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Treatment of hepatocellular carcinoma by transcatheter hepatic arterial injection of radioactive iodized oil solution*,**

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Summary. After 12 days of culture, VX2 carcinoma cells were inoculated into the liver of 16 rabbits; 14 days later, ^{131}I-labeled iodized oil ([^{131}I]-Lp) suspended in lipiodol was injected into the hepatic artery. Selective accumulation of the contrast material in the tumor for an extended time was evident on X-rays and hepatic scintiphotographs. The antitumor effect was remarkable. [^{131}I]-Lp agents warrant further examination for their clinical usefulness. Internal radiation therapy by transcatheter hepatic arterial injection of [^{131}I]-Lp (group A) was evaluated in 9 patients with hepatocellular carcinoma (HCC, tumor stage III or IV) associated with liver cirrhosis (LC) and compared with combination therapy of Lp-TAE (group B) in 18 patients with HCC (tumor stage III or IV) associated with LC. In group A, serum AFP levels dropped rapidly in eight of the nine patients who had an elevated initial level of more than 500 ng/ml. The average reduction in tumor size was 50% in eight cases as determined by computed tomography. Histological examination of one resected liver specimen at 3 months after the third injection of [^{131}I]-Lp revealed microscopic features highly suggestive of a radiation effect in the [^{131}I]-Lp-containing area. The 1-year survival value for patients with HCC was estimated at 49.0% using the Kaplan-Meier method. The survival of patients treated with internal radiation therapy tended to be better than that of those treated with Lp-TAE ($P = 0.119$).

Introduction

Internal radiation therapy of hepatic cancer by intra-arterial administration of radioactive particles (^{90}Y microspheres) was first described about two decades ago [1]. Konno et al. [7] treated hepatocellular carcinoma (HCC) patients with SMANCs (an anticancer drug derived from neocarzinostatin) dissolved in lipiodol (Lp) by arterial infusion via the tumor-feeding artery. Numerous investigators have reported that when iodized oil is infused into the hepatic artery, it accumulates selectively in hypervascular tumors of the liver and is retained there for long periods [7, 9, 12, 16]. In 1980, we reported the biodistribution and in vivo kinetics of [^{131}I]-Lp and estimated the potential for internal radiation therapy of HCC by transcatheter intra-arterial infusion of [^{131}I]-Lp [15]. Nakajo et al. [11] have suggested that Lp might be useful as a carrier of therapeutic agents in the treatment of liver tumors. Internal radiation therapy with [^{131}I]-Lp has recently been tested in patients with HCC [6, 13]. In this paper, we report the initial results obtained using transcatheter hepatic arterial injection of radioactive iodized oil solution (TAIR) and TAIR plus TAE for the treatment of transplanted rabbit VX2 hepatic tumors. In an attempt to improve the therapeutic outcome of HCC, Lp-TAE was combined with TAIR in the same patients.

Subjects and methods

Preparation of [^{131}I]-Lp. Iodine [^{131}]-Lp was prepared by the isotopic exchange reaction by Daiichi and Dainabot Radioisotope Laboratories Ltd., Tokyo, Japan.

Antitumor effect of [^{131}I]-Lp on VX2 carcinoma in rabbit liver. This study was carried out in 16 white adult rabbits weighing 2.0–3.5 kg. Anesthesia was induced by intravenous administration of sodium pentobarbital at 30 mg/kg, with supplemental doses being given when needed. VX2 carcinoma cells were transplanted into the liver of each rabbit according to the method of Baba et al. [2]. The tumor became visible at about 14 days after the inoculation, and the largest tumor in each animal was chosen as the target for treatment. A 27-gauge catheter was inserted into a femoral artery and the proper hepatic artery feeding

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Table 1. Results of transcatheter arterial infusion of [^{131}I]-Lp for the treatment of transplanted rabbit VX2 hepatic tumors

Group	Rabbit number	Body weight (kg)	LP (ml)	[^{131}I]-Lp (MBq)	Tumor size (cm)	
					Pretreatment	2 weeks posttreatment)
I	1	2.1	–	–	1.8×1.8	2.5×2.5
	2	2.0	–	–	2.0×1.8	3.0×3.2
	3	2.2	–	–	2.1×2.0	3.1×3.0
II	1	2.0	0.6	–	1.8×1.7	3.6×2.6
	2	2.1	0.6	–	2.1×2.1	3.4×3.0
	3	3.5	0.5	–	2.0×1.8	3.5×2.5
	4	2.0	0.4	–	2.2×2.0	3.0×2.5
	5	2.2	0.5	–	2.1×2.0	3.2×3.1
III	1	2.0	0.5	148	3.2×2.0	2.6×2.4
	2	2.0	0.4	74	3.5×2.5	2.0×2.0
	3	3.5	0.8	140	3.4×2.5	3.1×1.8
	4	2.5	0.7	122	2.8×2.5	2.5×3.2
	5	2.2	0.8	148	3.2×2.5	2.9×2.0
IV	1	3.4	0.6	133	3.2×2.6	2.5×2.0
	2	2.2	0.5	130	2.5×2.4	1.9×1.8
	3	2.2	0.4	141	2.8×2.4	2.0×1.8

Table 2. Summary of the clinical data of group A patients with HCC and therapeutic results

Patient number	Age (years) sex× (M/F)	Main tumor size (mm)	Weight (g)	Location	NT	Distribution	P/V	IM	M	Stage	Child's class
1	49, M	35×22	8.8	M-LPA	4	T4	1/x	3	0	IV	B
2	68, M	128×92	567.0	M-PA	2	T3	4/0	1	0	IV	C
3	47, M	63×80	166.3	M-PA	1	T2	2/2	0	0	III	B
4	48, M	63×51	85.7	M-AL	4	T3	0/0	3	0	IV	B
5	65, M	87×60	163.8	M-PAM	4	T4	3/0	3	0	IV	C
6	76, M	60×60	133.2	M-PAM	4	T3	1/0	3	0	III	B
7	56, M	65×50	85.0	M-PAM	3	T3	2/1	1	1	IV	B
8	70, M	50×48	60.3	M-PAM	2	T3	0/0	1	0	III	B
9	57, M	60×72	135.6	M-PAM	4	T3	3/0	3	0	III	B

Table 2.

