TREATMENT OF HEPATOCELLULAR CARCINOMA BY INJECTION OF IODINE*131 LABELLED LIPIODOL INTO HEPATIC ARTERY.

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ABSTRACT

Purpose: To study therapeutic efficacy of iodine*131 labelled Lipiodol in the treatment of hepatocellular carcinoma (HCC). The results of the treatment were evaluated in 4 aspects, 1 size of the tumor, 2 serum alphafetoprotein level 3. the quality of patient's life, and 4 the survival rate.

Materials and methods. The hepatocellular carcinoma was diagnosed by evidence of mass in the liver by computed tomography or ultrasonography with tissue biopsy and/or high level of alphafetoprotein more than 500 U. 20 patients were randomized into 2 groups for comparison. The patients in group A were treated by intrahepatic injection of iodine*131 labeled Lipiodol 60 miliCuries (mCi). The patients in group B were treated by intrahepatic injection of mixture of Lipiodol and chemotherapeutic agents, mitomicin c 20 mg., and 5-fluouracil 500 mg. and followed by selective hepatic artery embolization of small pieces of gelatin sponge (gelfoam). Both groups were evaluated by computed tomography (CT) and possible repeating treatment protocol in 2 months.

Results. There was no serious side-effect or major complication in both groups of patients. The patients' conditions got worse by 40% in both groups. The tumors' sizes remained unchanged by 50% in both groups. The serum alphafetoprotein levels had increased by 40% in group A, and remained unchanged by 50% in group B.The survival rate at 1 and 2 years in group A were 20%, 20%, and in group B were 30%, 0%, respectively.

Conclusion Satisfactory results were obtained in the treatment of a small HCC, size less than 5 cm. with intrahepatic artery injection of iodine*131 labeled Lipiodol. In the large HCC (>10cm) there was no response of the tumor in both groups. This was the first study performed in Thailand.

Introduction Hepatocellular carcinoma (HCC) is one of the most common malignant tumor in the Thai population, especially in the male patients. The incidence in Thailand are 36 cases/100,000/year in male, and 14 cases/100,000/year in the female

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population. There are several risk factors for the Thai people; hepatitis B and C, represented 10% of the population or around 6 millions people. Cirrhosis, food additives, toxins, parasitic infestation, etc. are included in the causative agents of the tumor. Today, HCC can be found in the younger age group, 20-40 years, who are active working - people. Furthermore, most of the patients came to see the doctor, when they had already been in advanced and late stages. This was because there were no symptoms yet when the sizes of the HCC in the liver were small. So the sizes of the HCC in the patients were often larger than 10 cm and/or there were vascular invasion, and they were unresectable. Although the tumor was small, surgical resection was often not indicated because the liver had already got advanced cirrhosis, multiple focalities, or vascular portal vein invasion.

For the treatment of the unresectable HCC, systemic chemotherapy, ligation of hepatic artery, and now - a -day, trans-catherized arterial oily chemoembolization (TOCE) were used. Nakakuma found that an oily contrast medium, Lipiodol used for contrast lymphagiograms injected through hepatic artery was selectively retained in HCC. The computed tomography (CT) performed after TOCE showed that the small droplets of lipiodol remained in the tumor vascular bed for months. Furthermore, Lipiodol has been used as a carrier for therapeutic agents in chemotheurapy for HCC. Lipiodol is an ethyl ester of poppy seed oil fatty acid that contains 38% stable iodine127 by weight. By exchange method, labeling of Lipiodol with radioactive iodine 131(I*131) can be achieved. Intrahepatic artery injection of Lipiodol-I*131 showed a high tumor to nontumor ratio and longer effective half life in the vascular HCC than the normal hepatic parenchyma. One reason is that HCC was mainly supplied by hepatic artery. There were many reports of therapeutic trial of internal radiation therapy for HCC with this Lipiodol-I*131.

