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Clinical evaluation of intermittent arterial infusion chemotherapy with an implanted reservoir for hepatocellular carcinoma*

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Summary. A total of 45 patients with advanced hepatocellular carcinoma were treated at Osaka City University Hospital by intermittent arterial infusion chemotherapy with an implanted reservoir. The treatment consisted of intermittent infusion of doxorubicin (5–20 mg/body), mitomycin C (4–10 mg/body) or degradable starch microspheres (600–1200 mg/body) plus doxorubicin (30 mg/body). In all, 26% of the patients received this treatment for disease recurrence following transcatheter arterial embolization (TAE). Among 43 evaluable patients, 4 showed a complete remission (CR) and 16 showed a partial response (PR) on computed tomograms and angiograms. For all 45 patients, the 1-year survival value was 41% and the 2-year value was 14%. Of the 20 patients who showed a CR or PR, 77% survived for 1 year and 29% survived for 2 years. Tumor regression showed a close relationship with the duration of survival. Intermittent arterial infusion with an implanted reservoir caused the least adverse reactions and seems to be appropriate for use in patients with advanced tumor extension or stenosis of the hepatic artery caused by repeated TAE.

Introduction

Since approximately 80% of patients with hepatocellular carcinoma (HCC) in Japan also have liver cirrhosis, hepatic resection is often impossible [6]. Various efforts have recently been made to treat HCC with modalities such as percutaneous transhepatic ethanol injection (PEIT) and temporary or consecutive hepatic arterial infusion (HAI) of anticancer agents [8, 13, 14]. However, systemic administration of anticancer agents alone has been associated with a partial response rate of 10%–24% and seems to have little effect on survival [10]. Arterial infusion of anticancer agents by Seldinger's technique has also been disappointing [12]; indeed, in our past series of HAI of doxorubicin (DR) and mitomycin C (MMC), we obtained a response rate of only 14%.

To date, intermittent arterial infusion of anticancer agents with an implanted reservoir (IAIR) has been used mainly for the treatment of metastatic liver cancer, and it has achieved high response rates [1, 2, 7]. The present report describes our preliminary study of IAIR of DR and MMC or DR with degradable starch microspheres (DSM) for the treatment of unresectable HCC and discusses the criteria used for the selection of patients for application of this therapy.

Patients and methods

Patients' characteristics. A total of 45 patients with unresectable HCC were treated by IAIR between March 1984 and October 1990 at Osaka City University Hospital. The study population included 41 men and 4 women aged 31–71 years (mean, 58 years). The diagnosis was made on the basis of the alpha-fetoprotein (AFP) test and imaging procedures such as computed tomography (CT), ultrasonography (US), angiography, and/or transhepatic tumor biopsy. All of these patients had associated liver cirrhosis. The tumor extension was measured from angiograms or CT films, and the patients were divided into the following four groups in accordance with the classifications established by the Liver Cancer Study Group of Japan [5]: E_1, the tumor occupied less than 20% of the whole liver; E_2, more than 20% but less than 40%; E_3, 40%–60%; and E_4, more than 60%. The degree of extension into the portal vein was classified as follows: Vp_0, the absence of tumor casts in the portal vein (14 patients); Vp_1, existing tumor thrombus within a subsegmental portal vein (6 subjects); Vp_2, existing tumor thrombus within a segmental portal vein (8 patients); and Vp_3, total occlusion of the portal trunk (10 subjects).

The 45 patients were divided into 2 groups on the basis of the first treatment: group 1 consisted of 19 patients with very advanced tumor extension and/or accompanying advanced liver cirrhosis at the first diagnosis, and chemotherapy was the only treatment used, since TAE and/or resection were precluded; group 2 consisted of 26 patients who were first treated by TAE and subsequently underwent IAIR due to recurrence of the tumor and/or occlusion of the hepatic artery due to repeated TAE (Table 1).

