

## Phase I/II study of the lipiodolization using DDP-H (CDDP powder; IA-call<sup>®</sup>) in patients with unresectable hepatocellular carcinoma

Yamashita, Yo-ichi

Department of Surgery, Hiroshima Red Cross Hospital, Atomic Bomb Survivors Hospital

Taketomi, Akinobu

Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University

Itoh, Shinji

Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University

Harimoto, Norifumi

Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University

他

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## **Phase I/II study of the lipiodolization using DDP-H (CDDP powder; IA-call®) in patients with unresectable hepatocellular carcinoma**

Yo-ichi Yamashita, M.D., Ph.D.<sup>1), 2)</sup>,      Akinobu Taketomi, M.D., Ph.D.<sup>1)</sup>,  
Shinji Itoh, M.D., Ph.D.<sup>1)</sup>,      Norifumi Harimoto M.D., Ph.D.<sup>1)</sup>,  
Kazutoyo Morita, M.D.<sup>1)</sup>,      Takasuke Fukuhara, M.D.<sup>1)</sup>,  
Shigeru Ueda, M.D.<sup>1)</sup>,      Kensaku Sanefuji, M.D.<sup>1)</sup>,  
Keishi Sugimachi, M.D., Ph. D.<sup>1)</sup>,      Tsuyoshi Tajima, M.D., Ph.D.<sup>3)</sup>,  
Yoshihiko Maehara, M.D., Ph.D., F.A.C.S.<sup>1)</sup>

<sup>1)</sup> Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi , Higashi-ku, Fukuoka 812-8582, Japan

<sup>2)</sup> Department of Surgery, Hiroshima Red Cross Hospital and Atomic Bomb Survivors Hospital, Senda-machi 1-9-6, Naka-ku, Hiroshima 730-8619, JAPAN

<sup>3)</sup> Department of Clinical Radiology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, 812-8582, Japan

Corresponding Author:

Yo-ichi Yamashita, M.D., Ph.D.

Department of Surgery,

Hiroshima Red Cross Hospital and Atomic Bomb Survivors Hospital,

Senda-machi 1-9-6, Naka-ku, Hiroshima 730-8619, JAPAN

Tel: +81-82-241-3111

Fax: +81-82-246-0676

E-mail: yamashi@surg2.med.kyushu-u.ac.jp

## Abstract

**Purpose:** Lipiodol Ultra-Fluid (Lipiodol ®), an oily contrast medium, is selectively retained in hepatocellular carcinoma (HCC) through hepatic arterial infusion. DDP-H (IA-call®) developed as a CDDP powder, and may be a possible chemotherapeutic agent with lipiodol. We carried out a phase I/II trial of the lipiodolization using DPP-H in patients with unresectable HCC.

**Methods:** Phase I and pharmacokinetic study: The dose-limiting toxicity (DLT), the maximum tolerance dose (MTD), and the recommended dose (RD) were determined using a modified Fibonacci scheme. The concentration-time profile of total platinum in plasma was analyzed. Phase II study: Thirty-five patients with unresectable HCC received with lipiodolization using DDP-H under RD, and the efficacy and safety were assessed.

**Results:** DLT was grade 3 vomiting at 40 mg/m<sup>2</sup>. Therefore, MTD and RD were 35 mg/m<sup>2</sup>. The peak of total platinum in plasma was over 1.0  $\mu$  g/ml at 40 mg/m<sup>2</sup> at 30 minutes after infusion. Of the 35 patients, 16 (45.7%) demonstrated a complete responses (CR), and 4 (11.4 %) demonstrated partial responses (PR) with an additional 9 patients (25.7 %) having stable diseases (SD), as assessed by RECIST. Grade 3 thrombocytopenia was found in 1 patient (2.9%), grade 2 hyperbilirubinemia was found in 2 patients (5.7%), and grade 2 vomiting was found in 4 patients (11.4%).

**Conclusion:** Lipiodolization using DDP-H at 35 mg/m<sup>2</sup> is effective and well-tolerated in patients with unresectable HCC.

**Key words:** Hepatocellular carcinoma • lipiodolization • DDP-H (CDDP powder; IA-call®) • phase I/II study • Pharmacokinetics

## INTRODUCTION

Lipiodol Ultra-Fluid (Lipiodol®, Laboratoire Guerbet, Aulnay-sous-Bois, France), an oily contrast medium, comes from the ethyl ester found in the fatty acid of poppyseed oil and has been used for hysterosalpingography and lymphography (1), and has been found to be selectively retained in hepatocellular carcinoma (HCC) when injected intra-arterially (2). Our colleagues have reported that intra-arterial injection of doxorubicin suspended in lipiodol is more effective than intra-arterial injection of doxorubicin alone for VX2 carcinoma inoculated into rabbit hindlimb, and also that Lipiodol Ultra-Fluid has the potential to be applied as a carrier of anticancer drugs (3). The term “lipiodolization”, which has been previously reported by our colleagues (4), refers to the administration of chemotherapeutic agents suspended in this oily contrast medium and given through feeder arteries. Lipiodolization using doxorubicin or epirubicin is thus a selective cancer chemotherapy now widely used in Japan, that provides effective treatment for unresectable HCC (2, 4, 5).

Cisplatin (cis-diaminedichloroplatinum; CDDP) is one of the most effective drugs in the treatment of malignancies, and excellent anti-cancer effects and prolongation of survival using CDDP with lipiodol via hepatic artery for the patients with unresectable HCC have recently been reported (6, 7). To overcome the incompatibilities of water-soluble CDDP with oily lipiodol, H<sub>2</sub>O was evaporated and NaCl was excluded with some tedious procedures (8).

DDP-H (CDDP-powder; IA-call®, Nipponkayaku, Japan) suitable for the preparation of high-concentration aqueous solutions has been developed for the intra-arterial chemotherapeutic agents for HCC. Recently, a phase II study of this new drug via hepatic arterial infusion was reported (9). Good clinical results such as an overall response rate 33.8% and a 1-year survival rate of 67.5% were reported, but substantial toxicity such as grade 3/4 anorexia 22.5% and grade 3/4 thrombocytopenia 25% were reported.

