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Effective cases of transcatheter arterioportal chemoembolization with high-dose iodized oil for hepatocellular carcinoma

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Abstract. By administering an excessive amount of iodized oil via the hepatic artery, anticancer drugs in the iodized oil flow into the portal vein through the arterioportal communication. This phenomenon permits chemotherapy against extracapsular infiltration by a hepatocellular carcinoma (HCC) nourished by the portal blood flow. From May 1983 through July 1992, 240 cases of HCC underwent transcatheter arterioportal chemoembolization (TAPCE) with more than 5 ml of iodized oil (mean, 15 ml) in our hospital. In all, 32 patients survived for more than 3 years, and the factors favoring the efficacy of TAPCE therapy were investigated. Doxorubicin (mean, 46 mg) was given to 31 patients and 20 mg mitomycin C was given to 1 patient. The patients included one Stage 1 case, 13 Stage 2 cases, 17 Stage 3 cases, and one Stage 4 case. The mean tumor size was 5.0 cm, and portal invasion was suggested in 8 cases by angiography. The tumors were divided into 5 types: 13 cases of the single nodular type (SN), 7 cases of the single nodular type with proliferation (SN-P), 3 cases of the multinodular fused type (MN-F), 5 cases of the multinodular type (MN), and 4 cases of the massive type. A complication of liver dysfunction was detected in 14 cases, and half of them were Child's class C. In all, 7 patients underwent hepatectomy and 6 received percutaneous ethanol injection after TAPCE. The treated area of TAPCE was classified as segmental, lobar, or total. Segmental and lobar administration of TAPCE yielded statistically effective results, and their tumor response rate was 86%. All of the MN-F and massive types showed a good tumor response. The incidence of intrahepatic distant metastasis was higher in the localized TAPCE group than in the total TAPCE group. Segmental and lobar TAPCE should be applied for localized infiltrating HCCs, even in cases associated with liver cirrhosis, but these methods have a limited capacity to prevent distant intrahepatic metastasis.

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Introduction

Hepatocellular carcinoma (HCC) has a poor prognosis due to its rapid infiltrating growth and complicating liver cirrhosis [3]. Operation for HCC is rarely indicated when HCCs are multiple or the liver function is poor. Transcatheter arterial embolization with iodized oil is now the preferred therapy for HCC, since Nakakuma et al. [8] first reported selective intratumoral retention of iodized oil injected via the hepatic artery. We reported that the peripheral portal branches became visible after administration of an excess of iodized oil via the hepatic artery into the HCC unless there was no arterioportal shunt angiographically [10]. This phenomenon led us to develop transcatheter arterioportal chemoembolization (TAPCE) for HCCs using more than 5 ml of iodized oil [11]. The factors favoring the efficacy of TAPCE therapy were investigated retrospectively in 32 patients who survived for more than 3 years.

Patients and methods

From May 1983 through July 1992, 240 cases of HCC underwent TAPCE with more than 5 ml of iodized oil (Lipiodol; Andre Guerbet, Aulnay-sous-bois, France) in our hospital. In all, 32 patients survived for more than 3 years after the TAPCE. The mean survival of these patients was 4.2 ± 0.9 years. A total of 18 patients were alive when this survey was made. The treated area of TAPCE was classified as segmental, lobar, or total. Segmental TAPCE was performed in 14 cases; lobar TAPCE, in 14 cases; and total TAPCE, in 4 cases (Table 1). Segmental TAPCE included subsegmental treatment with TAPCE, lobar TAPCE was limited to a left or a right lobe, and total TAPCE was defined as TAPCE with a treated area of more than one lobe.

