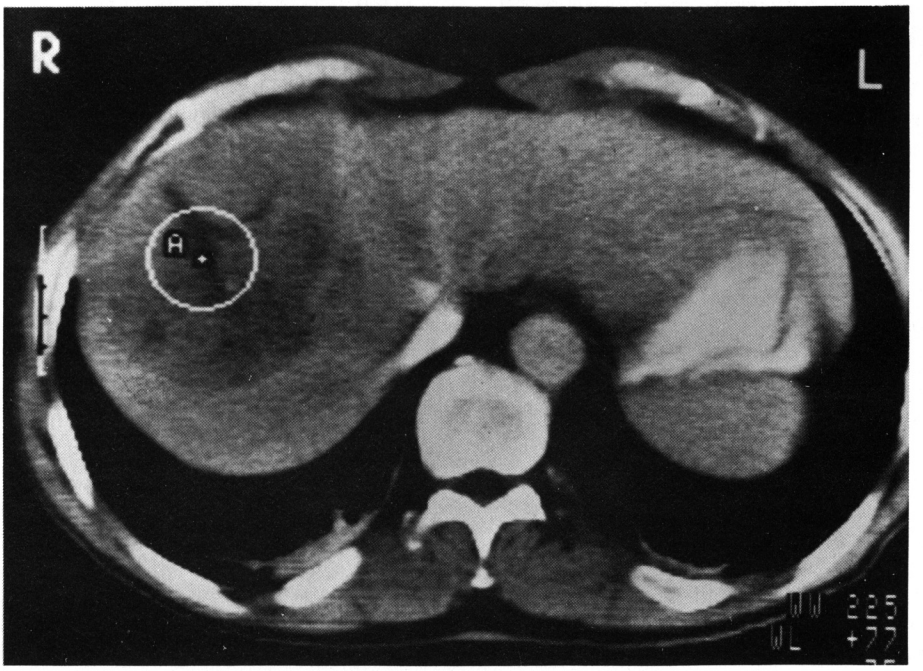

Fig. 1a: 6cm low density mass is seen in the right anterior segment of the liver.

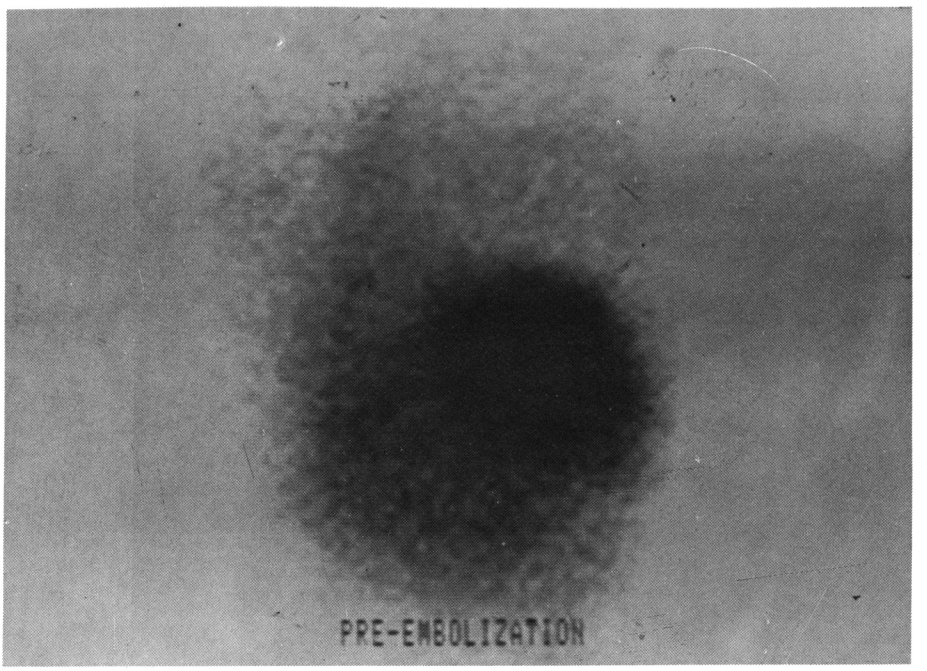

Fig. 1b: Lateral view of Ga-67 scan reveals marked increased uptake within the tumor.