To reduce the toxicities and to increase the anti-tumor activities of DDP-H, we have newly developed lipiodolization using DDP-H for patients with unresectable HCC. In the phase I study, the dose-limiting toxicity (DLT), the maximum tolerance dose

(MTD), and the recommended dose (RD) were determined using a modified Fibonacci scheme. At the same time, the concentration-time profile of total platinum in plasma was analyzed. Then, in the phase II study, 35 patients with unresectable HCC were received with lipiodolization using DDP-H under RD, and clinical efficacies and toxicities were evaluated.

## PATIENTS AND METHODS

### Eligibility

HCC patients were considered eligible for the study if they possessed all the following characteristics: unresectable HCC confirmed histologically or clinically diagnostic imaging such as computed tomography (CT); measurable lesions confined in the liver without extra-hepatic metastasis, and in principle, no thrombosis of the portal trunk, a prominent A-V shunt, or a prominent A-P shunt; no lingering effects of previous therapy (in principle, a 2-week interval was established for 5-fluorouracil (5-FU) drugs and biological response modifiers, and a 4-week interval for other anticancer agents and radiation therapy); performance status of Eastern cooperative Oncology Group of 0-2; Child-Pugh classification A or B; maintenance of adequate bone marrow, kidney, and cardiac functions, and meeting the following clinical laboratory test criteria (white blood cell counts  $\geq 3000/\text{mm}^3$ , platelet count  $\geq 5 \times 10^4/\text{mm}^3$ , hemoglobin concentration  $\geq 9.5$  g/dL, Serum creatinine value  $\leq$  the upper limit of normal range, blood urea nitrogen  $\leq 25$  mg/dL, and prothrombin activity  $\geq 50\%$ ); age  $\geq 20$ ; and predictive survival time  $\geq 3$  months. HCC patients were considered ineligible if they possessed one of the following characteristics: serious complications other than chronic hepatitis or liver cirrhosis;  $> 1$  active cancer; a history of serious hypersensitivity to drugs; pregnant or possibly pregnant women; breastfeeding; and any other reason that, as per the judgment of the attending physician, made the patient an unsuitable candidate for this study.

Written informed consent for participation in the study was obtained from each patient, and the protocol of this phase I/II study was approved by the ethics committee of the hospital.

### DDP-H with Lipiodol Ultra-Fluid

In this study, the fine-powder formulation of DDP-H was suspended directly into Lipiodol Ultra-Fluid. To observe the structure of DDP-H in Lipiodol Ultra-Fluid, DDP-H 100 mg, lipiodol 5 ml, and physiologic saline 5 ml were suspended in the 20-ml

syringe by pumping 20 times. The miscible suspension was observed using a digital microscope (VH-800, KEYENCE Inc., Osaka).

### **Method of administration and dose escalation of DPP-H**

The DPP-H-Lipiodol Ultra-Fluid suspension was administered via intra-arterial infusion using a catheter that was inserted into a nutrient artery of the HCC under X-ray fluoroscopy. The volume of the Lipiodol Ultra-Fluid was determined according to the tumor size (e.g., 2.0 ml of lipiodol for HCC with 3-cm diameter, 5.0 ml for 5 cm, 7.5 ml for over 8 cm). Additional trans-arterial embolization using gelatin sponge (songel®) was carried out, for example, in a very large tumor over 10 cm in diameter, in those with a high-flow feeding artery, and in those with an A-P shunt.

The starting dose of DPP-H was 25 mg/m<sup>2</sup>. Dose escalation was carried out according to a modified Fibonacci scheme. At least three patients were to be entered at each dose level. If no DLT was noted after the third patient, then the DPP-H dose was escalated to the next dose level. If one of the three patients experienced a DLT at any level, an additional three patients were entered at that level. If two of the initial three patients or two of the six patients experienced a DLT, this dose was considered to be an MTD dose +1. MTD and RD are the next lower level.

All toxicity was graded according to the National Cancer Institute Common Toxicity criteria version 3.0. DLT was defined as any of the following: (a) grade 3 or 4 drug-related non-hematologic toxicity such as nausea, vomiting, or diarrhea in the absence of optimal preventive and supportive measures: (b) grade 4 drug-related hematologic toxicity.

### **Pharmacokinetics**

Blood samples for the pharmacokinetic evaluation of total platinum concentrations in plasma were drawn in heparinized tubes at times 0.5, 2, 24, and 96 hours after lipiodolization using DPP-H. Total platinum was analyzed by using an aliquot of unfiltered plasma. Samples were stored at -20°C until analyzed, usually for a time period of a few weeks.

**Response and toxicity evaluation**

Patients were treated at the RD in Phase II. Patients were enrolled between January and December 2007. Tumor response was assessed using Response Evaluation Criteria in Solid tumors (RECIST) (10), with computer tomography scans at baseline and 2 weeks after treatment. Responses were confirmed by computed tomography at least 8 weeks later. We regarded lipiodol accumulation lesions in tumors as being not viable or necrosis, and these lesions were excluded from the tumor size. Also in this phase II study, all toxicity was graded according to the National Cancer Institute Common Toxicity criteria version 3.0. The primary end point of interest was the overall response rate, and the secondary endpoint was the safety and tolerability of the treatment.



## RESULTS

### DDP-H in Lipiodol Ultra-Fluid

The structure of DDP-H in Lipiodol Ultra-Fluid was demonstrated using a digital microscope (x 500 magnification), as shown in Fig. 1. The DDP-H attached to the surface of the Lipiodol Ultra-Fluid and gradually dissolved into the surrounding physiologic saline.