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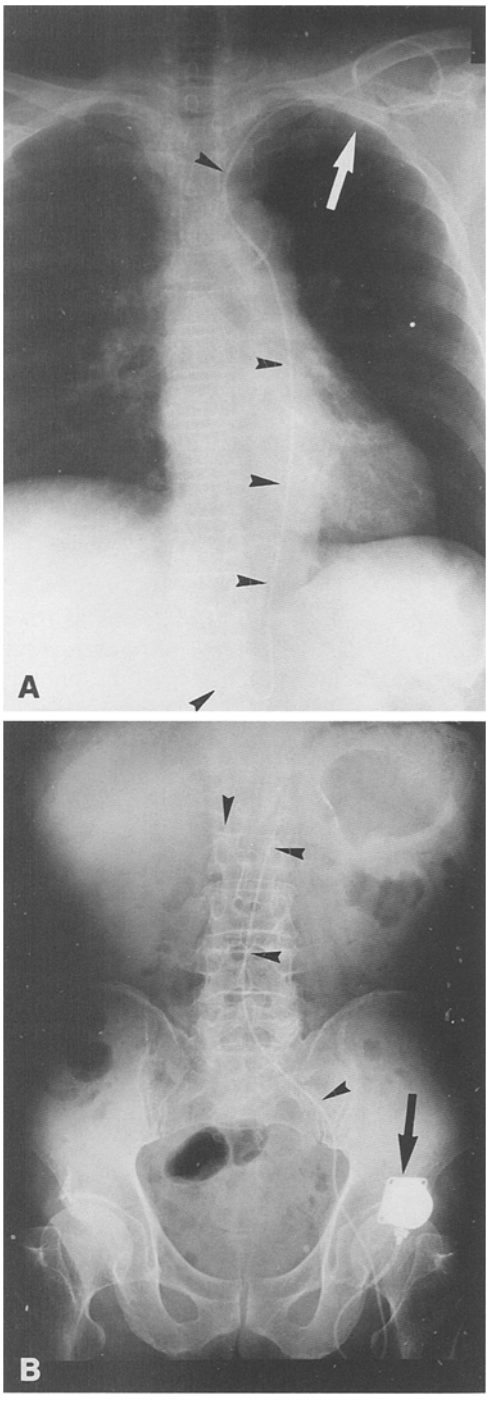

Fig. 1 A, B. Radiographs obtained after implantation of the reservoir and embolization with steel coils in the gastroduodenal artery through **A** subclavicular and **B** inguinal approaches. The *arrowheads* indicate the indwelling tube in the hepatic artery, and the *arrow* shows the subcutaneously implanted reservoir

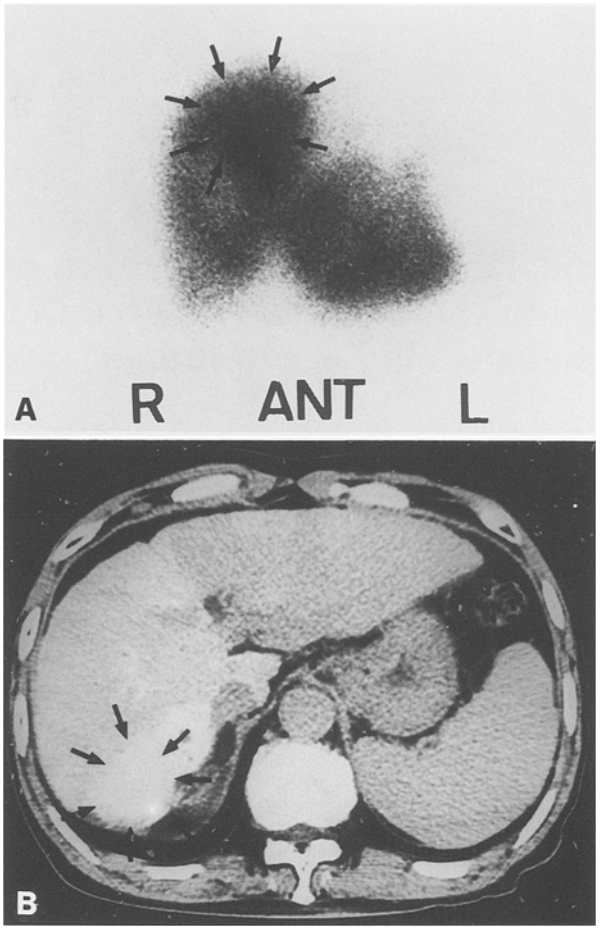

Fig. 2. A A CT image of injected contrast medium from the reservoir shows a strongly enhanced tumor (*arrows*). **B** A scintigram obtained after the injection of 3 mCi ^{99m}Tc-MAA indicates that the radioisotope remains within the liver, accumulating strongly therein (*arrows*)