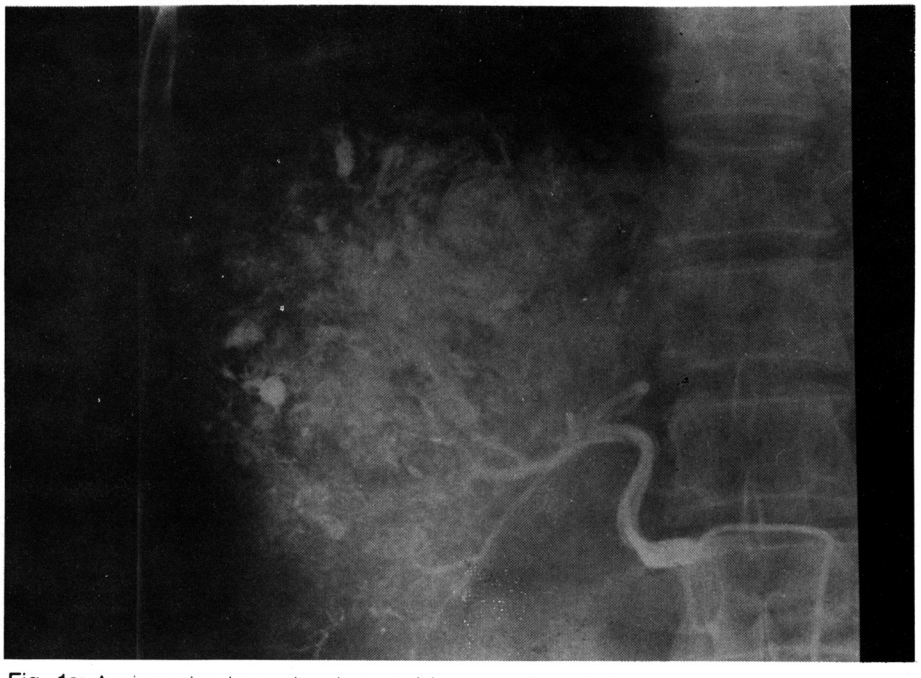

Fig. 1c: Angiography shows abundant arterial neovasculature in the mass.

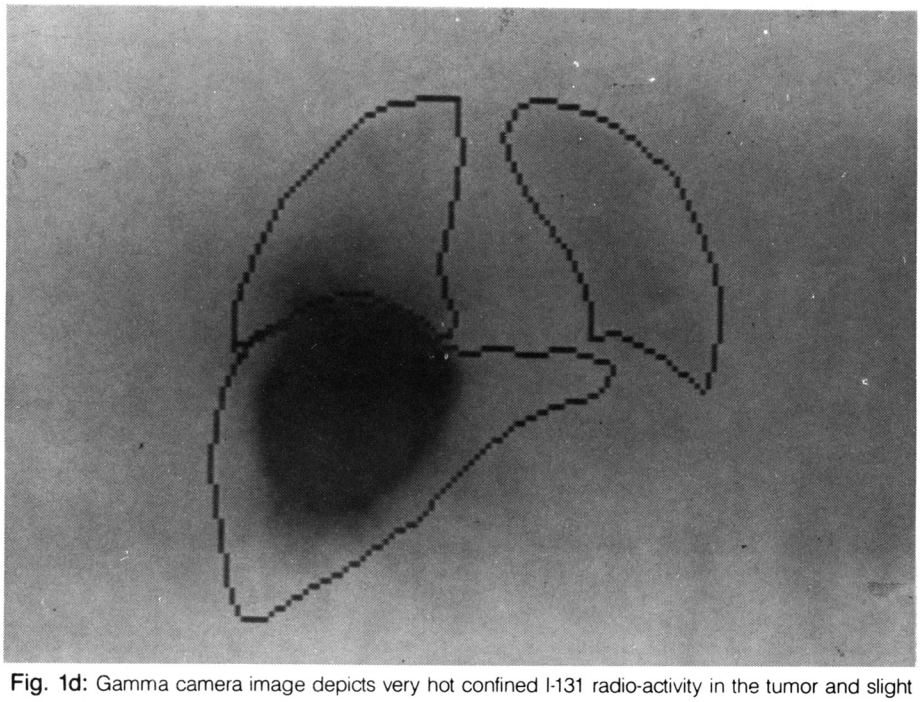

Fig. 1d: Gamma camera image depicts very hot confined I-131 radio-activity in the tumor and slight radioactivities in the both lung.