The purpose of this study is to evaluate and compare the therapeutic efficicacy between Lipiodol-I*131 and TOCE, in the treatment of HCC in 4 aspects, 1. the size of the tumor, 2. serum alphafetoprotein level, 3. quality of life and 4. survival rate.

Our project study was approved by the ethical committee of Faculty of medicine, Siriraj hospital, Mahidol University and research fund from Faculty of Medicine Siriraj Hospital.

MATERIALS AND METHODS

Patients: There were 20 patients,19 were male, and only 1 was female. The patients were 28 to 72 years old, average 46 years old. All of them had evidences of mass in the liver, by computed tomography (CT), or ultrasonography (US). The diagnosis of HCC was confirmed by tissue biopsy, with pathological diagnosis and/or serum alphafetoprotein was greater than 500 units. The patients were randomized and divided symmetrically into 2 groups, A and B.

MATERIALS

Lipiodol is an oily contrast medium used

in lymphangiography. It is a lipid compound derived from or ethylester of poppy seed oil. It contains stable iodine 127, 38% by weight. One dose of Lipiodol is 10-15 ml depending on the volume of HCC. When injected into the hepatic artery, it is selectively retained in the HCC for more than 2 months.

Lipiodol-I*131, its trade name is "Lipiocis". It was manufactured by CIS biointernational company in France. One dose of Lipiodol-I*131 contains radioactive I*131,60 miliCurie (mCi) or 2220 MBq. The radioactive I*131 emits 2 kinds of radiation , A. electron emission or beta rays, with the main energy of 0.61 Mev, B. photon emission or gamma rays, with the main energy of 0.36 Mev. The physical half life of I*131 is 8 days. So after Lipiodol-I*131 was manufactured, it was sent directly and immediately by airplane to the hospital. After injection into the hepatic artery, the biological half life is 5 days.

METHODS

Treatment protocol

Enrolled patients
↓
confirm diagnosis by tissue pathology or alphafetoprotein>500 u.
↓
interviewing and consent
↓
randomized grouping
↓

group A	group B
Rx Lipiodol I*131	Rx TOCE
↓	↓
Evaluation by clinical examination, CT, and blood exam.	
↓	↓
repeat Rx (2 months interval)	repeat Rx

↓
follow up, and medical supportive Rx

IN GROUP A,LIPIODOL-I*131

The hepatic angiography was performed, by Seldinger's technique via femoral artery approach. The cobra 4 or 5 French size catheter was selected inserting into the subsegmental branch of hepatic artery that supply to the HCC, then the patient was moved from angiographic room to cancer ward ,for radiation protection reason. The Lipiodol-I*131 2ml,or radioactivity 60 mCi ,in the leaded protected glass syringe was slowly injected by radiologist into the HCC via catheter. After injection, the patient was on his bed, where there were lead-shield blocks around the patient's bed, for 24 hours, and was in an isolated radiation protective room for 6 days (figure 1a,1b). There was monitoring for radiation exposure recorded during, and after injection procedure.

Fig. 1A. **1A**
Showing the lead shield syringe.