Patient number	Infused artery	[^{131}I]-Lp (MBq)	Tumor dose (Gy)	AFP (ng/ml)		Tumor reduction (months)	Survival (days)	Outcome	Treatment after radiotherapy[a]
				Pretreatment	Posttreatment (months)				
1	RHA	370	188	WNL	WNL (6.0)	PR (6.3)	246	D(C)	Lp-TAE
2	RHA	740+370	48	3,235	525 (1.5)	NC (1.5)	55	D(B)	Lp-TAI
3	RHA	370+380	113	2,082	19 (2.7)	PR (5.0)	619	D(R)	Lp-TAE, Lp-TAI
4	LHA,RHA	360+390	85	4,925	95 (2.0)	PR (5.0)	519	D(B)	Lp-TAI
5	RHA	740+370	25	50,046	761 (4.6)	MR (3.0)	98	D(R)	Lp-TAE, Lp-TAE
6	RHA	370×2+390	135	9,562	90 (4.6)	PR (5.0)	534	D(B)	Lp-TAE, Lp-TAI
7	RHA	370×2+350	109	5,638	523 (4.5)	MR (5.0)	155	D(C)	Lp-TAE
8	PHA	370×2+400	78	14,036	38 (3.6)	PR (5.0)	929	D(B)	OP, Lp-TAE, Lp-TAE
9	RHA	370×2+340	154	14,842	862 (7.3)	MR (5.5)	253	D(*)	Lp-TAE, Lp-TAE

[a] Treatment after internal radiation therapy D, Death; D(B), death due to gastrointestinal bleeding; D(R), death due to tumor rupture; D(C), death due to hepatic coma; D(*), cancer death; Lp-TAE, transcatheter arterial injection of carcinostatic agents, including both Lp-soluble SMANCS (styrene maleic anhydride neocarzinostatin) and Adriamycin (doxorubicin hydrochloride) suspended in Lp, plus transcatheter arterial embolization; Lp-TAI, transcatheter hepatic arterial infusion of Lp-carcinostatic agents

the VX2 carcinoma. Various drugs were infused at a rate of 0.5 ml/min (0.4 ml/kg body weight) via the celiac artery, and scintiphotographs were taken (see Fig. 1). The agents were given to a total of 16 rabbits divided into 4 groups as follows (Table 1): group I, 0.4–0.6 ml normal saline ($n = 3$); group II, 0.4–0.6 ml Lp ($n = 5$); group III 0.4–0.8 ml Lp and 4–8 GBq [^{131}I]-Lp ($n = 5$); and group IV, 0.4–0.6 ml Lp and 4–8 GBq [^{131}I]-Lp plus TAE ($n = 3$).

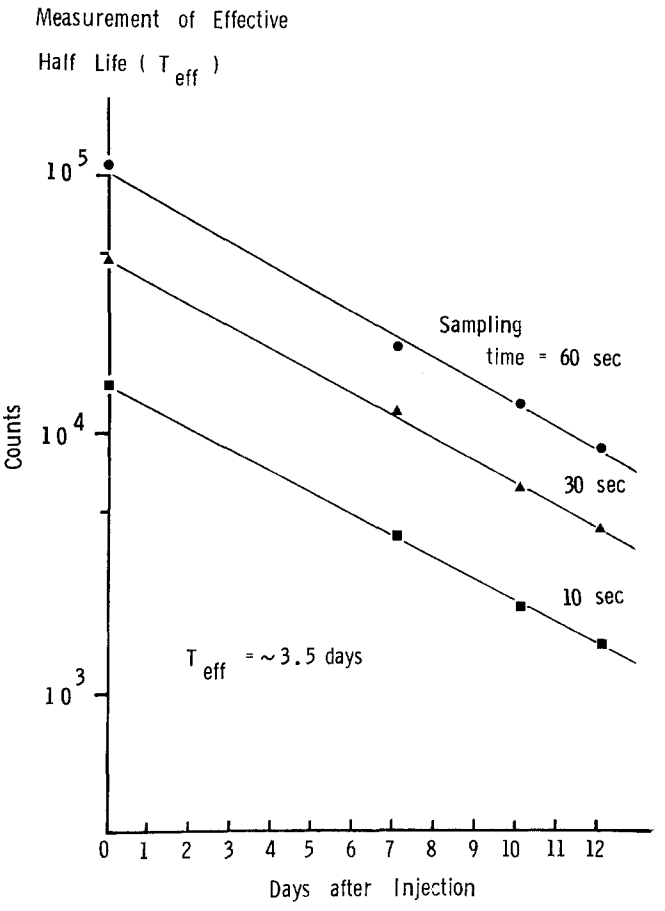
The tumor was closely observed for changes in size after treatment, and the sizes of the tumors in treated and untreated livers were compared. At about 2 weeks after treatment, all rabbits were killed by intravenous administration of sodium pentobarbital. X-rays taken immediately thereafter showed selective accumulation of contrast medium in tumors in the treated livers (see Fig. 2).

Subjects. A total of 27 patients with HCC associated with liver cirrhosis (19 men and 8 women, ranging in age from 46 to 76 years; mean, 60.2 years) were treated with [^{131}I]-Lp (group A) or Lp-TAE (group B). The characteristics of the patients in group A are shown in Table 2 along with the clinical results. The tumor stage as determined according to the guidelines issued by the Liver Cancer Study Group of Japan was III or IV in all cases. Group A consisted of 4 stage III patients and 5 stage IV subjects, and group B comprised 8 stage III patients and 10 stage IV subjects (Table 3).

Internal radiation therapy of HCC patients with radioactive iodized oil. After blockade of the thyroid, selective catheterization was generally performed via the femoral artery under fluoroscopy using Seldinger's method. A therapeutic dose (340–740 MBq) of radioactive iodized oil was slowly infused into the proper hepatic artery or peripheral hepatic branches supplying the target tumor in the liver. The injected volume of radioactive iodized oil ranged from 2.0 to 12.5 ml. The total dose was 370–1,140 MBq [^{131}I]-Lp. In eight patients, a second injection was performed about 2 months after the first injection. Four of these subjects were given a third injection after an additional 2 months. After one to three treatments with TAIR, eight of the nine patients were treated with Lp-TAE or Lp-TAI (Table 2).