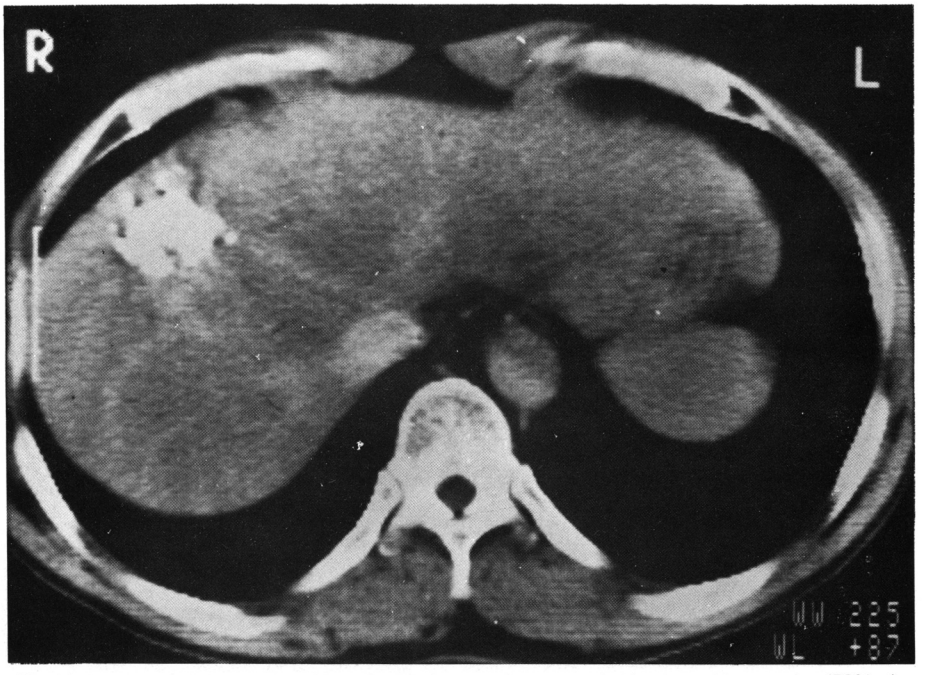

Fig. 1e: Follow-up CT scan at 3 month after the treatment reveals decreased tumor size (58% size reduction) and residual Lipiodol in the tumor.

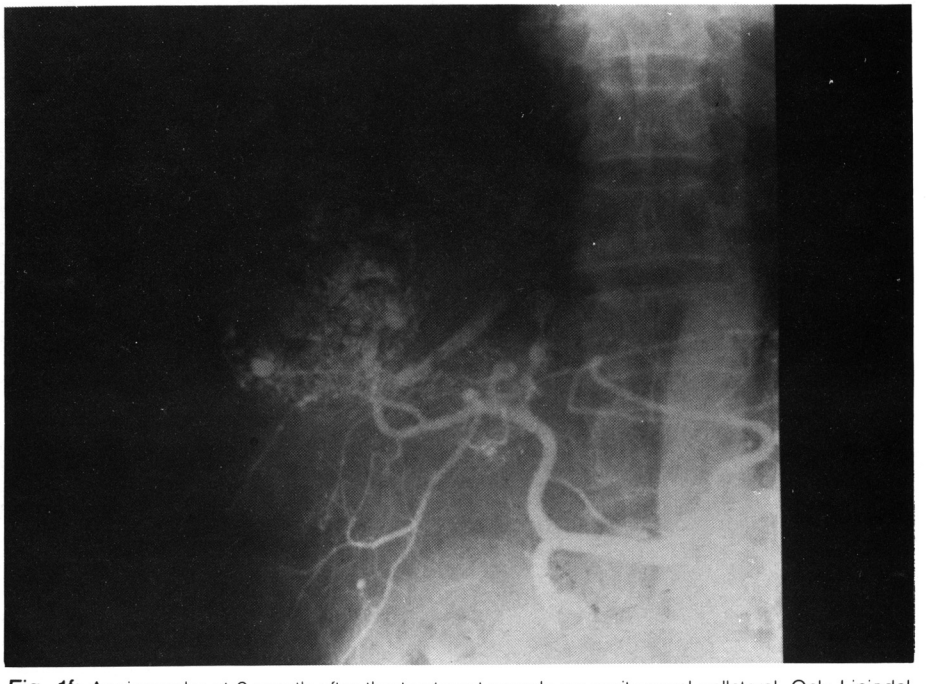

Fig. 1f: Angiography at 3 month after the treatment reveals no peritumoral collateral. Only Lipiodol density in the tumor is noted.