Table 1. Patients' characteristics

Variable	Total ($n = 45$)	Group 1 ($n = 19$)	Group 2 ($n = 26$)
Age (years)[a]	58 ± 8	57 ± 11	59 ± 6
Sex (M/F)	42/ 3	18/ 1	24/ 2
Vp factor (Vp–/Vp+)[b]	16/29	11/ 8	11/15
E factor ($E_{1,2}/E_{3,4}$)[c]	26/19	10/ 9	16/10
Drug (DR and MMC/DR with DSM)	19/26	6/13	13/13

Patients in group 1 were treated with chemotherapy alone; group 2 patients were treated with IAIR after recurrence of the tumor or hepatic occlusion due to repeated TAE

[a] Data represent mean values ± SD

[b] Degree of tumor extension to the portal vein

[c] Percentage of occupancy of the entire liver by the tumor

Surgical procedure. By means of an inguinal (or subclavicular) incision, a femoral (or subclavian) artery was exposed and secured with tape. The lateral femoral circumflex (or lateral thoracic) artery was cannulated with a 5-F heparin-coated Anthron tube (Toray Medical; Tokyo, Japan), the tip of which was inserted selectively into the common or proper hepatic artery. The opposite end was connected to a reservoir, which was then implanted subcutaneously in the ipsilateral thigh (or subclavicular region) according to the method described by Arai and associates [1].

To ensure that more of the drugs to be injected would reach the liver and to avoid perfusion of the injected anticancer agents into the stomach and/or duodenum, the trunk of the gastroduodenal artery was embolized with steel coils in all cases (Fig. 1). Thereafter, digital subtraction angiography (DSA) and scintigraphy with the injection of 3 mCi macroaggregated albumin labeled with 99 m technetium (Tc-MAA) were performed and the distribution of the injected agents was observed (Fig. 2).

Table 2. Response to treatment

	CR	PR	NR	PD	Response rate (CR+PR)	
Total ($n = 43$	4	16	11	12	20/43 (47%)	
Group 1 ($n = 19$)	3	9	2	5	12/19 (63%)	$P < 0.001$
Group 2 ($n = 24$)	1	7	9	7	8/24 (33%)	
DR with DSM ($n = 26$)	4	9	6	7	13/26 (50%)	NS
DR and MMC ($n = 17$)	0	7	5	5	7/17 (41%)	

NS, Not significant

Table 3. Survival of patients

	Median survival (months)		Survival value (%)	
			1-year	2-year
Total ($n = 45$)	7		41	14
CR+PR ($n = 20$)	18	$P < 0.001$	77	29
NC+PD ($n = 23$)	2		7	0
Group 1 ($n = 19$)	10	NS	45	0
Group 2 ($n = 24$)	6		36	18

NS, Not significant

Treatment. The therapy consisted of intermittent infusion of DR at 5–20 mg/body and MMC at 4–10 mg/body in 19 patients and of the infusion of DSM at 600–1200 mg/body and DR at 30 mg/body in 26 subjects. These treatments were carried out in the outpatient clinic; DR and MMC were infused once weekly over a period of about 10 min, and infusion of DR and DSM was performed every 2 weeks by puncture of the reservoir with a 21-gauge Huber needle. One course of chemotherapy consisted of four infusions, after which the results were evaluated for the first time. Therefore, the infusions were continued once weekly or every 2 weeks until toxicity appeared or the catheter failed. The median number of infusions given was 6.8 (range, 2–19), and the dose of DSM ranged from 1500 to 7790 mg (mean, 3237 mg).

The tumor response was evaluated by CT and/or DSA performed every 1 or 2 months. The interval between treatment courses depended on the degree of myelosuppression or stomatitis experienced by the patient during or after the previous course. A complete remission (CR) was defined as the complete disappearance of all evidence of the existing tumor(s) as determined by the imaging techniques. A partial response (PR) was defined as a reduction of 50% or more in the size of the main tumor as indicated by a combination of the two largest tumor masses shown on the CT image and the absence of growth in other, smaller lesions.

Results

Response to treatment

The data on the response to treatment are presented in Table 2. Among 43 evaluable patients who received at least 1 course of chemotherapy, the overall response rate was 47%. We observed a CR in 4 patients, a PR in 16 subjects, and no change (NC) in 11 patients, whereas 12 patients showed progressive disease (PD). All four complete responders were patients treated by infusion of DR and DSM, although the rates of response to infusion of DR and MMC and to infusion of DR and DSM showed almost no difference (41% and 50%, respectively). During the course of treatment, the CT patterns of the lesions showed various changes from an enhanced mass to a lack of enhancement or from a large mass to a small one and angiography indicated the disappearance of tumor staining (Fig. 3).