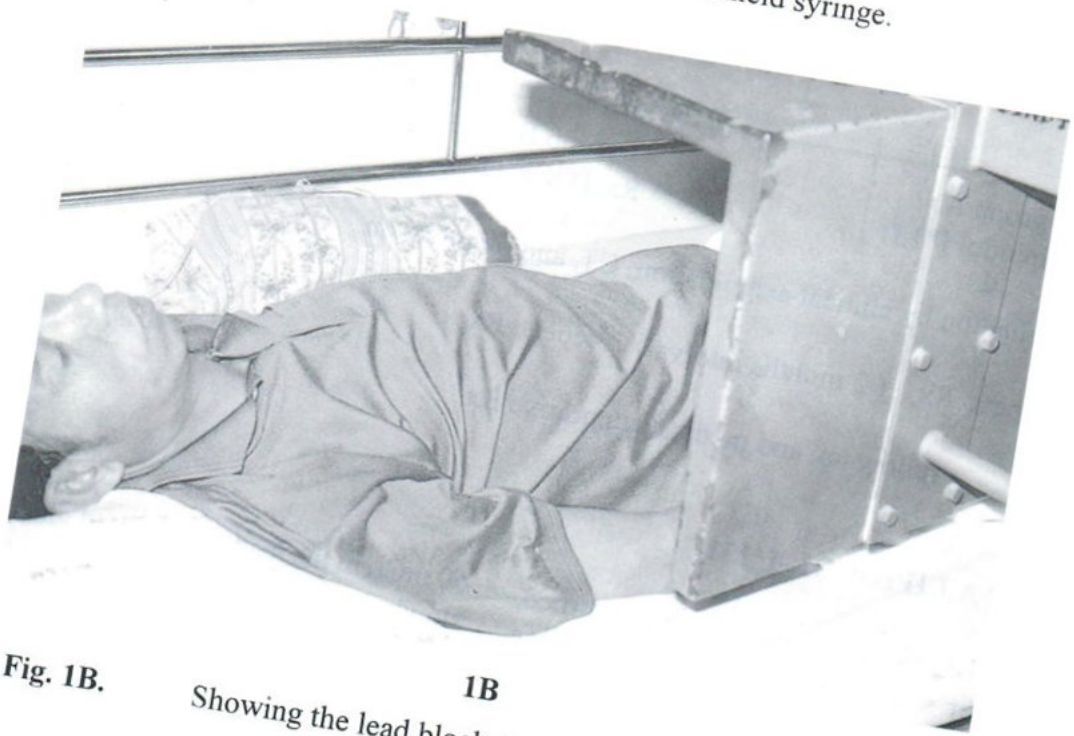


Fig. 1B. **1B**
Showing the lead block around the abdomen of the patient.

IN GROUP B,TOCE

The hepatic angiography was performed, by Seldinger's technique. The 3 to 5 French size catheter was selected inserting into the sub segmental branch of hepatic artery that supply to HCC. We mixed 5 ml of Lipiodol and mitomycin C 20 mg solution, and another 5 ml of Lipiodol and 5 fluorouracil 500 mg solution. The suspension were pushed to and fro between 2 syringes and 3 ways stop cock so as to turn the two suspensions into a fine droplets of oil suspension. Then we injected the oil mixtures into the sub segmental branch of hepatic artery feeding HCC via catheter. After that, if the patient had normal portal vein, we embolized the branch of hepatic artery with small pieces of gelfoam(size 0.5 mm.), or gelatin sponge.

Evaluation. The patients in both groups were evaluated by complete clinical examination, every 2-4 weeks, with computed tomography of abdomen, chest film, complete blood examination, complete blood count, liver function test,and alphafetoprotein level, in every 2 months. All of the patients also had medical supportive treatment. And in the Lipiodol-I*131 group, gamma camera scintigraphy of the whole body was performed, in the first 1-2 weeks ,after injection of Lipiodol -I*131.

RESULTS

The data of both groups were as the followings **(table 1).**

	A,Lipiodol-I*131	B,TOCE
1. patients	9 male,1 female	10 male
2. ages	32-59 ,mean=47	28-72, mean=45 years.
3. virus hepatitis B	2	6 cases
4. Okuda*classification stage 1: 2 : 3	6 : 4 : 0	4 : 6 : 0 cases
5. tumor sizes <5 : 5-10 : >10 cm.	1 : 4 : 5	2 : 4 : 4 masses
6. location of tumors both lobes: right : left lobes	3 : 7 : 0	2 : 8 : 0 lobes
7. alphafetoprotein levels	3.2-204800	6.2-1050 units
8. portal vein thrombosis	3	3 cases
9. number of treatment injections	1 injection for 6 2 injections for 1 3 injections for 3	1 injection for 4 cases 2 injections for 2 cases 3 injections for 1 cases 4 injections for 1 case 5 injections for 1 case 6 injections for 1 case

* Okuda's classification for cirrhosis :
Signs
a. serum albumin <3 gm.%
b. total bilirubin >3 mg.%
c. ascites
d. tumor size is greater than 50% of the liver volume.
Stage 1 have none of these signs.
Stage 2 have one, or two signs.
Stage 3 have more than two signs.