Table 1 shows the characteristics of these 32 patients and the treated area of TAPCE. In all, 23 patients were men and 9 were

Table 1. Patients' characteristics and TAPCE-treated area

		Segmental	Lobar	Total
Stage:				
	1	1	0	0
	2	7	5	1
	3	6	9	2
	4	0	0	1
Portal vein invasion:				
	Vp_0	13	8	3
	Vp_1	1	6	0
	Vp_2	0	0	1
Tumor size (mean ± SD, cm)		5.2±2.6	4.8±2.1	5.2±2.3
Capsule:				
	Fc (+)	9	9	4
	Fc (–)	5	5	0
Liver cirrhosis:				
	Child A	8	8	2
	Child B	4	2	1
	Child C	2	4	1
Doxorubicin (mean ± SD, mg)		42.9±16.4	47.7±13.0[a]	51.3±11.8
Lidiodol (mean ± SD, ml)		13.7± 5.2	14.9± 5.0	16.5± 4.4
Totals		14	14	4

No statistically significant difference was found
[a] Dose of mitomycin C in one case is not included

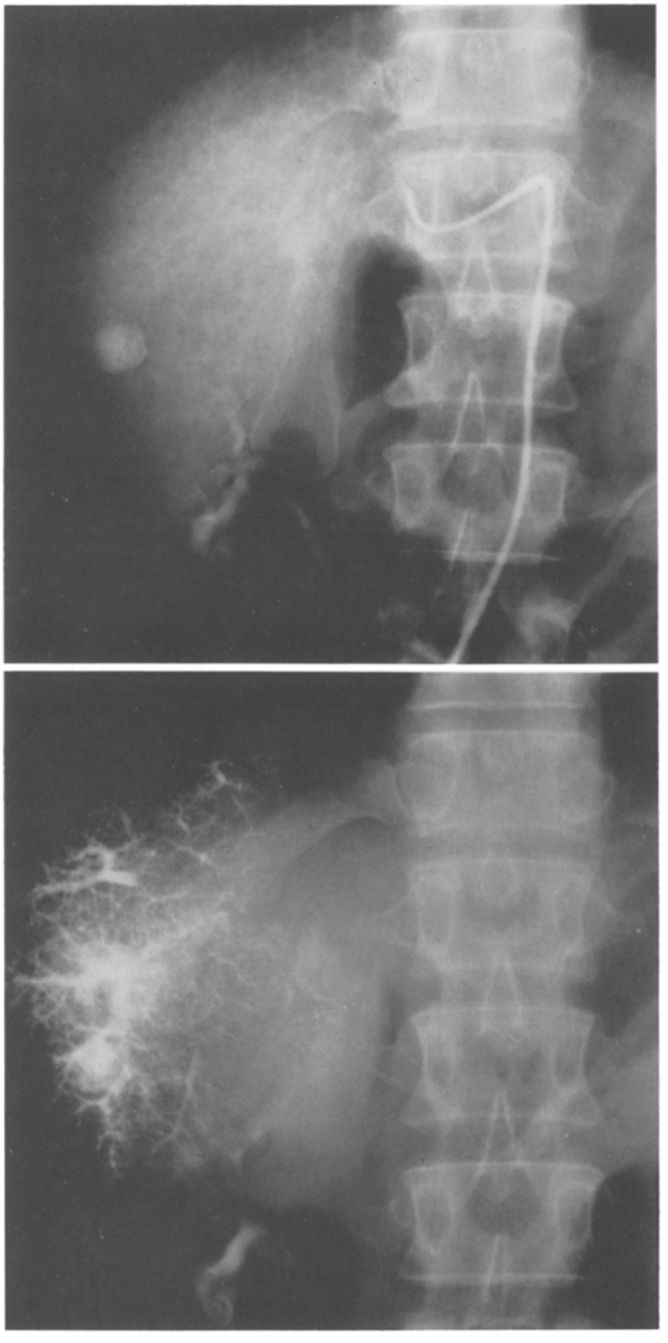

Fig. 1. Portal vein branches as visualized by iodized oil. (**A**) HCC recognized at S5 by hepatic angiography in a 40-year-old woman (**B**) Portal branches of the anterior segment as visualized after TAPCE

women, and they ranged in age from 36 to 80 years (mean, 58.3±10.7 years). The disease was stage 1 in 1 case, stage 2 in 13 cases, stage 3 in 17 cases, and stage 4 in 1 case. The mean tumor size was 5.0±2.3 cm (range, 1.5–11 cm), and portal invasion was suggested by angiography in 8 cases. Invasion of the third or more-distal portal branch was detected in 7 cases; invasion of the second branch, in 1 case; and no invasion, in 24 cases. Capsules of the tumors were diagnosed in 22 cases by ultrasound, CT examination, and/or angiography. A complication of liver cirrhosis was diagnosed in 18 cases as Child's class A and in 7 cases each as Child's class B and C.