The response rates obtained in group 1 and group 2 were 63% and 33%, respectively ($P < 0.001$, generalized Wilcoxon test). Among the 19 patients in group 1 who were treated with chemotherapy alone, we observed 3 CRs, 9 PRs, 2 NCs, and 5 PDs. Similarly, among the 24 patients in group 2 who underwent treatment after recurrence of the tumor or occlusion of the hepatic artery due to repeated TAE, we noted 1 CR, 7 PRs, 9 NCs, and 7 PDs (Figs. 4, 5).

Survival

The survival of patients was measured from the 1st day of IAIR by the Kaplan-Meier method. The 45 patients attained a 1-year survival value of 41% and a 2-year value of 14%. The overall median survival was 7 months from the initiation of IAIR. The duration of survival showed a close relationship with the tumor regression; the median survival of the 20 patients who achieved a CR or PR was 18 months, whereas that of the 23 patients who showed NC or PD was 2 months ($P < 0.001$, generalized Wilcoxon test). Moreover, whereas the 20 patients who achieved a CR or PR showed 1- and 2-year survival values of 77% and 29%, 22 of the 23 NC or PD patients died within 1 year due to gastrointestinal bleeding or hepatic insufficiency caused by the cancer (Table 3).

Of the 19 evaluable patients in group 1, 7 lived for more than 1 year from the beginning of this treatment; the longest survival period was 23 months, and 5 patients remain alive at the time of this writing. Of the 24 evaluable patients in group 2 who were treated by IAIR instead of further TAE, lived for more than 1 year after the first TAE; 94% survived for 1 year and 38%, for 2 years. From the beginning of IAIR, 6 patients lived for more than 1 year. No significant difference in survival as measured from the beginning of IAIR was found between the patients in group 1 and those in group 2; the patients in group 1 showed a median survival of 10 months vs 6 months for the patients in group 2 (Table 3).

Side effects

The side effects and complications associated with IAIR included myelosuppression in four patients, functional disturbance of the kidney in one subject, and headache in one patient. All of the patients experienced transient gastrointestinal discomfort, nausea, vomiting, and abdominal pain immediately after treatment.

Discussion

Chemotherapy of HCC, including systemic and arterial locoregional administration of anticancer agents, has to date yielded rather unsatisfactory results in terms of response and survival [10, 12]. Okuda et al. [8] employed Gelfoam embolization and/or chemoembolization with