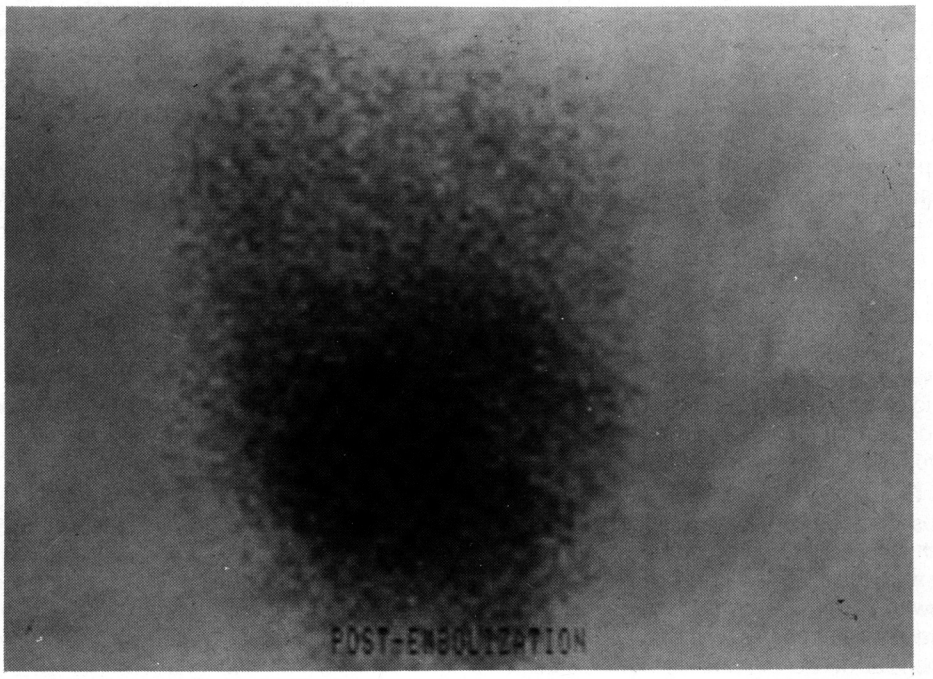

Fig. 1g: 6 months follow-up Ga-67 scan reveals cold uptake in the tumor consistent with devascularization or tumor necrosis.

confined radioactivity in the tumor with slight uptakes in the lungs (Fig. 1d). Cumulative radiation dose to the tumor was estimated to be more than 12,000cGy. The 3 month follow-up CT revealed decreased tumor size (2.5cm in diameter) with residual Lipiodol in the tumor (Fig. 1e). At the same time, angiography disclosed a markedly decreased tumor size with devascularization. Only residual Lipiodol deposition of tumor was identified on angiography without evidence of peritumoral collateral vessels (Fig. 1f). Follow-up Ga-67 scan showed a cold defect consistent with fibrosis or tumor necrosis (fig. 1g). No definite tumor cells were identified on aspiration biopsy at the 6 months follow-up and no evidence of recurrence appeared for up to 34 months.

DISCUSSION

It is well known Lipiodol is selectively deposited in the HCC, remains for a long pereiod of time, and is used for the detection and treatment with anticancer drug emulsions (Nakakuma et al., 1979; Iwai et al., 1984; Ohishi et al., 1985). The clinical results of Lipiodol infusion alone has no effect on tumor necrosis (Takayasu et al. 1987). Lipiodol plus anticancer drug emulsions such as mitomycin C, adriamycin, SMANCS (Stylene Maleic Acid Neocarzino Statin) or cisplatinum with or without gelfoam embolization gave more effective therapy (Konno et al., 1984; Sasaki et al., 1987). However, the effectiveness has been shown to be still inadequate for the treatment of HCC mainly because of the rapid development of collateral vessels with the 2 to 3 weeks when embolization was performed.

Internal radiation of liver tumors had been used with Yttrium-90 bound to resinous microspheres 15μm in diameter (Grady 1978; Mantravadi, et al., 1982) or with intravenous isotopic immunoglobulin therapy using anti-CEA and antiferritin anti-bodies labeled with I-131 (Order et al., 1985). Unfortunately, these methods failed to show a high tumor to non-tumor ratio and bone marrow depression. Lipiodol labeled with radioactive iodine (I-131) has the advantage of high tumor uptake and little activity outside the liver when injected into the hepatic artery (Kobayashi et al., 1986; Park et al., 1986; Yoo et al., 1986).

It is also possible to trace the biodistribution of Lipiodol and to calculate the tumor doses delivered to the lung and whole body using gamma camera. Biodistribution and in vivo kinetics of intrahepatic I-131 Lipiodol on patients with HCC have shown: (a) stability of this radio-label in vivo. (b) effective half life in tumors of 4-6 days which is longer than the adjacent hepatic

tissues and lungs. (c) 10-15% localization of the injected dose within the HCC when injected at the level of right or left hepatic artery branch. (d) high tumor to adjacent hepatic tissue uptake ratio of 7.5-21 (10 on the average). (e) negligible uptake of extrahepatic and extrapulmonary organs. (f) urinary (30-50% of I-131 over an 8 day period) and biliary (3% over a 5 day period) excretion (Kobayashi et al., 1986; Yoo et al., 1986; Madsen et al., 1983; Nakajo et al., 1988; Raoul et al., 1988).