Evaluation of therapeutic efficacy. The therapeutic efficacy was evaluated on the basis of the change in tumor size as observed by CT before and after infusion and at monthly follow-up sessions for 3–15 months. The changes in the lesions of the nine group A patients were assessed using angiography, CT, and ultrasonography (US) at 1- to 3-month intervals. The reduction in tumor size was determined from the tumor area calculated by measuring and multiplying the two longest perpendicular diameters of the lesion. The responses were classified as follows: complete response (CR), partial response (PR), moderate response (MR), no change (NC), and progressive disease (PD), whereby the tumor diameter had decreased in two directions by 100%, by more than 50%, by 25%–50%, by less than 25%, and negative regression, respectively, over a period of more than 1 month.

Other therapeutic effects were estimated by following the sequential changes in alpha-fetoprotein (AFP) levels and in survival values calculated by the Kaplan-Meier method. The survival curves were produced by the Kaplan-Meier method, and statistical analysis of the curves was performed according to the generalized Wilcoxon test.



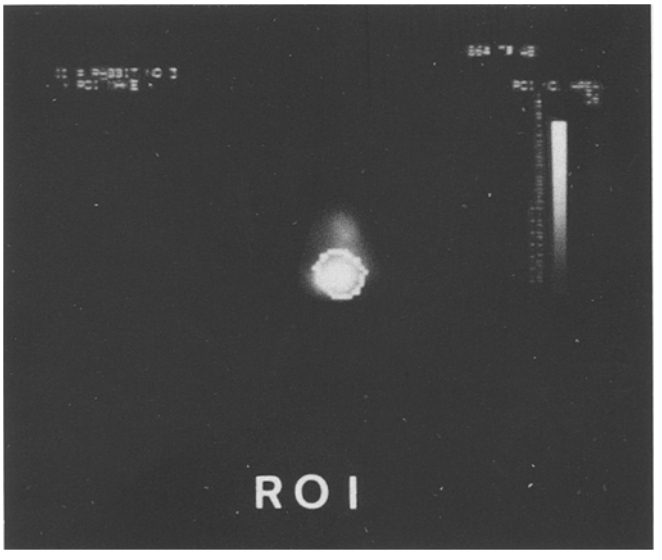


Fig. 1. Scintiphotograph of a transplanted rabbit VX2 hepatic tumor obtained after hepatic arterial injection of [^{131}I]-Lp and daily time-activity relationships of [^{131}I]-Lp in the tumor. The effective half-life is 3.5 days

Results

Therapeutic efficacy of TAIR against rabbit liver tumors

The effective half-life of [^{131}I]-Lp in the rabbit tumors ranged from 3.3 to 3.5 days (Fig. 1). In groups I and II, no evidence of a decrease in tumor size or a cure was observed in any of the rabbits (Table 1). In group III, a marked decrease in tumor size was noted, and histological examination revealed complete necrosis of the lesions except for an area of partial necrosis around the hepatic artery in the center of the tumor in four of five rabbits (Fig. 2) and complete necrosis in the other animals. In group IV, a decrease in tumor size was observed and the lesions had become completely necrotic, even in the center.

Table 3. Summary of the clinical data of group B patients with HCC and therapeutic results obtained after two Lp-TAE treatments

Patient number	Age (year)	Sex (M/F)	Main tumor size (cm)	Location	NT	Distribution	Stage	Child's class
1	51	M	4.7 × 5.7	M-PA	2	T4	III	B
2	51	M	13.0 × 8.0	M-LPA	3	T3	III	B
3	57	M	4.6 × 5.1	M-PA	2	T2	III	B
4	76	M	7.0 × 6.9	M-AL	4	T3	IV	B
5	54	M	13.5 × 7.0	M-PAM	4	T4	IV	A
6	66	F	6.7 × 7.1	M-PAM	4	T3	IV	C
7	56	M	3.5 × 4.1	M-PA	2	T3	III	B
8	61	M	8.4 × 8.4	M-PAM	3	T4	IV	B
9	66	F	4.6 × 3.5	M-PA	3	T3	III	C
10	55	M	3.3 × 3.3	M-LPA	3	T4	IV	C
11	68	M	8.0 × 5.0	M-AL	3	T3	IV	A
12	72	M	6.7 × 6.0	M-PA	2	T3	III	A
13	46	M	10.0 × 15.0	M-PAM	4	T4	IV	A
14	66	M	6.5 × 6.8	M-PAM	4	T4	IV	A
15	61	M	8.1 × 6.4	M-PA	2	T3	III	B
16	52	M	12.2 × 8.3	M-PA	2	T3	IV	A
17	61	F	8.0 × 5.9	M-PAM	3	T4	IV	B
18	71	M	4.2 × 4.4	M-PAM	4	T3	III	B

Table 3.

Patient number	AFP (ng/ml)		Tumor reduction	Survival (days)	Outcome	Therapy after 2 Lp-TAE treatments
	Pretreatment	After 2nd Lp-TAE				
1	31,295	18,411	MR	751	D(C)	Lp-TAE, chemotherapy
2	845	67	MR	555	C(R)	Lp-TAE
3	837	121	NC	332	D(C)	Lp-TAI, immunochemotherapy
4	137	14	NC	165	D(B)	Lp-TAE, Lp-TAI
5	495,661	119,224	PD	105	D(B)	Lp-TAE, PEIT
6	752	197	NC	314	D(B)	Lp-TAE, PEIT
7	32,269	722	PR	1,350	D(C)	Lp-TAE, PEIT
8	6	3	PR	172	D(C)	Lp-TAE, PEIT, chemotherapy
9	30,900	10,612	MR	513	D(B)	Lp-TAE, Lp-TAI
10	949	29	NC	270	D(B)	Lp-TAI, PEIT
11	3,408	1,238	PD	219	D(R)	Lp-TAE, Lp-TAI
12	11	34	MR	176	D(B)	Lp-TAI, Lp-TAE
13	727,742	567	PR	902	D(B)	Lp-TAE, Lp-TAI, PEIT
14	2,175	2,408	NC	125	D(C)	Lp-TAE, PEIT
15	2,024	209	MR	65	D(R)	Lp-TAI, PEIT
16	90,126	12,800	PD	125	D(B)	Lp-TAE, Lp-TAI
17	15,607	9,497	PD	42	D(B)	Immunochemotherapy
18	5,356	1,775	NC	54	D(B)	PEIT