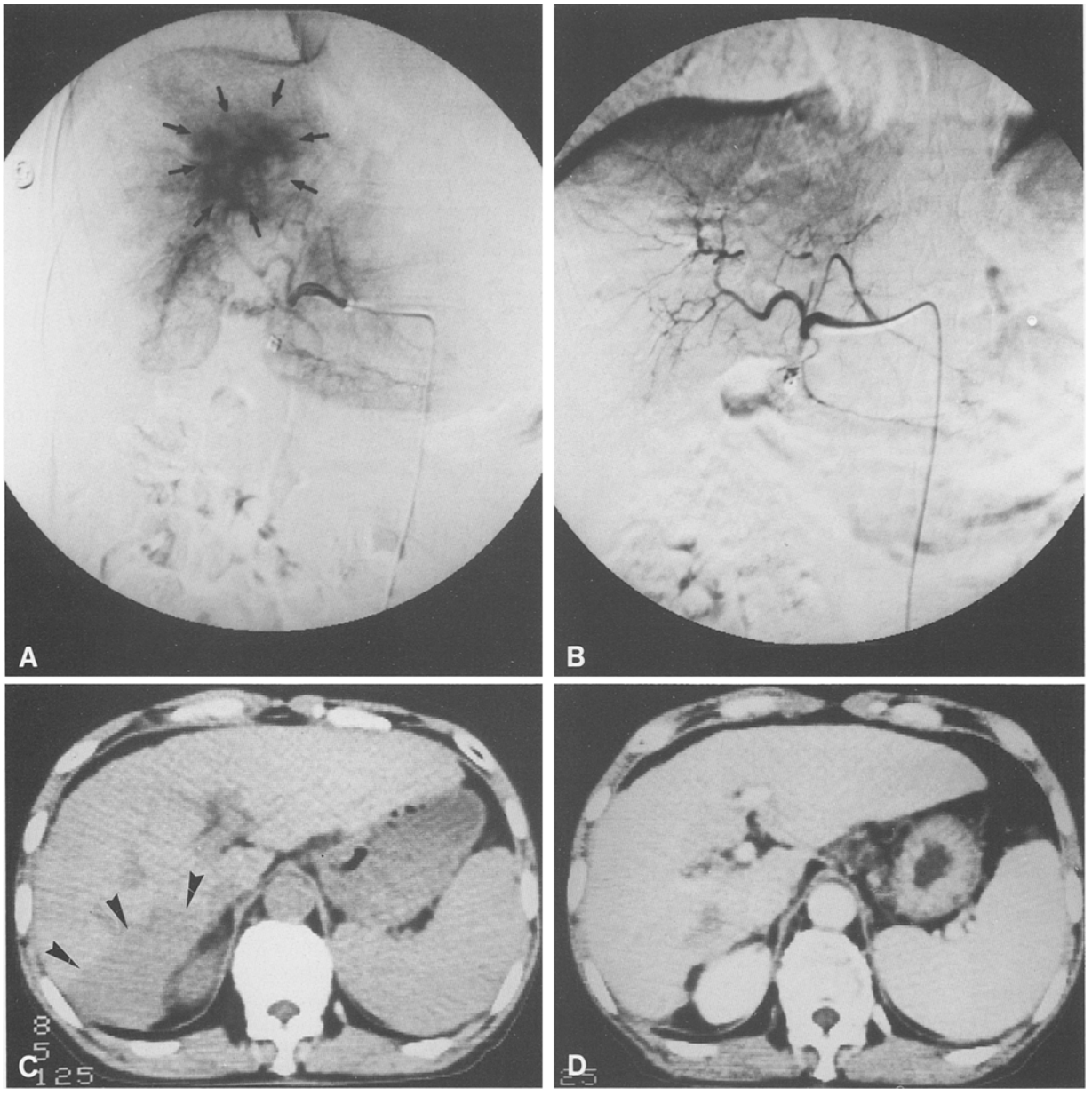

Fig. 3 A – D. DSA performed **A** prior to and **B** 4 weeks after treatment shows that the tumor stain in the right lobe of the liver has disappeared. CT images obtained **C** prior to and **D** after treatment show that the low-density area (*arrowheads*) in the right lobe of the liver has disappeared after 6 weeks of treatment

MMC microcapsules and reported survival of 9.5 months for the embolized patients vs 3.7 months for subjects treated with arterial chemotherapy and 2.5 months for those given systemic chemotherapy. It seems that TAE achieves the best outcome in palliative therapy of unresectable HCC, and it has thus gained widespread acceptance, especially in Japan. However, sometimes HCC cannot be treated with TAE because the patients have contraindicating advanced tumor extension or superimposed liver cirrhosis [14]. Hirai et al. [4] obtained relatively good results following HAI treatment using a high dose of MFC or AFC (mitomycin C, 5-fluorouracil, and cytosine arabinoside or doxorubicin); for 191 patients, the 1-year survival value was 22%, and 8.9% survived for 2 years.

IAIR was first reported in 1981 [3], and it has been used mainly for metastatic liver tumors [2, 7]. IAIR has almost never been applied to HCC. However, in view of both the 4 CRs and 11 PRs achieved among our 45 patients with advanced HCC and the 1- and 2-year survival values of 41% and 14%, IAIR also seemed to result in improved response rates and survival as compared with those previously reported for HAI. In addition, in our series of patients, we found a close relationship between the response (tumor regression) and survival, regardless of the degree of tumor extension. That is, the 20 patients who showed a CR or PR lived significantly longer than did the 23 patients who showed NC or PD (18 months vs 2 months; $P < 0.001$; generalized Wilcoxon test), indicat-