Doxorubicin (Adriamycin; Farmitalia Carlo Erba, Milan) was given to 31 patients and mitomycin C (Kyowa Hakko Kogyo Co., Ltd., Tokyo) was given to 1 patient. These drugs were dissolved in a 50% diatrizoate solution and emulsified with 2–3 vols. of iodized oil. These emulsions were infused into the hepatic artery until the portal branches could be visualized fluoroscopically (Fig. 1). The mean doses of doxorubicin, mitomycin C, and iodized oil were 46±14.4 mg, 20 mg, and 14.6±5.0 ml, respectively. The delivered amount of anticancer drug and iodized oil became greater as the treated area increased in size.

No significant difference was found in the patients' characteristics among the treated areas. The tumors were divided into five types according to the General Rules for the Clinical and Pathological Study of Primary Liver Cancer [7]: the single nodular type (SN), the single nodular type with proliferation (SN-P), the multinodular fused type (MN-F), the multinodular type (MN), and the massive type. In all, 7 patients could undergo hepatectomy after TAPCE, and 6 received both TAPCE and percutaneous ethanol injection.

The therapeutic effect was evaluated on the basis of tumor necrosis seen in operative specimens and the tumor response rate as determined within 6 months after TAPCE in nonoperative cases. The response was assessed on the basis of a combination of the tumor size regression as determined by CT examination and the serum alpha-fetoprotein (AFP) level. A CR was defined as the disappearance of all detectable disease and/or normalization of the AFP value. A PR was defined as a 50% or greater reduction in the product of the two largest diameters of the tumor and/or a reduction in the AFP value to 50% or less of the initial level. When the reductions in both the tumor size and the AFP level were less than 50%, the disease was defined as NC. PD was defined as growth of the tumor or disappearance of the iodized oil that accumulated in the tumor via the TAPCE therapy and/or an increase in the AFP level.

Recurrence of the disease was divided into two types: local recurrence and intrahepatic distant metastasis. Intrahepatic distant metastasis was defined as the appearance of a new disease after TAPCE. Tumor recurrence was monitored by ultrasonography, CT, MRI, and angiography.