PEIT, Percutaneous ethanol injection therapy

Tumor response in patients with HCC

To evaluate the efficacy of TAIR against HCC, we followed the clinical course using image diagnosis by CT and US. Tumor regression was observed in all group A patients. The reduction in tumor size as evaluated by CT ranged between 50% and 70% over a period of 4–7 weeks. Regression of the main lesion was observed in 7 of 9 cases (77.8%). In the lesions in which [^{131}I]-Lp had accumulated well, slow regression was observed by CT. However, despite the slow rate of tumor regression, two subjects showed the rapid development of complete necrosis as determined by histological examination (Figs. 3, 4). These cases were considered to be NC on the basis of CT examination, indicating the limitations of image diagnosis in accurately evaluating the effect of the therapy. To evaluate the changes in tumor size and in serum AFP levels, we examined the values obtained on the 70th day after initiation of the therapy. The responses of the 9 patients in group A consisted of 5 PRs, 3 MRs, and 1 NC. The tumor responses observed in the 18 group B subjects included 3 PRs, 5 MRs, 6 NCs, and 4 PDs (Table 3). The response rates were 50% in group A and 16% in group B, showing the superiority of TAIR. Table 2 summarizes the results obtained using TAIR.

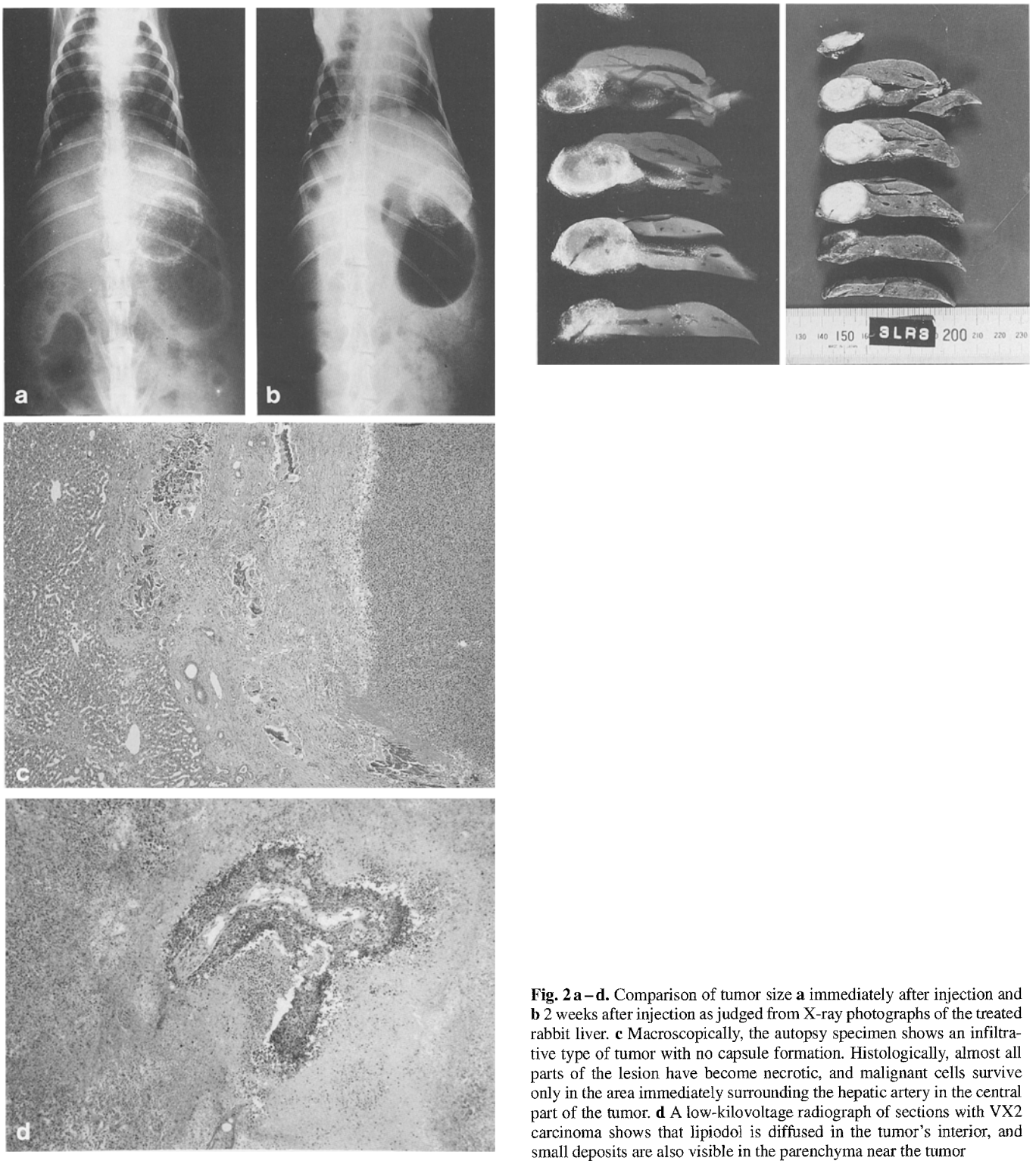


Fig. 2 a–d. Comparison of tumor size **a** immediately after injection and **b** 2 weeks after injection as judged from X-ray photographs of the treated rabbit liver. **c** Macroscopically, the autopsy specimen shows an infiltrative type of tumor with no capsule formation. Histologically, almost all parts of the lesion have become necrotic, and malignant cells survive only in the area immediately surrounding the hepatic artery in the central part of the tumor. **d** A low-kilovoltage radiograph of sections with VX2 carcinoma shows that lipiodol is diffused in the tumor's interior, and small deposits are also visible in the parenchyma near the tumor