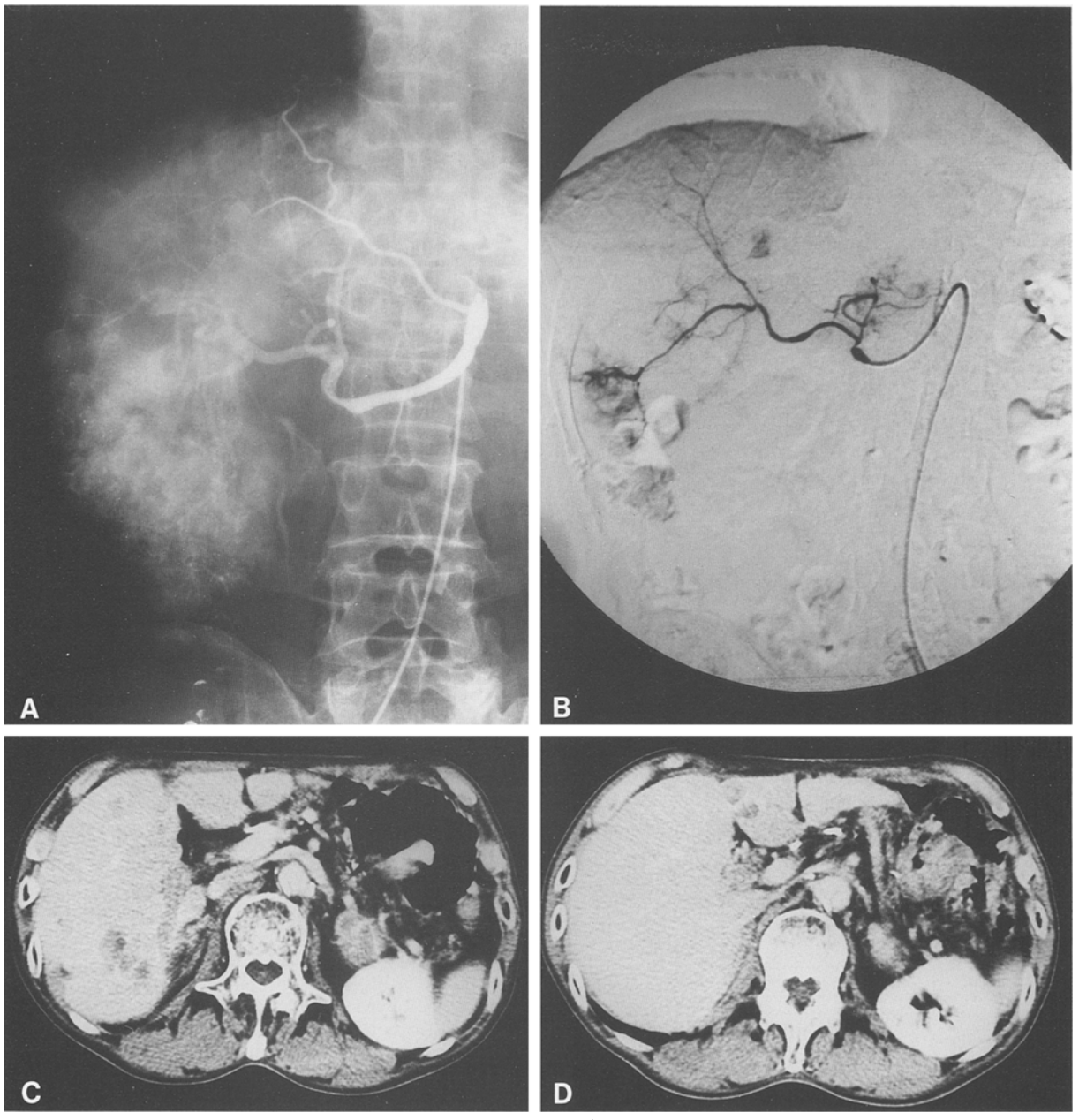

Fig. 4 A – D. Group 1 patient. The multiple tumor stains visible in the right lobe of the liver on the hepatic angiogram obtained before treatment (**A**) have become smaller after 5 weeks of treatment (**B**). CT images obtained **C** prior to and **D** after treatment show shrinkage of the low-density area

ing that the sensitivity of the tumor to the drugs contributes to survival. The mean number of chemotherapy courses given was 7.3 in the 4 CR patients, 8.4 in the 16 PR subjects, and 6.8 in the 23 patients who showed NC or PD, indicating the significance of repeated administration of anticancer agents.