### DLT, MTD, and RD

The results of Phase I study to determine the MTD are summarized in Fig. 2. Dose escalation of DPP-H was performed from 25 mg/m<sup>2</sup> with a 5 mg/m<sup>2</sup> increase, respectively. Three patients each was treated at the dose levels 25 mg/m<sup>2</sup>, 30 mg/m<sup>2</sup>, 35mg/m<sup>2</sup>, and 40 mg/m<sup>2</sup>, and 11 patients were enrolled this Phase I study as a result. Lipiodolization using DDP-H at 35 mg/m<sup>2</sup> could be infused without DLT. However, grade 3 vomiting was reported in 2 of 2 patients at 40 mg/m<sup>2</sup>. Therefore, DLT was vomiting at 40 mg/m<sup>2</sup>, MTD and RD were 35 mg/m<sup>2</sup>. Grade 3 or 4 drug-related hematologic toxicity did not occur.

### Pharmacokinetics of DPP-H

The concentration-time profiles of total platinum in plasma are described in Fig. 3. To analyze the effects of Lipiodol Ultra-Fluid to the pharmacokinetics of DPP-H, the samples were collected from patients with intra-arterial infusion of DPP-H at 25 mg/m<sup>2</sup> without Lipiodol Ultra-Fluid (9). The plasma concentrations of DPP-H with Lipiodol Ultra-Fluid were decreased by half or more compared with DPP-H without Lipiodol Ultra-Fluid. The peak of plasma concentrations of total platinum of DPP-H at 40 mg/m<sup>2</sup> reached over 1  $\mu$  g/ml at 0.5 hours from infusion.

### Patients' characteristics

From January to December 2007, 35 patients were enrolled in the phase II study. Lipiodolization using DDP-H at RD as 35 mg/m<sup>2</sup> was applied in this phase II study. Patient characteristics are summarized in Table 1. Continuous variables are

expressed as means  $\pm$  S.E. In all, 31 patients (88.6%) had recurrent HCC. Eight patients (22.9%) were positive for HBs-Ag, and 29 (82.9%) were positive for HCV-Ab. Twenty nine patients (82.9%) had Child-pugh A liver function, and 6 (22.9%) had Child-pugh B liver function. The mean tumor diameter was  $2.7 \pm 1.9$  cm, and the mean tumor number was  $3.6 \pm 1.8$ . The tumor-node-metastasis (TNM) stages according to the latest edition of the International Union against cancer (UICC) (11) I:II:III:IVA were 6:17:10:2.

## Response

The responses of all 35 patients against lipiodolization using DDP-H/lipiodol are summarized in Table 2. Sixteen patients (45.7%) achieved complete responses (CR), and 4 (11.4%) achieved partial responses (PR); therefore, the overall response rate was 57.1%. In addition, 9 patients (25.7%) had stable disease (SD); therefore, the disease control rate was 82.9%. Six patients (17.1%) showed sign of progressive disease (PD).

The CT imagings of the CR case are shown in Fig 4. Recurrent HCC was demonstrated as an early-enhancing tumor at Segment 8 based on Couinaud's classification (12) (left figure). Two weeks after lipiodolization using DDP-H, CT imaging revealed a complete accumulation of Lipiodol Ultra-Fluid in this recurrent HCC, and there was no enhancing lesion (middle figure). This Lipiodol Ultra-Fluid accumulation was maintained in the CT imaging 8 weeks after lipiodolization using DDP-H (right figure).

In contrast, the CT imagings of the PD case are shown in Fig. 5. Recurrent HCC was demonstrated as a slightly enhancing tumor at the Speigel lobe (left figure). Two weeks after lipiodolization using DDP-H, CT imaging revealed only partial accumulation of Lipiodol Ultra-Fluid in this recurrent HCC, and there were a small enhancing lesion (middle figure). The size of this enhancing lesion on recurrent HCC increased on CT imaging 8 weeks after lipiodolization using DDP-H (right figure).

## Toxicities

Toxicities were evaluated in all patients and are summarized in Table 3.

According to the hematologic toxicity, grade 3 thrombocytopenia developed in 1 patient (2.9%), and grade 2 hyperbilirubinemia developed in 2 patients (5.7%). Non-hematologic toxicity was more significant, but severe toxicity such as grade 3 or 4 was not seen in this phase II study. Grade 2 vomiting developed in 4 patients (11.4%), and grade 1 vomiting developed in 8 patients (22.9%). Grade 1 appetite loss, grade 1 diarrhea, and grade 1 constipation developed in 1 patient (2.9%), respectively.

## DISCUSSION

Although the mechanism by which Lipiodol Ultra-Fluid selectively accumulates in HCC is not well understood, the aim of using Lipiodol Ultra-Fluid in the present study was to achieve a targeting delivery system resulting in long-lasting drug accumulation in HCC and slow release, with accompanying augmented anticancer effects and reduced systemic side effects. Microscope observation of DDP-H in Lipiodol Ultra-Fluid with physiologic saline demonstrated that the DDP-H attached to the surface of the Lipiodol Ultra-Fluid, and then gradually dissolved into the surrounding physiologic saline. This finding suggested the possibility that DDP-H with Lipiodol Ultra-Fluid could demonstrate better anti-tumor effects and improved safety. The particles of DDP-H with Lipiodol Ultra-Fluid, however, were unequal, with many large particles more than 10  $\mu$  m in diameter. It is an important challenge to control the size distribution of DDP-H particles with Lipiodol Ultra-Fluid.

In 1984, our colleagues found that water-soluble anti-cancer agents, including almost all of the currently available drugs for treating cancers that do not dissolve in oil, could be effectively mixed with lipiodol when a water-soluble contrast medium (Urographin®) was intermediate (13). At present, anti-cancer drug/lipiodol suspensions are made by employing various homemade mixtures under many tedious procedures. In addition, CDDP is poorly soluble in water, and the solubility in water is only 1 mg/ml. In lipiodolization, an anti-cancer drug/lipiodol suspension is infused in a “one-shot style” from a nutrient hepatic artery. Therefore, the maximum total amount of suspension was considered to be approximately 10 ml or less. To overcome the low solubility of CDDP in water, CDDP powder was made by evaporation of H<sub>2</sub>O and exclusion of NaCl, as described previously (6), and DDP-H was developed. Takaki have recently demonstrated a suitable blending method for lipiodol-cisplatin powder as a suspension-emulsion that is a suspension of lipiodol and cisplatin powder emulsified with contrast medium by evaluation of sustained release and accumulation nature (14).