Biodistribution of [^{131}I]-Lp and dosimetry

Injection of [^{131}I]-Lp into the hepatic artery was studied scintigraphically in areas of tumor-bearing, nontumorous (liver cirrhosis), and lung tissues in five patients with HCC. [^{131}I]-Lp concentrated in the HCC tumor at a tumorous (T)-to-non-tumorous (NT) activity ratio (T/NT) of 0.31–5.6, at a T-to-lung (L) activity ratio (T/L) of 2.6–11.2, and at a lung-to-nontumorous ratio (L/NT) of 0.14–2.1. The effective half-life of [^{131}I]-Lp was more than 5.0 days (Table 4). Clearance from the tumor was slower than that from the normal liver. In patient 5, who had a hepatic arterioportal shunt, the radioactivity in the lung field increased and the L/NT ratio was 5.0; therefore, the

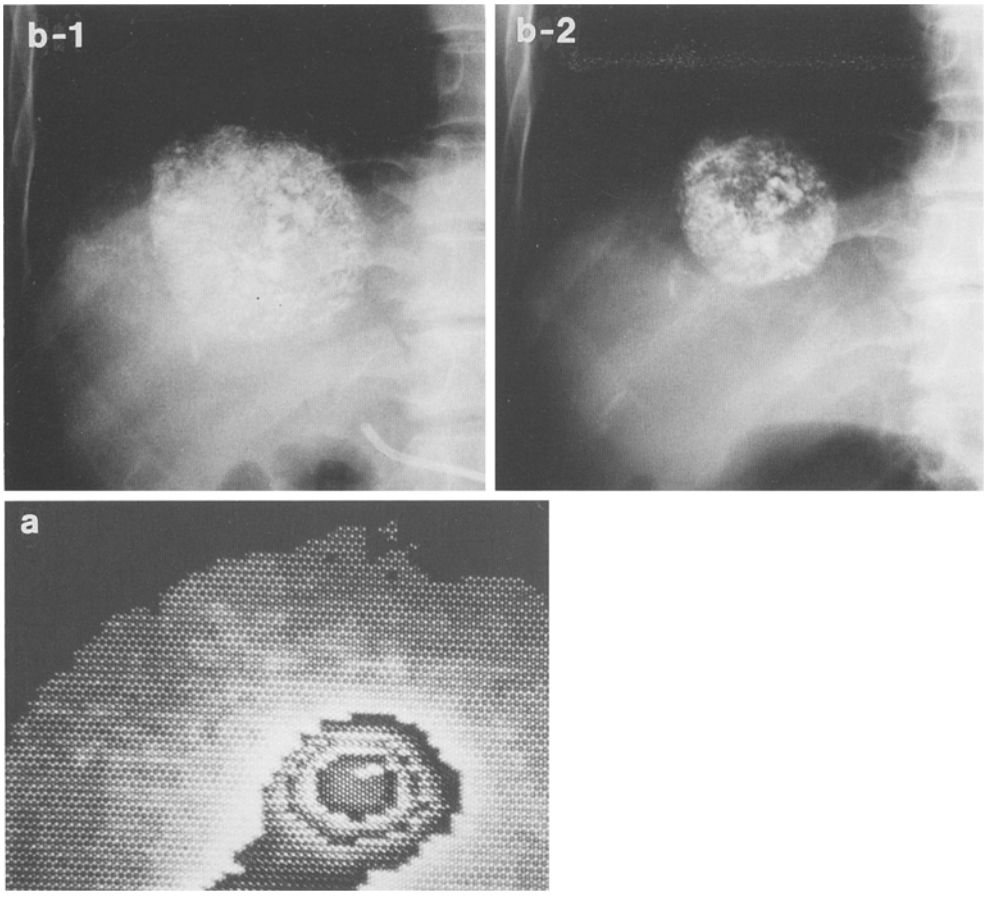


Fig. 3 a, b. Patient 7. **a** A hepatic scintiphotograph prepared just after injection of [^{131}I]-Lp reveals a high accumulation of ^{131}I in the tumor. **b** Comparison of the plain upper abdominal radiograph obtained a few days after [^{131}I]-Lp injection (**b-1**) and that obtained 5 months later (**b-2**) shows that the tumor has decreased considerably in size

Table 4. Tumor/nontumor, tumor/lung, and lung/nontumor radioactivity ratios in internal radiation therapy

Ratio	Patient number	Time after [^{131}I]-Lp infusion				
		2 h	1 day	3 days	5 days	7 days
Tumor/nontumor in the liver	1	3.5	3.4	3.7	4.4	4.8
	2	2.6	3.5	2.8	2.9	3.6
	3	1.7	1.7	1.8	2.2	3.5
	4	0.26	0.32	0.32	0.29	0.31
	5	4.1	3.6	3.6	4.1	5.6
Tumor/lung	1	9.5	8.8	8.8	10.9	11.1
	2	12.0	10.2	9.6	9.8	11.2
	3	4.8	4.2	4.2	5.5	5.8
	4	2.5	2.6	2.5	2.8	2.6
	5	3.4	2.4	2.4	2.7	2.9
Lung/nontumor	1	0.36	0.36	0.38	0.40	0.48
	2	0.21	0.23	0.28	0.30	0.39
	3	0.26	0.41	0.42	0.44	0.46
	4	0.13	0.12	0.12	0.14	0.16
	5	1.12	1.38	1.47	1.59	2.02

lung RI image showed a higher level of radioactivity as compared with the tumor-free liver in scintiphotographs (Fig. 5). The range of the calculated radiation dose [3, 8, 11, 14, 17] was 39–137 Gy within the tumor, 2–15 Gy within the nontumorous liver, and less than 2.5 Gy within the lungs in our patients.