After the patients were treated by injection of Lipiodol-I*131,and TOCE ,as in the protocol, the results were

1. Immediate results

1.1 For the group of Lipiodol-I*131 treatment. The patients were observed for possible side effect, but neither symptoms nor change of vital signs developed after injection of radioactive Lipiodol-I*131.Patients'compliant of slight abdominal pain in the area of the liver, and mild fever developed within few days after injection. There were 3 cases of low grade fever, and 4 cases of mild abdominal pain, no evidence of leukopenia or gastro-intestinal complication.

1.2 For the TOCE treatment group ,there were 2 cases of low grade fever, 4 cases of mild abdominal pain, and two cases of nausea, vomiting, but no evidence of leukopenia was noted.

2. As for the patient condition , a period after the treatment in the Lipiodol-I*131 group, there were improvement in 3 cases, no changes in 3 cases and getting worse in 4 cases. In the TOCE group, there were improvement in 3 cases, no changes in 3 cases and getting worse in 4 cases.

3. For the tumor sizes, in the Lipiodol-I*131 group, there were decreasing size in 3 cases, unchanging size in 5 cases and increasing size in 2 cases.

In the TOCE group, the tumor sizes a showed a decreasing size in 2 cases, unchanging in 4 cases and increasing in 3 cases.

4. About the portal vein thrombosis, the patients in both Lipiodol-I*131 and TOCE groups showed no change of portal vein thrombosis, after treatment.

5.The alphafetoprotein level, in the Lipiodol-I*131 group, the ratio of increasing : unchanging :decreasing was 4:3:3,while the TOCE group was 3:4:3.

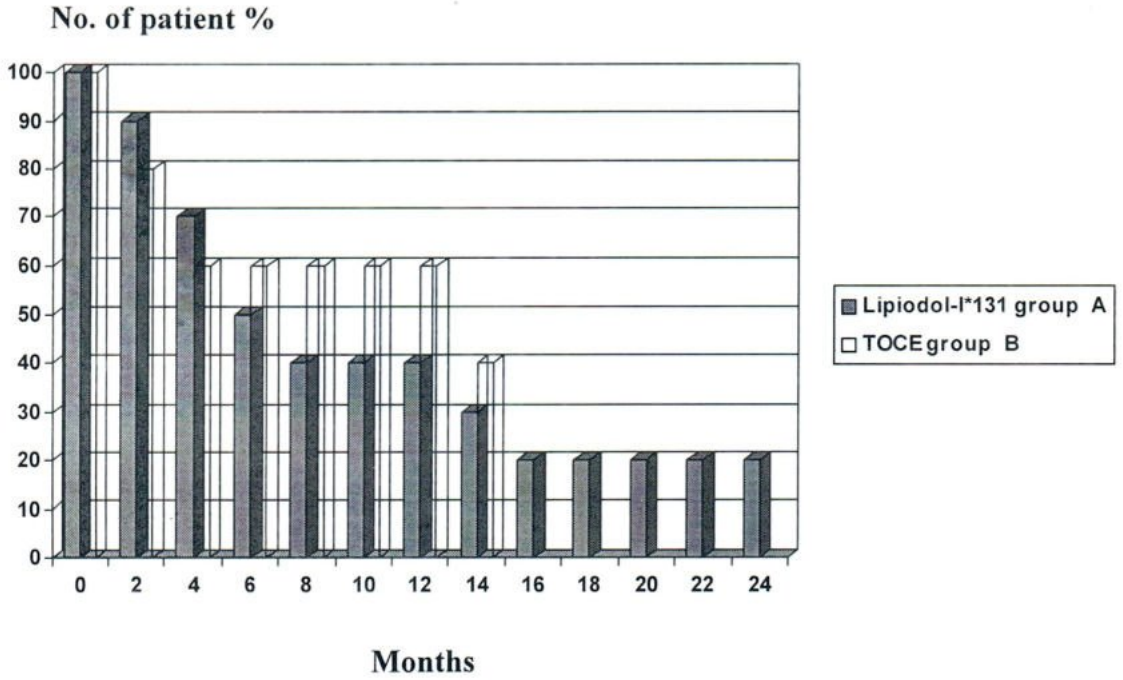
6.The survival rates :In Lipiodol-I*131 group there was 20% survival rate in 12 months and 20% in 24 months.