We conducted a phase I study for the purpose of determining DLT, MTD, and RD of lipiodolization using DPP-H. The RD in hepatic arterial infusion of DPP-H for

advanced HCC was determined at a dose of  $65 \text{ mg/m}^2$  and at a rate of  $2.8 \text{ mg/min}$  (9). However, we should newly determine the MTD and RD of lipiodolization using DPP-H, as we infused DPP-H with Lipiodol Ultra-Fluid in a “one-shot style”. Dose escalation from  $25 \text{ mg/m}^2$  was carried out according to a modified Fibonacci scheme, and our phase I study determined that DLT was vomiting at  $40 \text{ mg/m}^2$ , MTD and RD were  $35 \text{ mg/m}^2$ . DLT (vomiting) occurred within 1 hour after infusion; therefore we will routinely use 5-HT<sub>3</sub> receptor antagonist before lipiodolization in the next phase II study.

In our pharmacokinetic study, the peak plasma concentrations of total platinum of DPP-H at a dose of  $40 \text{ mg/m}^2$  reached over  $1 \mu \text{ g/ml}$  after 0.5 hours from infusion. Hirata has discussed that the limit of accompanying severe adverse effects during CDDP infusions is  $1 \mu \text{ g/ml}$  (15); therefore the occurrence of DLT at  $40 \text{ mg/m}^2$  was related to the excess over  $1 \mu \text{ g/ml}$  of total platinum concentrations in plasma. In another CDDP-Lipiodol Ultra-Fluid clinical studies, Shibata reported the results of a pharmacokinetic study of CDDP from hepatic arterial infusion (8). They reported that the peak plasma total platinum concentrations occur 5 to 60 minutes after the infusion, and reach  $2.78 \pm 0.98 \mu \text{ g/ml}$  when 40-100 mg CDDP is infused. They also reported that the concentrations of total platinum gradually fell after 60 minutes, but maintained relatively high concentrations as  $1.26 \pm 0.74 \mu \text{ g/ml}$  after 7 days. Compared to their reports, the peak of plasma total platinum concentrations in the present study was low, and speedily fell down to  $0.5 \mu \text{ g/ml}$  or below at 4 days after infusion. These results could indicate better and more long-lasting local accumulations of DDP-H on HCC in our study, but it will be essential to analyze the total platinum concentrations in tissue by our methods compared to their results. Fujiyama have similarly reported a low peak of plasma concentrations of total platinum as  $10 \text{ ng/ml}$  or below in their newly developed SM-11355/lipiodol complex study (17).

DDP-H was originally developed to be used in hepatic arterial infusion. Yoshikawa have reported relatively mediocre clinical results from a phase II study of the hepatic arterial infusion of DDP-H without Lipiodol Ultra-Fluid (9). Their response rate was 33.8%, and severe adverse effects (grade 3 or more) sometimes occurred including anorexia in 22.5%, vomiting in 6.3%, thrombocytopenia in 25%, neutropenia in 13%, and elevation of serum aspartate aminotransferase in 32.5%. Our

good clinical results (response rate; 57.1%) and low toxicity (grade 3 thrombocytopenia; 2.9%) might have been brought about by the good targeting delivery system of Lipiodol Ultra-Fluid on HCC.

Some reports have demonstrated the good clinical effects of lipiodolization using CDDP against advanced HCC (6-8, 16, 17) and the superiority of the clinical results of lipiodolization using CDDP compared to those of doxorubicin (7, 18, 19). Maeda have reported an overall response rate of lipiodolization using homemade CDDP powder of 59.4% (142/239 cases), and Okusaka have reported that the CR rate of lipiodolization using SM-11355 is 56.3% (9/16 cases) (6,17). Despite the differences in evaluation rules, our results for a phase II study for which the overall response rate was 57.1% (20/35 cases) and the CR rate was 45.7% (16/35 cases) should be comparable to the above good results. Almost all CR cases in the above studies including ours, HCC did not disappear but had complete accumulation of lipiodol on tumors. On the other hand, Okusaka have reported a relatively high rate of toxicity for which the grade 3 toxicities included neutropenia (19%), total bilirubin elevation (19%), aspartate aminotransferase (AST) elevation (44%), and alanine aminotransferase (ALT) elevation (19%) (17). But in our phase II study with respect to severe toxicity, there was only 1 case with grade 3 thrombocytopenia (2.9%). One of the possible causes of our improved clinical results of lipiodolization using DDP-H compared to historical results of lipiodolization using CDDP would depend on the better and longer lasting local accumulations of DDP-H on HCC. But this hypothesis has no evidence and should be confirmed by analyzing the total platinum concentrations in HCC.

There are some technical differences in how lipiodolization is carried out, especially regarding inserting into the nutrient hepatic artery, and these differences may lead to differences in clinical results. Another possible causes of our improved clinical results of lipiodolization using DDP-H compared to historical results of lipiodolization using CDDP would depend on the superior technique in inserting into the nutrient hepatic artery. Therefore, further study is necessary to compare the clinical results of lipiodolization using DDP-H or doxorubicin/epirubicin in our own institution. In conclusion, lipiodolization using DDP-H at 35 mg/m<sup>2</sup> is effective and well tolerated in patients with unresectable HCC.

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## FIGURE LEGENDS

Figure 1. The structure of DDP-H in Lipiodol Ultra-Fluid was demonstrated using a digital microscope (x 500 magnification). The DDP-H was attached to the surface of the Lipiodol Ultra-Fluid, and gradually dissolved into surrounding physiologic saline.