In 1983, Yamada et al. [14] reported the survival of patients after TAE treatment of HCC: 51% at 1 year and 28% at 2 years as a result of repeated TAE. However, patients with occlusion of the hepatic artery or tumor extension could not be controlled by TAE, and the prognosis for such patients remains poor. In the present study, the patients in group 2 were treated with IAIR after TAE, and IAIR prolonged their survival. The 24 patients in group 2 lived significantly longer than did the patients who were treated in our hospital with TAE only in over the last 12 years (94% vs 79% for 1-year survival; $P < 0.1$; chi-square test). Although the median survival of groups 1 and 2 did not significantly differ (10 months vs 6 months), 22 of the 26 group 2 patients lived for more than 1 year after the first TAE, showing a median survival of 26 months. From the beginning of IAIR, 6 patients lived for more than 1 year, showing prolonged survival due to the combination of this treatment modality with TAE.

To improve the therapeutic effect of HAI on HCC, several administration regimens and methods have been attempted, including continuous infusion, balloon-occluded infusion, infusion with administration of angioten-

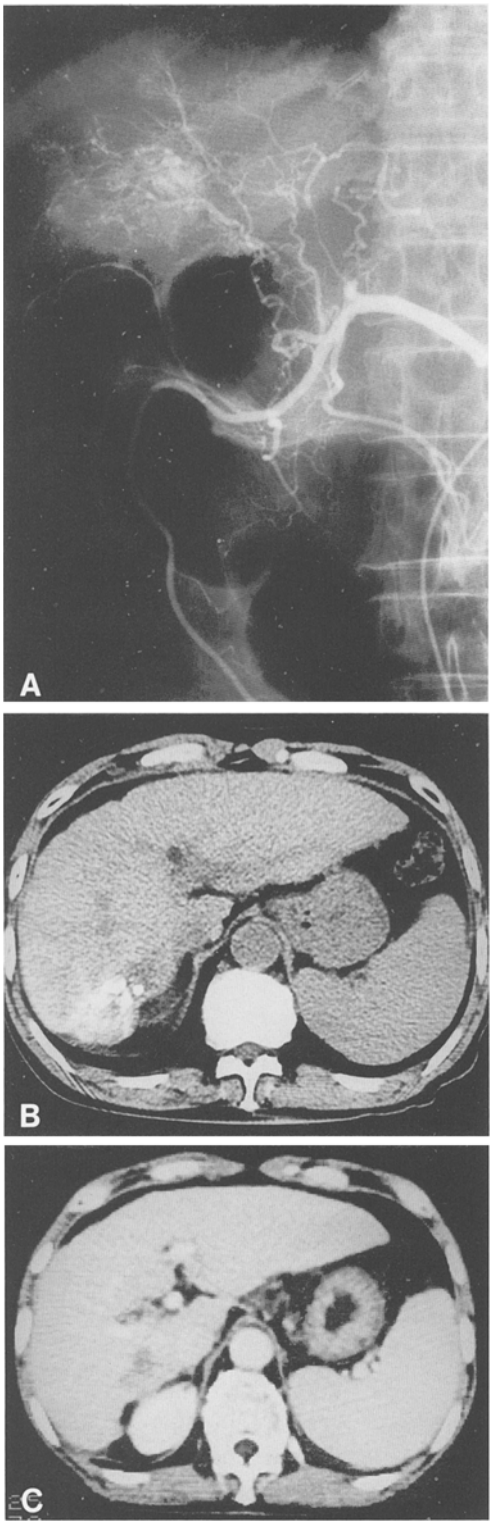

Fig. 5 A – C. Group 2 patient. A hepatic angiogram obtained prior to implantation of the reservoir shows that occlusion of the proper hepatic artery with multiple collaterals due to repeated TAE (**A**). The tumor, which is seen to retain iodized oil on the CT image obtained prior to treatment (**B**), has disappeared after 3 months of treatment (**C**)

sin II, SMANCS, MMC microcapsules, and DSM [9, 11, 13]. DSM was developed to increase the delivery of anticancer agents to the tumor by transient blockage of the blood flow. We used DR and MMC or DR and DSM as anticancer agents, and although the response rates did not differ significantly, all four complete responders were patients who had been treated with DR and DSM.

In summary, intermittent arterial infusion chemotherapy with an implanted reservoir (IAIR) achieved good results in patients with HCC, with few side effects being encountered. The advantages of IAIR over HAI are clear: the easy performance of frequent arterial infusion of anticancer agents, the feasibility of treatment in outpatient clinics, and the avoidance of infections.

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