Treatment-related changes in serum AFP levels

Figure 6 illustrates the changes in serum AFP levels in patients with HCC following treatment with [^{131}I]-Lp-TAE. The serum AFP levels in group A showed transient decreases in all cases. Eight of the nine group A subjects

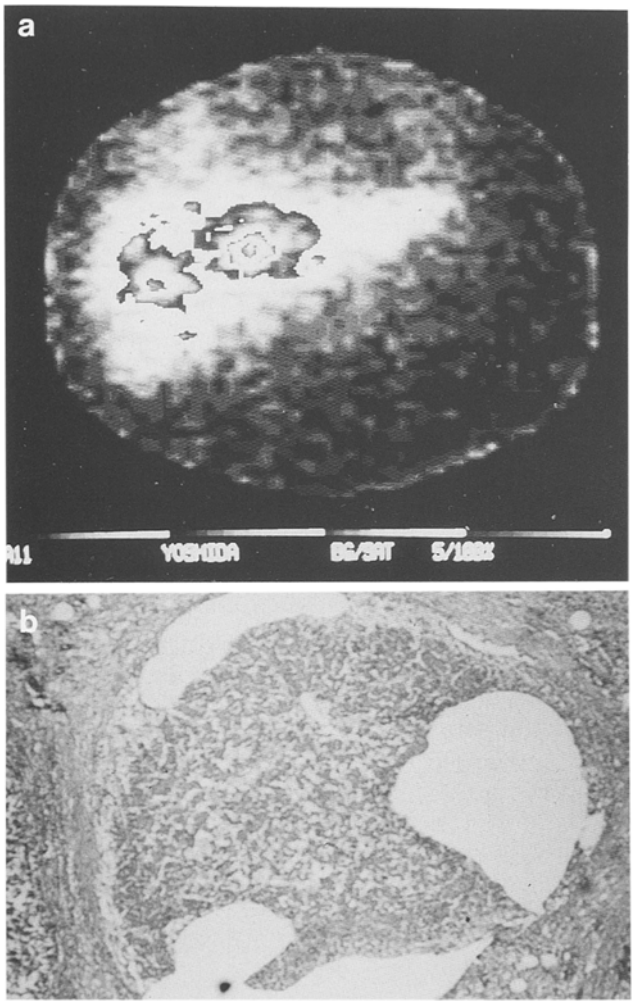


Fig. 4 a, b. Patient 8. **a** A hepatic scintiphotograph obtained 2 days following [^{131}I]-Lp injection reveals hot areas corresponding to the CT findings. **b** Histopathological specimens show coagulation necrosis of cancer cells

showed a 50%–90% reduction in serum AFP values within 1–5 months; this parameter remained at its lowest level for 3–4 weeks, after which it increased again in all cases. The prcentage of reduction in serum AFP levels was greater in group A than in group B. In the five patients who received additional injections, the values decreased again, even in one patient who had not responded to the first injection.

Survival

The median survival period was 12.6 months in group A and 7.9 months in group B. The survival of patients in group A, who had been treated with [^{131}I]-Lp, tended to be better than that of the Lp-TAE group (group B; $p = 0.119$; Fig. 7).

Side effects

The patients were carefully observed for possible side effects, but neither symptoms nor changes in the vital signs appeared during or immediately after the infusion of [^{131}I]-Lp. Within a few days after the infusion, liver-function tests showed few changes except for transient elevations in the serum glutamic oxalate transaminase (S-GOT) and/or glutamic pyruvic transaminase (S-GPT) levels in three cases that lasted for several days following the infusion of [^{131}I]-Lp. One patient with severe liver cirrhosis developed ascites and renal dysfunction at 7 days after the infusion of [^{131}I]-Lp.

Liver dysfunction was found in all cases, with three patients having S-GOT and S-GPT levels higher than 50 units. Serum bilirubin values also increased in 30% of the cases, but these increases were transient. Slight renal dysfunction was detected in three subjects, but it was transient and later disappeared. In both group A and group B, similar degrees of myelosuppression and liver as well as slight renal dysfunctions were detected.

Discussion

After intra-arterial injection of Lp, high accumulation of lipids in malignant liver lesions has been reported [7, 9, 12, 16]. On the basis of preliminary results [13, 15], internal radiation therapy with [^{131}I]-Lp was tested in patients with HCC. The present study is the first to demonstrate that the distribution of a therapeutic dose is similar to that of a tracer dose. To calculate accurately the doses absorbed in the tumor, in tumor-bearing liver tissue, and in the lungs, the doses from nearby tissues must be considered in addition to the "self" dose in the tumor. The interpolated S values for ^{131}I are used to calculate the self doses in the tumor and in tumor-bearing liver tissues. Although the safe levels of radiation for the liver and lungs in the case of internally delivered radionuclides are unknown, the tolerable dose might be about 2,600 MBq for the liver and about 1,500 MBq for the lung as based on MIRD dosimetry. Kobayashi et al. [6] found that HCC showed a good response to internal radiation, and the estimated tumor dose ranged between 40 and 190 Gy, with the regions adjacent to the HCC presumably receiving less than approximately 17 Gy. Grady [4] also reported that the delivery of 30 Gy internally and 42 Gy externally did not cause side effects.

Reasonable guidelines for a safe whole-organ dose would appear to be 30 Gy for the liver and 11 Gy for the lungs [6] as based on the lowest values reported by Ingold et al. [5] and Margolis and Phillips [10]. Thus, the safe level of activity would be 2,886 MBq in the whole liver, 1,739 MBq in half of the liver, and 592 MBq in the whole lung, and 1,110 MBq may be a safe infusion dose for use in an initial therapeutic trial. Patient 5, who had arterioportal shunts and showed a high L/NT ratio after TAIR, may not be considered to be an appropriate candidate for this internal radiation therapy combined with Lp-TAE, because the tumor dose would be below 29 Gy if the radiation dose to the lungs were kept below the safe level of 11 Gy. This patient would have suffered from radiation pneumonitis after receiving a tumor dose of 100 Gy. Therefore, combined treatment with [^{131}I]-Lp and Lp-TAE was given to patient 5.