Figure 2. The results of a Phase I study to determine the MTD. Dose escalation of DPP-H was performed from 25 mg/m<sup>2</sup> with a 5 mg/m<sup>2</sup> increase, respectively. Grade 3 vomiting was reported in 2 of 2 patients at 40 mg/m<sup>2</sup>. Therefore, DLT was vomiting at 40 mg/m<sup>2</sup>, MTD and RD were 35 mg/m<sup>2</sup>.

Figure 3. The concentration-time profiles of total platinum in plasma were described. The plasma concentrations of DPP-H with Lipiodol Ultra-Fluid were decreased by half or more compared with DPP-H without Lipiodol Ultra-Fluid. The peak plasma concentrations of total platinum of DPP-H at 40 mg/m<sup>2</sup> reached over 1 μg/ml 0.5 hours after infusion.

Figure 4. The CT imagings of the CR case were demonstrated. Recurrent HCC was demonstrated as early-enhancing tumor at Segment 8 (left figure). Two weeks after lipiodolization using DDP-H, CT imaging revealed a complete accumulation of Lipiodol Ultra-Fluid to in this recurrent HCC, and there were no enhancing lesions (middle figure). This Lipiodol Ultra-Fluid accumulation was maintained at CT imaging 8 weeks after lipiodolization using DDP-H (right figure).

Figure 5. The CT imagings of the PD case were demonstrated. Recurrent HCC was demonstrated as a slightly enhancing tumor at the Speigel lobe (left figure). Two weeks after lipiodolization using DDP-H, CT imaging revealed only a partial accumulation of Lipiodol Ultra-Fluid in this recurrent HCC, and there were a small enhancing lesion (middle figure). The size of this enhancing lesion on recurrent HCC increased on CT imaging 8 weeks after lipiodolization using DDP-H (right figure).