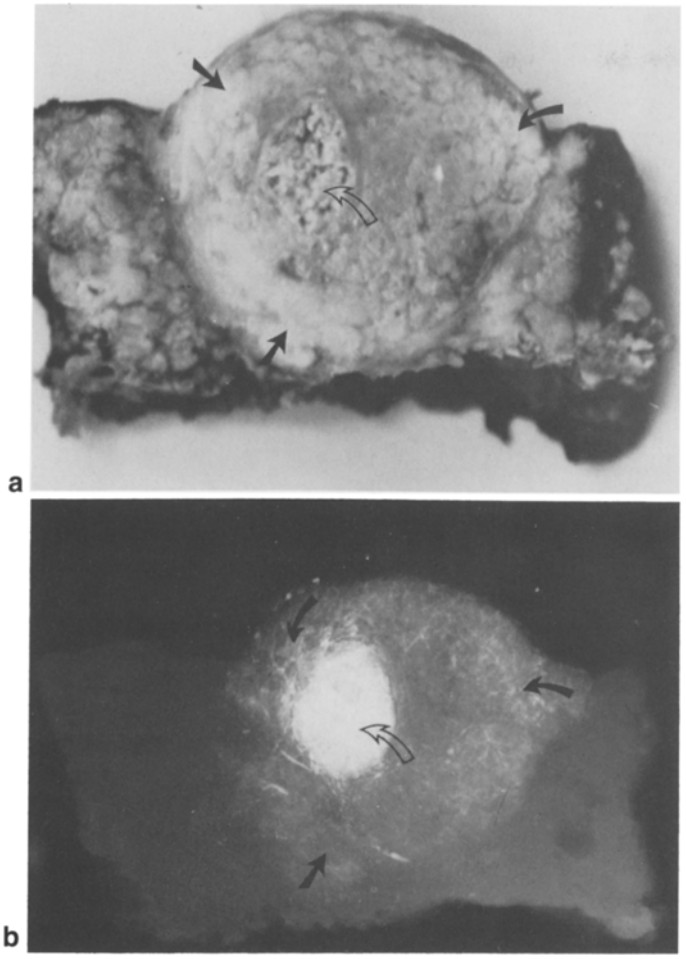

Fig. 2. (**A**) Necrosis of the liver parenchyma (*black arrow*) surrounding complete tumor necrosis (*white arrow*) as seen in an operative specimen from the patient shown in Fig. 1 (**B**) Soft X-ray film of this specimen reveals dense accumulation of iodized oil in the tumor (*white arrow*) and slightly opaque necrotic liver parenchyma (*black arrow*)

Results

All 14 segmental TAPCE cases and 10 of 14 lobar TAPCE cases showed a good tumor response of PR or better (Table 2). Segmental and lobar TAPCE produced statistically effective results, and their tumor response rate was 86%. On the other hand, three of four total TAPCE cases showed a poor tumor response. The mean delivered doses of anticancer drug and iodized oil did not differ between the effective cases and the poor response cases. Five of seven operative specimens after TAPCE showed complete necrosis of the tumor, and the other two showed more than 90% necrosis. One specimen of open biopsy also showed complete necrosis of the tumor. Four of the operative specimens had an accompanying necrosis of the noncancerous region adjacent to the tumor (Fig. 2).

The tumors were divided into 13 cases of SN, 7 cases of SN-P, 3 cases of MN-F, 5 cases of MN, and 4 cases of the massive type on the basis of the iodized oil accumulation as determined by CT and abdominal X-ray films obtained after angiography (Table 3). All of the MN-F and massive type cases showed a good tumor response. In all, 12 of the

Table 3. Patients' characteristics and tumor responses

		CR	PR	NC	PD
Stage:					
	1	0	1	0	0
	2	4	7	1	1
	3	6	7	1	3
	4	0	0	0	1
Portal vein invasioon:					
	Vp_0	7	12	2	3
	Vp_1	3	3	0	1
	Vp_2	0	0	0	1
Capsule:					
	Fc (+)	6	10	1	5
	Fc (–)	4	5	1	0
Tumor type:					
	SN	2	10	1	0
	SN-P	4	1	0	2
	MN-F	1	2	0	0
	MN	1	0	1	3
	Massive	2	2	0	0

No statistically significant difference was found

Table 2. Treated areas and tumor responses (n = 32)

		CR	PR	NC	PD	
All cases		10	15	2	5	
Treated area:						
	Segmental	6	8	0	0	
	Lobar	3	7	2	2	
	Total	1	0	0	3	P <0.01
Doxorubicin	(mean ± SD, mg)	44.5 ± 14.6	47.9 ± 14.7	35 ± 5	48 ± 11.7	NS
Lipiodol	(mean ± SD, ml)	14.2 ± 5.65	14.9 ± 4.28	12.8 ± 5.25	15 ± 4.47	NS
Tumor size	(mean ± SD, cm)	5.2 ± 2.2	5.0 ± 2.5	4.1 ± 0.6	5.2 ± 1.5	NS
Liver cirrhosis:						
	Child A	7	7	1	3	
	Child B	3	4	0	0	
	Child C	0	4	1	2	NS

NS, Not significant

Table 4. Treated area of TAE and tumor recurrence

		Segmental	Lobar	Total
Mean survival (years)		4.19±0.84	4.17±0.84	4.10±0.58
Recurrence:				
	Local	2/14	6/14	3/4
	Intrahepatic metastasis	6/14	7/14	1/4

No statistically significant difference was found

13 SN cases (92%) and 5 of the 7 SN-P cases (71%) also showed a good response. However, 4 of the 5 MN cases (80%) showed a poor tumor response. No correlation was found between the stage or portal vein infiltration and the tumor response. The mean tumor size and complicating liver cirrhosis also had no effect on the tumor response. Capsules diagnosed before TAPCE also failed to show any correlation with the tumor response.