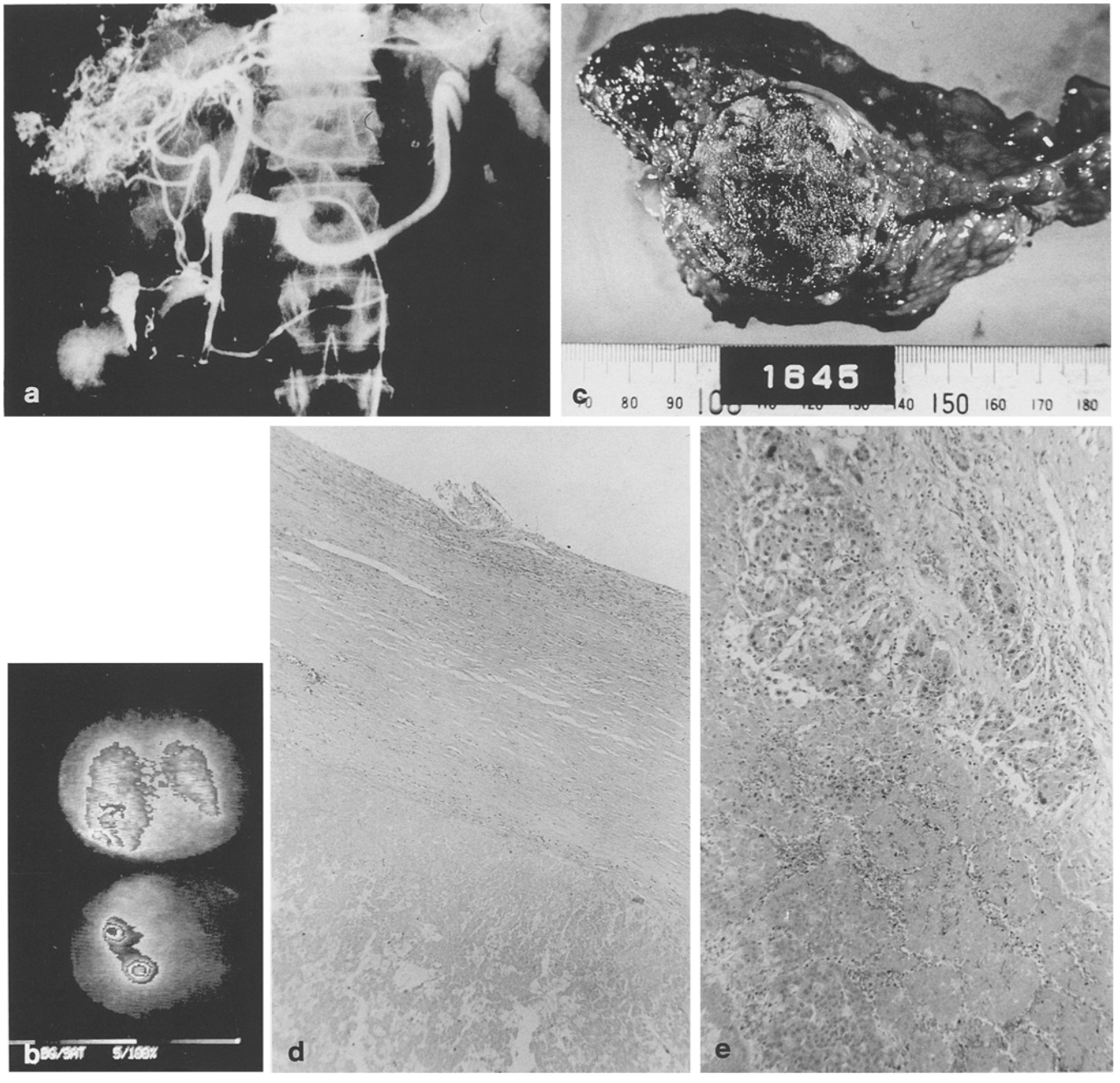


Fig. 5 a–e. Patient 5. **a** The early phase of right hepatic angiography clearly shows circumscribed nodules with an arterioportal shunt. **b** A hepatic scintiphotograph obtained 2 days following [^{131}I]-Lp injection combined with Lp-TAE discloses hot areas in the liver corresponding to the angiographic findings and a diffusely positive lung image. **c** Macroscopically, an autopsy specimen shows that all parts of the tumor have become necrotic expect for small subcapsular areas. Histologically, almost all parts of the tumor have become necrotic (**d**), and malignant cells survive in small subcapsular areas (**e**)

However, the efficacy of a single dose seems to be transient, and additional injections may be needed. Repetition raises the problem of late tolerance. In the present study, no major side effect was observed and tolerance was excellent as assessed clinically and biologically. The efficacy of the treatment was also confirmed on the basis of histological features highly suggestive of a radiotherapeutic effect, namely, the presence of coagulation necrosis and pleomorphism and the Lp-containing area but not in Lp-free areas (Fig. 4). These results are very similar to those obtained by Kobayashi et al. [6]. On the other hand, Bretagne and co-workers [3] reported that the therapeutic results of internal radiation therapy in patients with hepatic metastasis were disappointing because of the low uptake of Lp and the relatively high peritumoral concentration.

In conclusion, hepatic arterial injection of [^{131}I]-Lp suspended in lipiodol is an effective method for the treatment of HCC, particularly in cases of unresectable (huge or small) liver tumors. Tumor shrinkage usually occurs within a relatively short period. This is an important ap-

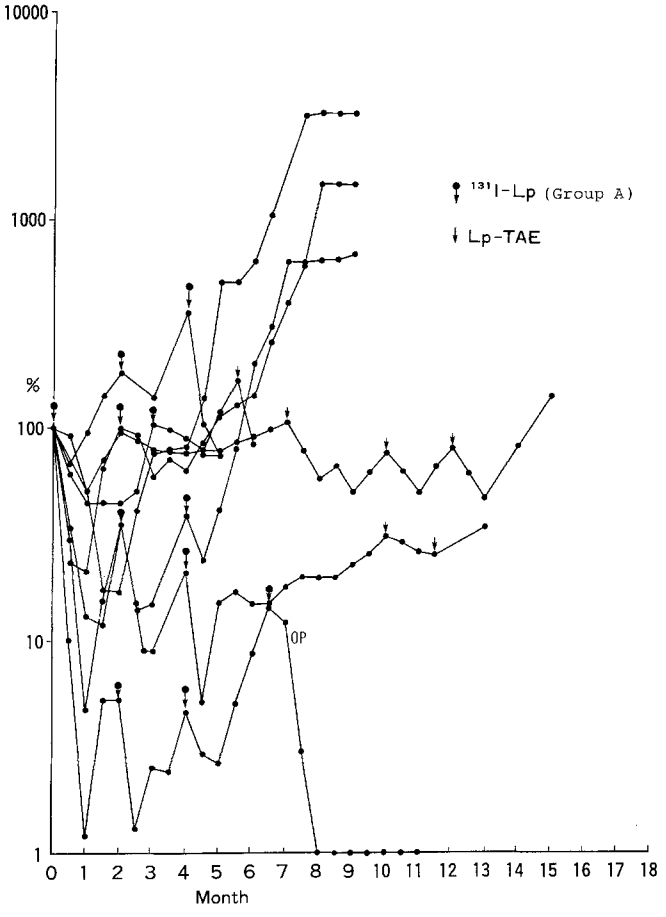


Fig. 6. Changes in serum AFP levels during the clinical course of HCC in patients receiving [^{131}I]-Lp as internal radiation therapy