In the TOCE group there was 30% survival rate in 12 months, and 0% in 24 months. The results of treatment of both groups were summarized as shown in the table 2.

Table 2.

The results after treatment	Lipiodol-I*131	TOCE	
Patient conditions			
improve:no change:worse	3:3:4	3:3:4	cases
Tumor size			
decrease:no change:increase	3:5:2	3:4:3	cases
Portal vein thrombosis			
no change	3	3	cases
AFP level			
increase:no change:decrease	4:3:3	3:4:3	cases
survival rate at			
1 year	20%	30%	
2 year	20%	0%	

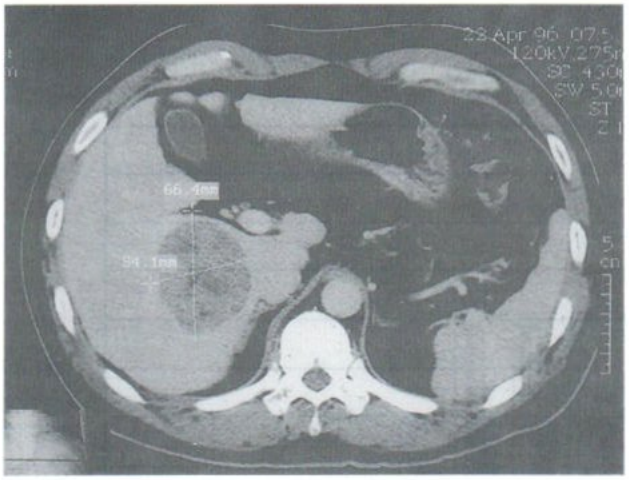
Table 3. survival rate curves.