Tumor recurrence was detected in 20 cases, an 11 of them were found as local recurrence of the primary tumor. Intrahepatic distant metastasis was found in 14 cases: in 46% of the localized TAPCE cases and in 25% of the total TAPCE cases (Table 4). Three of seven operated cases also showed intrahepatic distant metastasis. All of the recurrent patients underwent additional TAPCE and/or percutaneous ethanol injection.

No severe adverse reactions to TAPCE were observed in the present study, but atrophy of the liver parenchyma of the treated region was detected by CT in all of the good response cases.

Discussion

Transcatheter arterial embolization (TAE) without iodized oil is effective for the encapsulated type of HCC [2, 9]. However, the present study showed a good tumor response even for proliferative tumors such as the MN-F and massive types. Nonencapsulated HCCs have a high incidence of direct liver invasion, tumor microsatellites, and venous permeation [4]. These tumors have been reported to be resistant to conventional TAE [6, 16]. The infiltrating portion and nonencapsulated daughter nodules are nourished by both the portal vein and the hepatic artery [1, 15], and it is difficult to eradicate such nodules by TAE without using a high dose of iodized oil [6, 14]. Raoul et al. [13] reported that the best pharmacokinetic result in chemoembolization for HCC was achieved with an emulsion of 50 mg doxorubicin in 2.5 ml of ioxaglate and 10 ml of iodized oil with gelatin sponge. This emulsion shows dense intratumoral accumulation after injection via the hepatic artery, as we have also reported [11, 12].

Administration of antineoplastic drugs into both the hepatic artery and the portal vein is one method for treating the infiltrating portion of HCCs. The overflow of iodized oil from the hepatic artery into the portal vein through the arterioportal communication is the phenomenon that makes this treatment possible and effective [5, 10]. In the present study, nonencapsulated tumors showed the same good tumor response as did encapsulated tumors. Although all types of TAPCE showed good efficacy for infiltrating HCCs, the treated area of TAPCE affected the tumor response. Lobar TAPCE was less effective than segmental TAPCE, and total TAPCE gave the worst results.

Since antineoplastic materials flow into the normal liver parenchyma, noncancerous areas are also affected by antineoplastic drugs and the iodized oil, which acts as a microembolus. TAPCE shows a strong antitumor effect, but it also causes a strong adverse reaction of necrosis of the liver parenchyma around the tumor [12]. Localized application of TAPCE is necessary to avoid liver failure by sparing the intact liver parenchyma. The doses of anticancer drug and iodized oil per treated liver volume must be reduced for total TAPCE, which is the limitation of this method.

Although total TAPCE resulted in a low incidence of intrahepatic distant metastasis in the present study, it also produced a high incidence of local recurrence. No recurrent-free case was seen among our total TAPCE series. This was thought to be attributable to insufficient chemoembolization because of the reduced dose, which was insufficient for the volume of the main tumor.

On the other hand, localized TAPCE showed good efficacy against tumor recurrence. Especially, segmental TAPCE produced a good tumor response and a low incidence of local recurrence. Lobar TAPCE also yielded a satisfactory result, second to that produced by segmental TAPCE.

Even though complete suppression of the main tumor is successful by localized TAPCE, intrahepatic metastases in untreated areas remain alive. This is a limitation of localized TAPCE. Segmental and lobar TAPCE should be applied for localized infiltrating HCCs, even in cases associated with liver cirrhosis, but these methods have a limited capacity to prevent distant intrahepatic metastases.

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