Figure 1

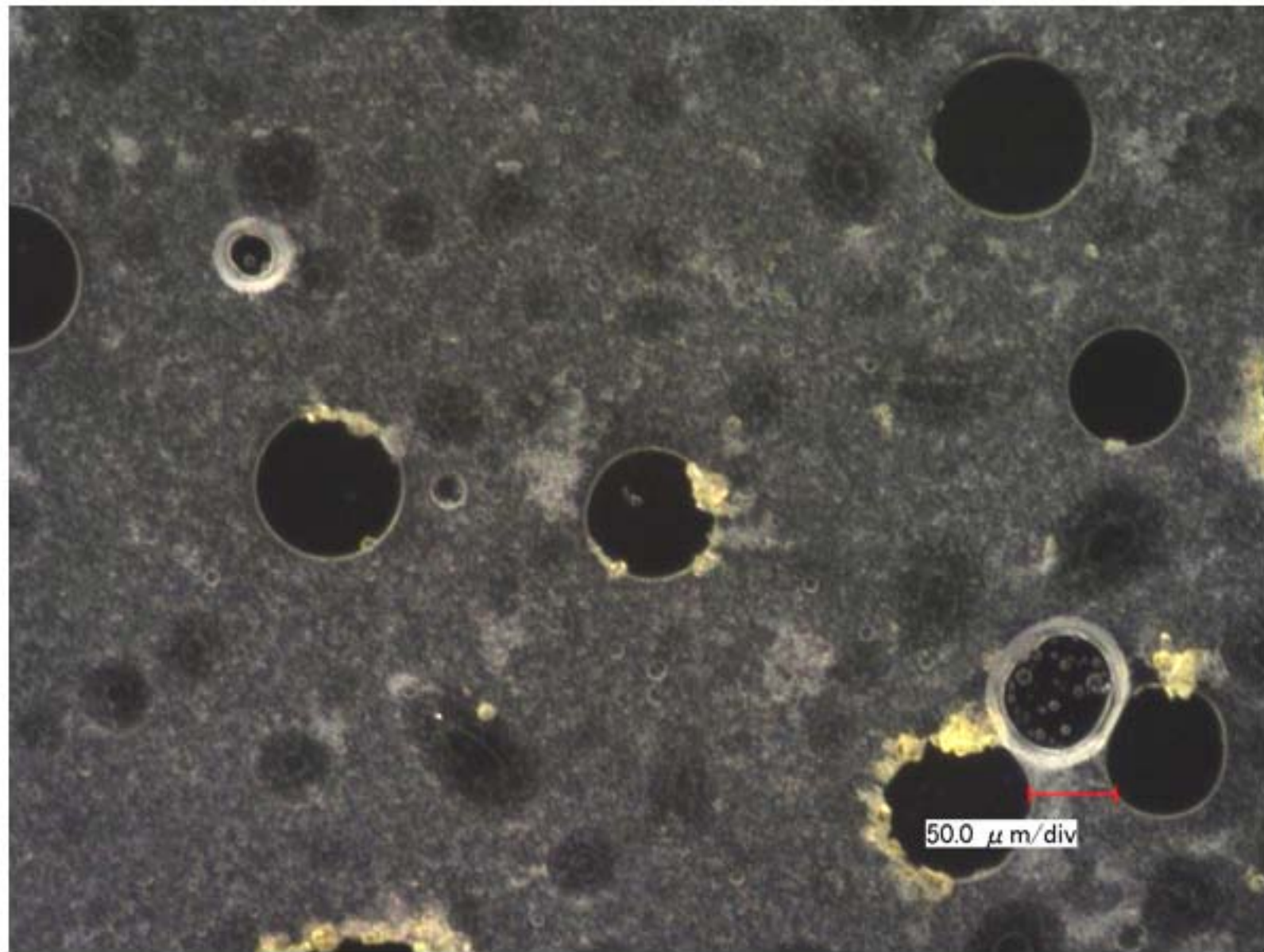


Figure 2

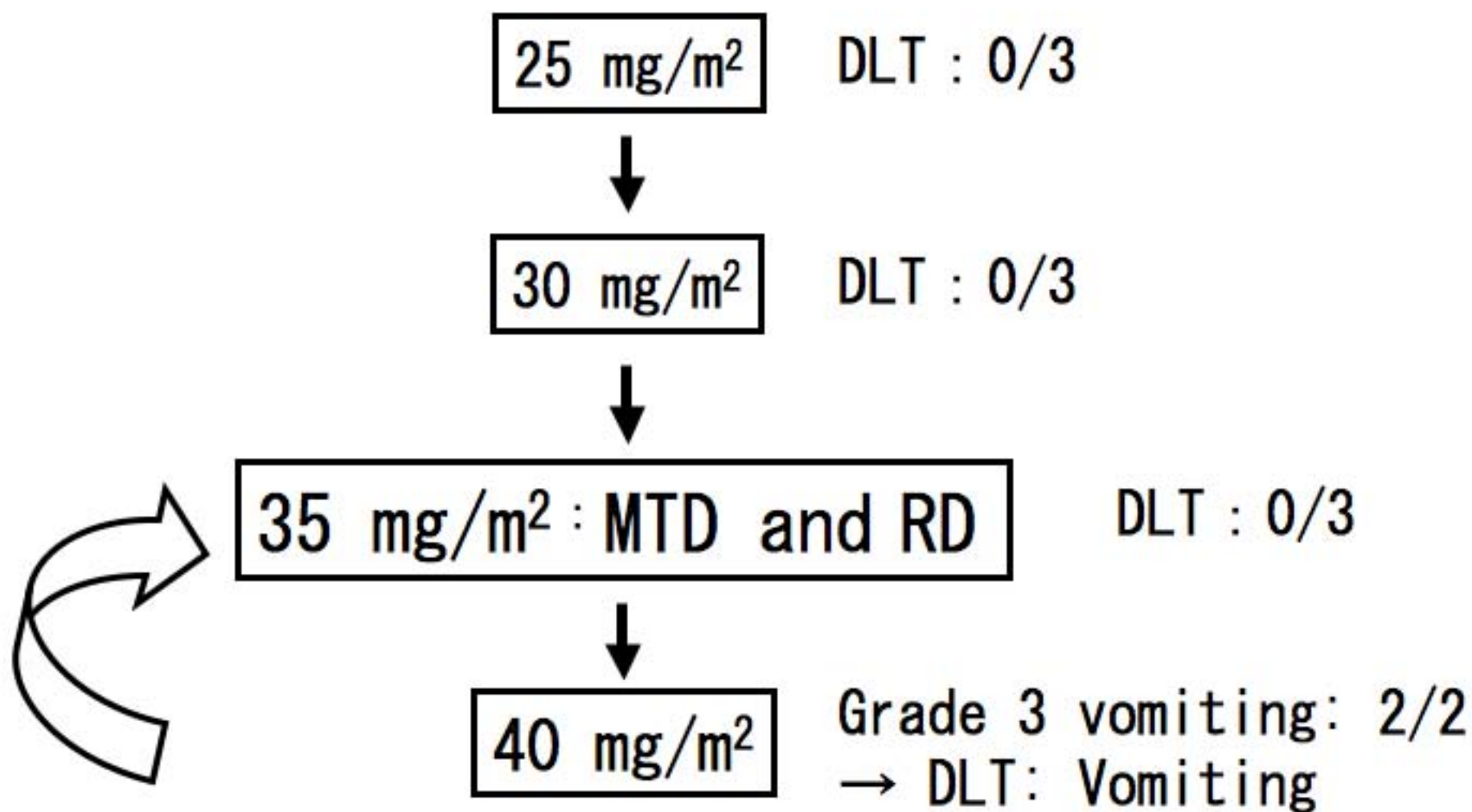


Figure 3

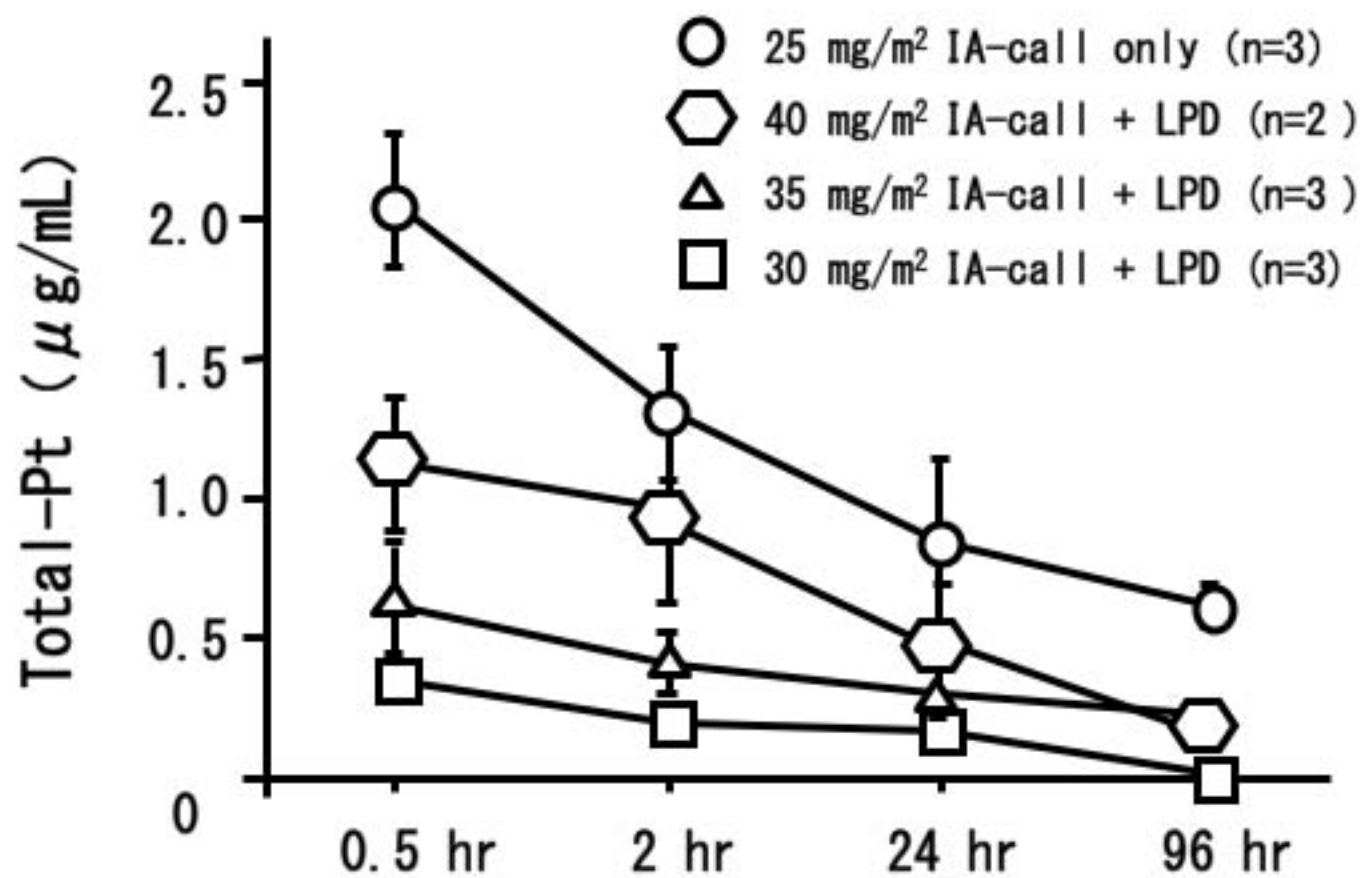


Figure 4

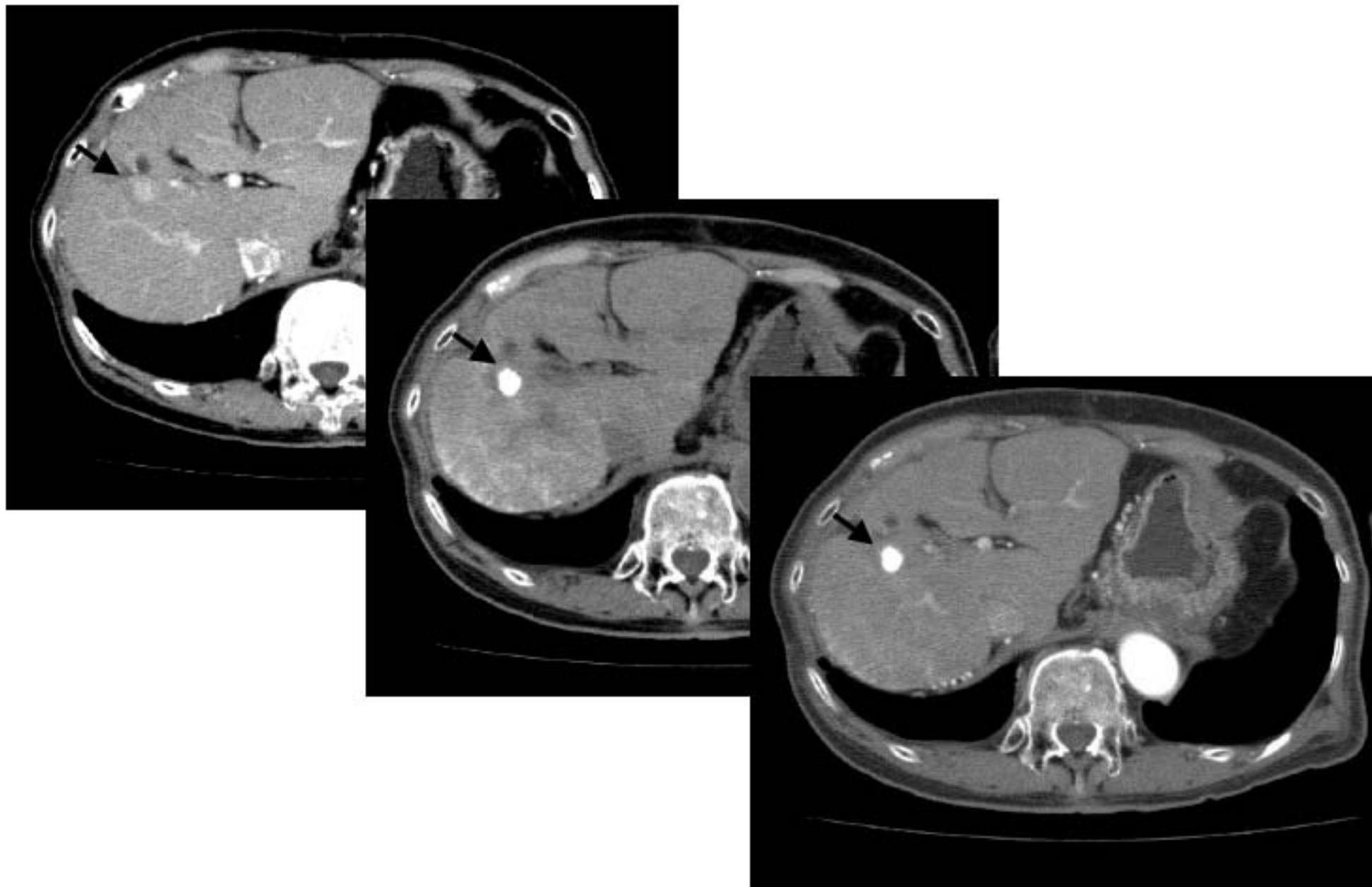


Figure 5

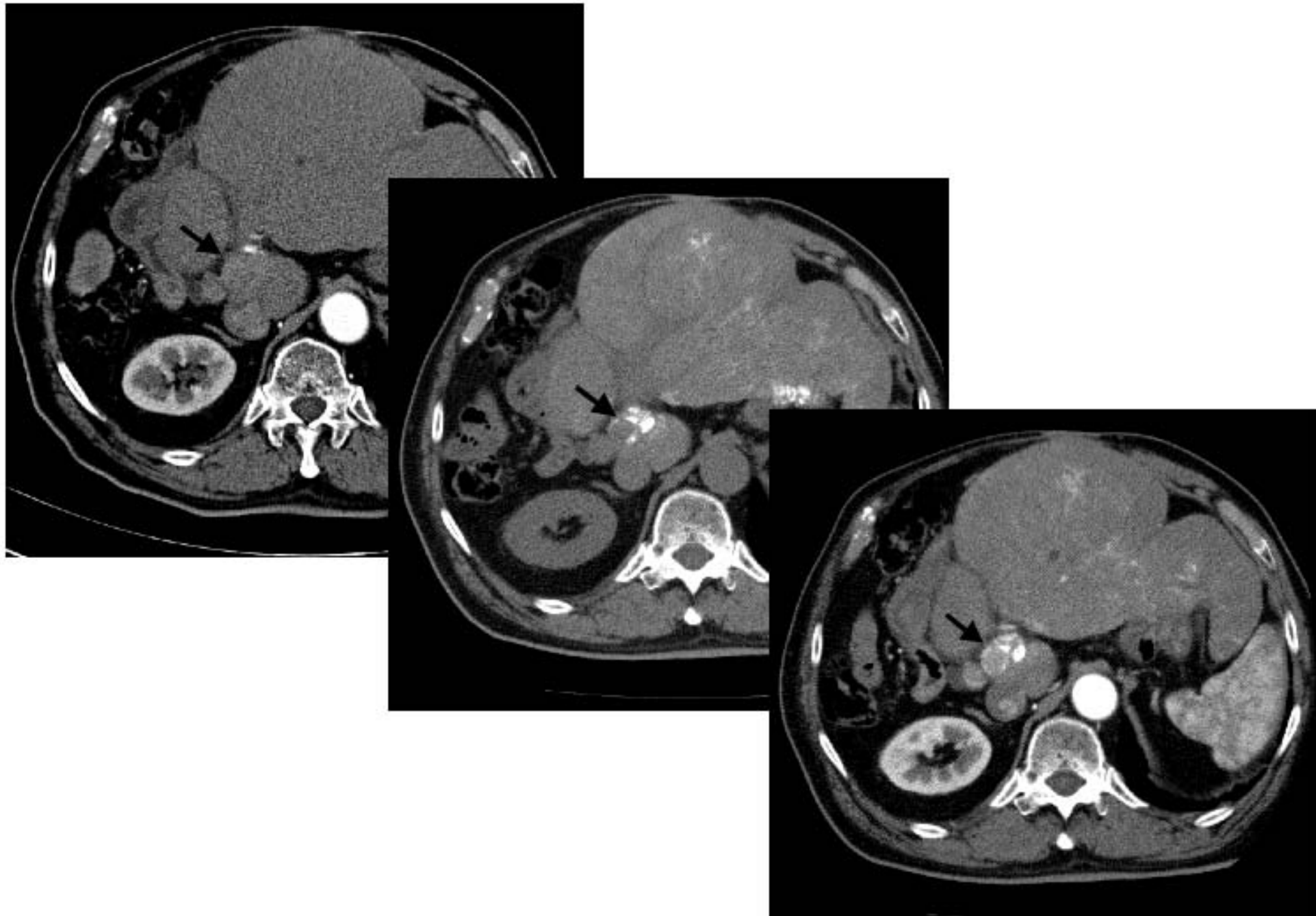




Table 1. Characteristics of patients enrolled in Phase II study

Variables	n=35
Back ground characteristics	
Age	69.2 $\pm$ 3.1
Male : Female	24 : 11
HBs-Ag (+) (%)	8 (22.9%)
HCV-Ab (+) (%)	29 (82.9%)
Platelet count ( $\times 10^4/\mu\text{L}$ )	13.2 $\pm$ 3.0
AST (IU/L)	66.0 $\pm$ 9.9