CASE REPORT

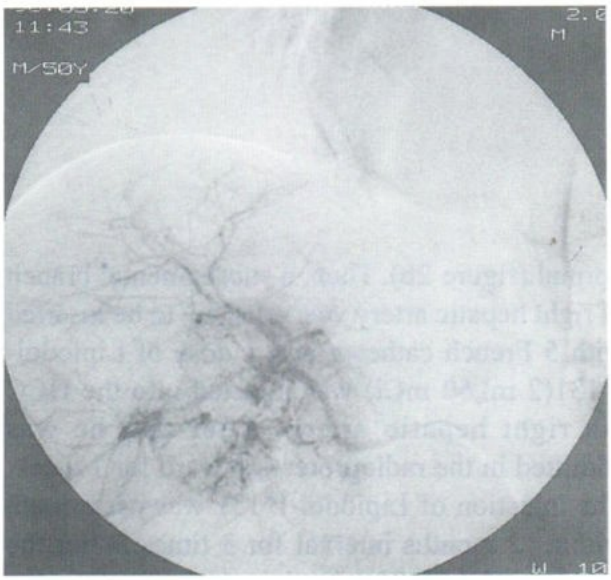
Lipiodol-I*131 treatment group

Case 1.This was the first case in Thailand who was treated by this drug. The patient was a Thai male, aged 50 years old. He had abdominal pain and weight loss for 2 months. The physical examination showed mild hepatomegaly, without ascites. The computed tomography of abdomen showed that there was a mass, sized 5x6x5 cu.cm. in the right lobe of the liver. The portal vein was patent.(figure 2a).The laboratory findings showed serum albumin at 4.7 mg%, total bili- rubin 1.3 mg% and alphafetoprotein was 63.9 ng/ml. The pathology of liver biopsy was hepatocellular carcinoma(Okuda class 1).He was admitted in Siriraj hospital for the treatment by injection of Lipiodol-I*131 into hepatic artery. The celiac angiography showed to have hypervascular mass about 5 cm. in size, with tumoral staining in the right lobe of the liver. The portal vein was normal.(figure 2b). Then, a subsegmental branch of right hepatic artery was selected to be inserted with 5 French catheter, and 1 dose of Lipiodol-I*131(2 ml,60 mCi) was injected into the HCC via right hepatic artery. After that he was admitted in the radioprotection ward for 1 week. The injection of Lipiodol-I*131 was performed, within 2 months interval for 3 times. After the first Lipiodol I*131 injection ,6 months later the HCC size had reduced to 2x3 cm. or about 75% reduction by volume (figure 3a-b).The patient's general condition was also improved, and he gained weight for 5 kgs. At that time, he was still alive for 24 months after treatment, the size of primary tumor was smaller and the primary tumor HCC was well controlled. But there was an evidence of right adrenal metastasis, after 2 years.

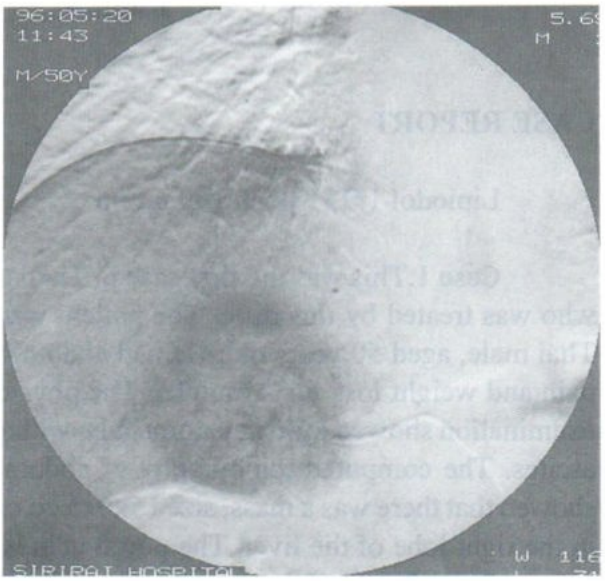


2A

Fig. 2A. The computed tomography of abdomen showed low density heterogenous mass, or HCC, size 5 cm. in the right lobe of the liver.

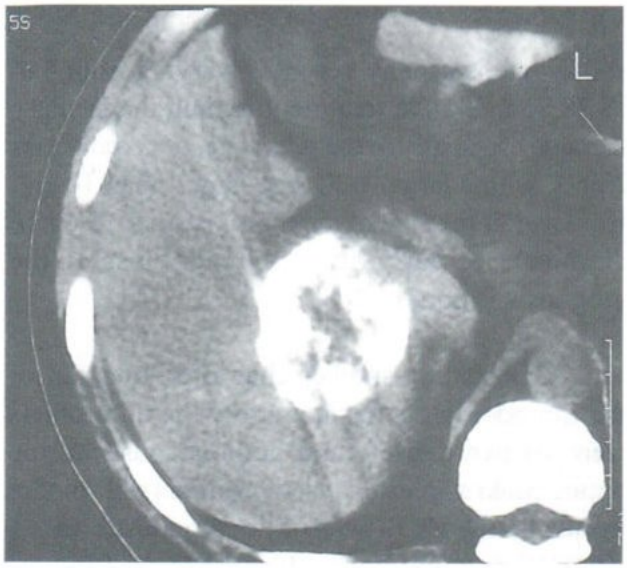


2B



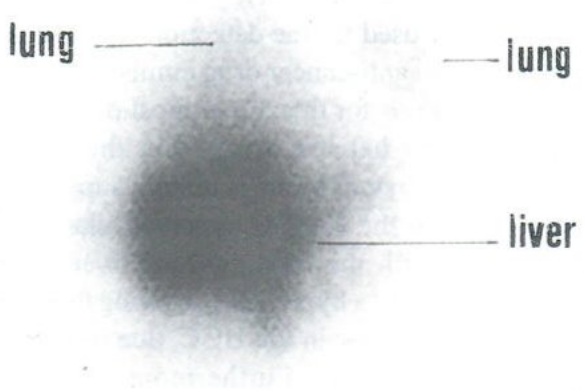
2C

Fig. 2B-C. The celiac angiography of the liver showed hypervascular mass, with staining in the right lobe of the liver