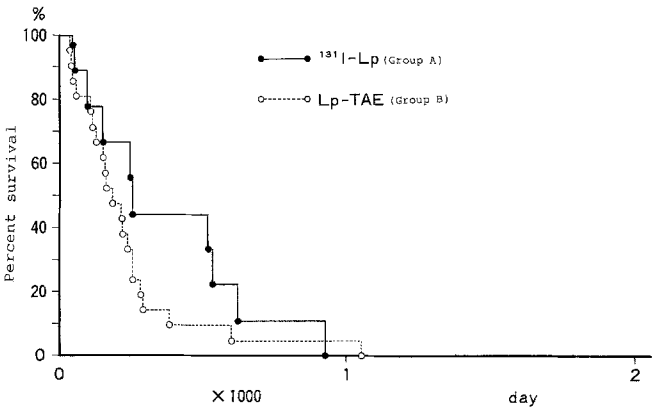


Fig. 7. Survival curves generated for patients with HCC following internal radiotherapy. The survival of group A (●) tended to be prolonged as compared with that of group B (○). Group A versus group B: $p = 0.119$ according to the generalized Wilcoxon test

proach for improving the therapeutic effects on primary liver cancer, and combination therapy with anticancer agents and internal radiation might be highly effective and useful in the treatment of HCC.

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References

1. Ariel IM (1965) Treatment of inoperable primary pancreatic and liver cancer by the intra-arterial administration of radioactive isotope Y^{90} radiating microspheres. Ann Surg 162: 267
2. Baba T, Kimura NT, Kanematsu T, Aoki K (1974) Regional perfusion and circulation-stop method for chemotherapy of cancer and metastasis. Jpn J Cancer Res 65: 285
3. Bretagne JF, Raoul JL, Bourguet P, Duvaufarrier R, Deugnier Y, Faroux R, Ram'ee A, Herry JY, Gastard J (1988) Hepatic artery injection of I-131-labeled lipiodol: II. Preliminary results of therapeutic use in patients with hepatocellular carcinoma and liver metastases. Radiology 168: 547
4. Grady ED (1979) Internal radiation therapy of hepatic cancer. Dis Colon Rectum 22: 371
5. Ingold JA, Reed GB, Kaplan HS, Bugshaw MA (1965) Radiation hepatitis. AJR 93: 200
6. Kobayashi H, Hidaka H, Kajiya Y, Tanoue P, Inoue H, Ikeda K, Nakajo M, Shinohara S (1986) Treatment of hepatocellular carcinoma by transarterial injection of anticancer agents in iodized oil suspension or of radioactive iodized oil solution. Acta Radiol [Diagn] (Stockh) 27: 139
7. Konno T, Maeda H, Iwai K, Tashiro S, Maki S, Morinaga T, Mochinaga M, Hiraoka T, Yokoyama I (1983) Effect of arterial administration of high-molecular weight anticancer agent, SMANCS, with lipid lymphographic agent on hepatoma: a preliminary report. Eur J Cancer Clin Oncol 19: 1053
8. Leichner PK, Klein JL, Garrison JB, Jenkins RE, Nickoloff EL, Ettinger DS, Order SE (1981) Dosimetry of ^{131}I-labeled anti-ferritin in hepatoma: a model for radioimmunoglobulin dosimetry. Int J Radiat Oncol Biol Phys 7: 323
9. Maki S, Konno T, Maeda H (1985) Image enhancement in computerized tomography for sensitive diagnosis of liver cancer and semiquantitation of tumor selective drug targeting with oily contrast medium. Cancer 56: 757
10. Margolis LW, Phillips TL (1969) Whole lung irradiation for metastatic tumors. Radiology 93: 1173
11. Nakajo M, Kobayashi H, Shimabukuro K, Shirono K, Sakata H, Taguchi M, Uchiyama N, Sonoda T, Shinohara S (1988) Biodistribution and in vivo kinetics of iodine-131 lipiodol infusion via the hepatic artery of patients with hepatic cancer. J Nucl Med 29: 1066
12. Nakamura K, Tashiro S, Uemura K (1979) Study on anticancer treatment with an oily anticancer drug injected into the ligated hepatic artery for liver cancer: preliminary report (in Japanese). Nichidoku Ihou 24: 675
13. Raoul JL, Bourguet P, Bretagne JF, Duvauferrier R, Coornaert S, Darnault P, Ram'ee A, Herry JY, Gastard J (1988) Hepatic artery injection of I-131-labeled lipiodol: I. Biodistribution study results in patients with hepatocellular carcinoma and liver metastases. Radiology 168: 541
14. Synder WS, Ford MR, Warner GG (1975) "S" absorbed dose per unit cumulated activity for selected radionuclides and organs. MIRD pamphlet 11. MIRD Committee, Society of Nuclear Medicine, New York
15. Yumoto Y, Jinno K, Tokuyama K, Moriwaki S, Ishimitsu T (1983) Positive delineation of hepatoma by transcatheter hepatic arterial infusion of ^{131}I-lipiodol ultra fluid. Jpn J Nucl Med 20: 1046
16. Yumoto Y, Jinno K, Tokuyama K, Araki Y, Ishimitsu T, Maeda H, Konno T, Iwamoto S, Ohnishi K, Okuda K (1985) Hepatocellular carcinoma detected by iodized oil. Radiology 154: 19
17. Ziessman HA, Thrall JH, Gyves JW, Ensminger WD, Niederhuber JE, Tuscan M, Walker S (1983) Quantitative hepatic arterial perfusion scintigraphy and starch microspheres in cancer chemotherapy. J Nucl Med 24: 871