ALT (IU/L)	39.2 $\pm$ 5.8
Total bilirubin (mg/dL)	0.9 $\pm$ 0.6
Albumin (g/dL)	3.7 $\pm$ 0.6
Prothrombin time (%)	84.2 $\pm$ 3.5
Child-Pugh; A : B	29 : 6
Tumor related factors	
Tumor size (cm)	2.7 $\pm$ 1.9
Tumor number	3.6 $\pm$ 1.8
VP (+) (%)	2 (5.7%)
Stage I: II: III: IV-A #	6:17:10:2
$\alpha$ -fetoprotein (ng/mL)	2765 $\pm$ 117
DCP (mAU/L)	618 $\pm$ 13.2

·Abbreviations: AST; aspartate aminotransferase, ALT; alanine aminotransferase, VP; Macroscopic portal invasion, DCP; Des- $\gamma$ -carboxy prothrombin.

·# UICC 1997 TNM Classification of Malignant Tumors, 5th edition.



## Table 2: Responses

Response	n (%)
CR	16 (45.7%)
PR	4 (11.4%)
SD	9 (25.7%)
PD	6 (17.1%)

Abbreviations: CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease,

Table 3. Toxicity profile

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Hematological				
Anemia	0	0	0	0
Leukopenia	0	0	0	0
Thrombocytopenia	0	0	1 (2.9%)	0
Hyperbilirubinemia	0	2 (5.7%)	0	0
Non-hematological				
Vomiting	8 (22.9%)	4 (11.4%)	0	0
Appetite loss	1 (2.9%)	0	0	0
Diarrhea	1 (2.9%)	0	0	0
Constipation	1 (2.9%)	0	0	0