3A

Fig. 3A. The computed tomography of abdomen, after injection of Lipiodol-I*131, showed dense Lipiodol I*131 in the periphery of the HCC.



3B

Fig. 3B. The total body radionuclide scan showed hot spot of radioactivity in the tumor in the liver.

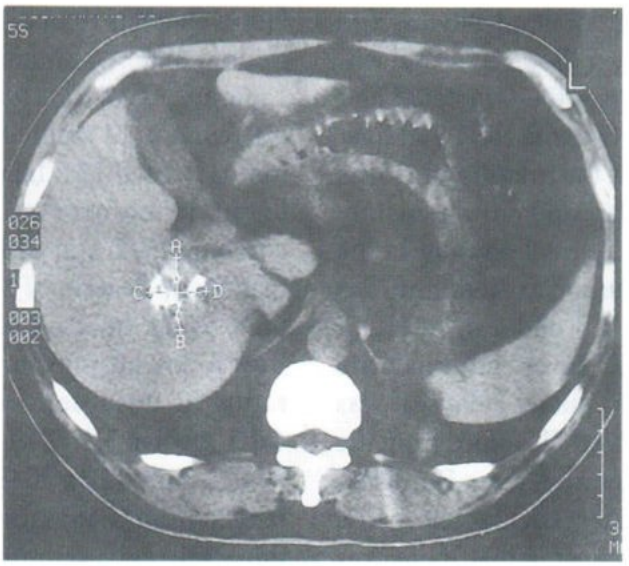


Fig. 4. Six months after the first injection of Lipiodol I*131, the computed tomography study of the abdomen showed the HCC was smaller than 2x3 cm.

DISCUSSION

Today ,we know that after injection of Lipiodol into the hepatic artery, the Lipiodol is selectively deposited in HCC, remains for a long time, and it is used for the detection for HCC and treatment with anti-cancer drug emulsions. There are many reasons for this. First ,most of the HCC is supplied by hepatic artery, but the normal hepatic parenchymal tissue is mainly supplied by portal vein. So the HCC is hypervascularized in comparison with the nontumorous liver tissue. Secondly, there is a hypothesis showing that there is a slow blood flow in the HCC, due to neovascularity in the tumor. Furthermore ,the architecture of the neovessels seems to account for an importance trapping of macromolecules into the extra capillary spaces, in HCC. Thirdly, the reduction or even absence of lymphatic vessel has also been suggested as a cause. And there is a poor reticuloendothelial system in HCC ,but not in a normal liver. The lipid droplets are captured by Kuffer cells, transferred to the hepatocytes, and then eliminated. J.Raoul studied the biodistribution of the I*131 labeled Lipiodol injected into the hepatic artery in the patient with HCC and liver metastasis, and showed that the investigation was extremely well tolerated. The Lipiodol was mainly in the liver, and there was a small amount in the lung. There was a high tumor to nontumorous activity ratio greater than 4.3 and 2.4, in HCC, and metastasis respectively. The effective half life of I*131 Lipiodol was more than 4.3 days. It was eliminated mainly in the urine. Clearance from the tumor was slower than the normal liver. Biodistribution did not change in the patients who had a second injection, which indicates that there was no saturation phenomenon. The study showed that the Lipiodol was a potential carrier vehicle for therapeutic agent, and for internal radiation of the tumor.