Nakajo et al (1988) had reported that if one wants to deliver 100GY to the tumor in patients with less than 4cm sized vascular HCC the total doses of activity to be infused into the hepatic artery would be around 35mCi which may deliver less than 5.9GY to lungs and 13.9GY to the normal adjacent hepatic tissues. The safe radiation doses to the liver and lungs with internally administered radionuclide are not known. However, Levine et al. (1957) reported that histologic evidence of liver necrosis was found only after 120GY in dogs ingested with colloidal Potassium-32 chromic phosphate and there were no significant alterations in liver functions below this level. Tolerance of the entire liver to external irradiation has been estimated to be 30GY with radiation hepatitis developing when this level is exceeded (Ingold et al., 1965). those results suggest that I-131 Lipiodol may be used as an intraarterial infusion agent to treat vascular hepatic tumors with acceptable burdens to normal tissues.

Kobayashi et al (1986) had treated seven patients of HCC less than 6.5cm in size with tumor doses of 40 and 190GY with 281-593 MBq of I-131 Lipiodol. Tumor regression was observed in all the cases upto 25 weeks follow-up period and no side effects or abnormalities in pulmonary and bone marrow function were noted. In our cases, 15 of 24 patients less than 6cm also showed tumor regression, however, masses larger than 6.0cm revealed funther tumor growth. For tumors smaller than 4cm in diameter, it is sufficient to destroy the tumor with single large doses upto 200GY. If the tumor is larger than 6.0cm, however, it is necessary to try multiple procedures within 2 month intervals. The main tumor feeding vessels must be kept patent because fine collateral vessels may cause difficulty in retreating the tumor when the main tumor vessel is occulded. If the tumor with A-V shunts larger than 6.1cm, it may be necessary to embolize with gelfoam or Ivalon.

According to the report of Nakajo et al (1988) hepatomas may have at least two decreasing components for Lipiodol retension: one rapid which may be due to A-V shunts and the other slow. On our studies, 5 of 8 tumor growth patients revealed significant A-V shunts which might rapid clearance of intratumoral I-131 Lipiodol have occurred. Thus it can be suggested that if the A-V shunts are prominent, it is necessary to occlude the tumor feeding vessels with Ivalon particles or with gelatin sponges to prevent rapid clearance of Lipiodol in the tumor.

Iwai et al (1984) demonstrated Lipiodol droplets in the tumor cytoplasm as well as in the tumor arterial lumens on hepatic cancer of rats bearing VX-2 tumor. Lipiodol in the tumor was consistently observed for 2 months which may be long enough to deliver cumulative radiations to the tumor cells and vessels. Our previous studies of resected specimen after 8 to 12 weeks of post-treatment also revealed deposition of Lipiodol droplets in the fine tumor vessels, cytoplasm of tumor cells as well as clumping of Lipiodol around the tumor cell membrane and coagulative necrosis of tumor (Yoo et al., 1986; park et al., 1990). These findings may suggest the possible destruction of tumor cells from the microembolization effect of Lipiodol and possible radiation fibrosis of tumor vessels enabling devascularization of tumor because vascular effects of radiation consist of endothelial proliferation and subendothelial hyaline deposition, with thickening of the vessel wall leading to vascular obstruction.

For observation of Lipiodol in the tumor, plain x-ray films and CT scan must follow if possible. However, to assess the response of tumor, it is necessary to follow with Ga-67 scan or angiography because plain x-ray or CT scan may miss the washed out Lipiodol in the peripheral portion of the tumor, mimicking decreased size of the tumor in follow-up. Ga-67 scan has the advantage of observation of tumor cell activity as well as of tumor vasculature. Angiography can provide the findings of tumor vasculature status after treatment.

All the cases revealed lung uptakes on gamma camera imaging which was not demonstrated on chest X-ray films. The exact mechanism of lung activity is not clearly established. The lipid particles may be small enough to pass through the capillary network of the liver and may be entrapped eventually in the capillary-alveolar spaces of the lungs after conjugation with serum lipoprotein and albumin (Iwai et al., 1984; Miller et al., 1987). In our cases, the activities in the lungs were found to be 5-10% of infusion doses, and no symptoms referable to its embolization were noted following treatment.

There were no demonstrable radioactivities in the spleen, thyroid and bone marrow in our studies. During the follow up period, no instance of hypothyroidism was seen, no intestinal symptoms developed and no effects either upon the hematologic elements or liver function tests which could be considered an adverse

reaction to the administration of radioactive isotope were noted.

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