The prognosis of the patients with unresectable HCC is very poor. And the resectability rate is usually very low, varying from 4 to 18 %.So palliative treatment remain the primary therapy, especially in the late stage, or Okuda class 2 or 3, with a large HCC size larger than 10 cm. However, if the size of the tumor is small (5 cm in diameter) or early stage, Okuda class 1, the prognosis is good.

Our study showed that after injection of the Lipiodol in the hepatic artery the oil droplets were stained densely and homogenously in the tumor. Maki suggested that the amount of Lipiodol uptake by the HCC, was of the prognostic value. If the HCC was larger than 10 cm. and the Lipiodol droplets were distributed heterogenously in the tumor, it needed an increasing amount of Lipiodol to cover the entire tumor volume. Furthermore, in the late stage, there was usually hepatoportal or hepatohepatic AV shunting. The Lipiodol passed through the AV shunting to the systemic circulation and was trapped by lungs. So it was a need to embolize AV shunting before the injection of Lipiodol. Radiation dosimetry, A. The patients S.Perring et al studied dosimetric assessment of radioactive I*131 label Lipiodol as a potential agent in colorectal liver metastases using combined CT and SPECT. Their report showed that quantification of SPEC images indicated that 86% of the injected activity was retained in the liver following injection, and the tumor to the liver ratios of dose delivered ranged from 1.2:1 to 4.7:1,median 3.1:1 .Tumor doses ranged from 11.8 to 43.3 mGy/MBq of I*131 injected. Dose to lungs ranged from 0-46%,median 16%.And in our study the total body scintigraphy images showed the main radioactivity was in the tumor. (very hot spot in the liver, figure 3b) There was minimal activity in the lungs. And there was no measurable uptake of I*131 in the thyroid .It was possible that the release of stable iodine 127 from the injected contrast medium used in angiography and Lipiodol effectively blocked the thyroid.

Radiolabeled I*131 Lipiodol has been observed to have a whole body retention of approximately 5 days. Considerations of radioprotection would therefore necessitate an extended periods of hospitalization with isolation following administration. One patient was still alive longer than 2 years after the initial treatment. He did not have complications related to radioactive iodine such as hypothyroidism and bone marrow suppression.

B.The mean radiation exposure to the radiologist who injected lipiodol-I*131 measured by TLD method were as the followings :

at right hand	0.9 mSV.
at left hand	0.4 mSV
at thorax	0.1 mSV

The maxinum permissible dose are as the followings :

in the period of	3 months	1 year
for extremities	400	750 mSV
for gonad	30	50 mSV

So we conclude that the procedure was safe for the patients and radiologists.

The indications for injection of Lipiodol-I*131 into hepatic artery are :

1.unrectable/untransplantable HCC.

2 HCC with portal vein thrombosis.

And contraindications are :

1. HCC with cirrhosis Okuda class 3 ,
2. extrahepatic metastasis
3. severe pulmonary, or renal insufficiency.
4. Leukopenia/thrombocytopenina
5. pregnancy/lactation.

In our study, there were problems to be solved.

1. The lipiodol-I*131 must be imported directly from France by the hospital. Sometimes there is a delay in transportation. So the study must be well planned.

2.Problem concerning the isolation ward for radioprotection : There is limitations in number of these special beds in the hospital, and it is mainly occupied for treatment of carcinoma of thyroid by I*131.

3.Problem due to radiation exposure to paramedic personal : Some persons are afraid of radiation.

4.The cost of Lipiodol I*131 is high(about 1500 US$/dose.) However, we are thankful to the CIS ,and Biogenetect company who supply the lipiodol I*131 free of charge for our project in some patients.

However, the fact is that this project study is a complex procedure requiring a certain good cooperation between the departments of nuclear medicine, radiology, and medicine. And the important thing is that we have got a very good cooperation from everybody, that make the project successful .

CONCLUSION

Treatment of HCC by injection of Lipiodol I*131 was well tolerated, and associated with a good tumoral response in the small tumor group, (figure 4) and the patient was in good health for 2 years after treatment. In the large HCC group, the results were the same as treated by TOCE.

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