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Transcatheter arterial embolization using iodized oil (lipiodol) mixed with an anticancer drug for the treatment of hepatocellular carcinoma

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Summary. The therapeutic results of Lp-TAE (transcatheter arterial embolization with Gelfoam particles preceded by the infusion of a mixture of lipiodol and an anticancer drug via the proper hepatic artery) were evaluated in hepatocellular carcinomas (523 non-resected and 24 resected cases). Excellent therapeutic effects were confirmed not only for the main tumor but also for the the daughter nodules by a histological examination of the liver tissues resected after Lp-TAE. The cumulative 1-year, 2-year and 3-year survival rates in the 523 non-resected cases were 60.4%, 42.9% and 28.0% respectively. These survival rates were all higher than those achieved by Gelfoam TAE. The above results suggest the usefulness of Lp-TAE in the treatment of hepatocellular carcinoma.

Introduction

In Japan recently, much attention has been focused on an oily contrast medium (Lipiodol Ultra Fluid, lipiodol) as an embolic material for transcatheter arterial embolization therapy (TAE) of hepatocellular carcinomas [1–8]. Infusion, via the proper hepatic artery, of lipiodol mixed with a lipophilic anticancer drug [3, 4, 8] or lipiodol mixed with an anticancer drug dissolved in a water-soluble contrast medium of approximately the same specific gravity as lipiodol [1, 2, 5–7] produces an excellent antitumor effect, because the anticancer drug is retained with lipiodol within the tumor and is slowly released.

The authors have so far performed TAE for the treatment of approximately 700 hepatocellular carcinomas. In TAE of approximately 500 of them, lipiodol was used in combination. This paper describes the advantages and long-range therapeutic effects of TAE by the use of lipiodol (Lp-TAE).

Materials and methods

From April 1979 to May 1987, TAE was performed on a total of 728 patients with hepatocellular carcinoma. Gelfoam particles impregnated with an anticancer drug solution were used as the embolic material in 181 patients (GS-TAE group). Infusion, via the proper hepatic artery, of lipiodol mixed with an anticancer drug, by the pumping method followed by an injection of Gelfoam particles was applied to 547 patients (Lp-TAE group). A hepatectomy was performed on 24 patients after Lp-TAE.

The anticancer drugs used in conjunction were adriamycin (20–60 mg) and mitomycin C (10–20 mg). They were used either singly or combined. In the recent 23 TAEs applied to 15 patients, 50 mg cisplatinum were infused intra-arterially after infusion of the first half of the mixture of lipiodol and adriamycin (50 mg). The second half of the mixture was then infused, and finally Gelfoam particles were injected (ACA-Lp-TAE).

Results

Lipiodol mixed with the anticancer drug, infused via the proper hepatic artery, was accumulated selectively and retained for a long time in the main tumor and daughter nodules. Computerized tomography after Lp-TAE, therefore, disclosed the tumor region as a distinct high-density area (Figs. 1, 2). Even small daughter nodules, undetected by other existing imaging techniques, were distinctly visualized as high-density spots (Fig. 2).

By infusion, via the proper hepatic artery, of a lipiodol suspension containing 50 mg adriamycin and 20 mCi $^{99}TcO_4^-$ dissolved in a water-soluble contrast medium, $^{99}TcO_4^-$ was found to remain for a long time in the tumor region, as compared to the non-tumor regions (Fig. 3 c, d). Even 24 h after the infusion, a high uptake of $^{99}TcO_4^-$ was demonstrated in the tumor region (Fig. 3 e, f).

In 17 of the 24 patients hepatectomized after Lp-TAE, lipiodol accumulated with a high concentration in the tumor region. A histological examination confirmed complete necrosis in 12 patients, with more than 95% necrosis in 5 (Fig. 1). The examination further confirmed extensive necrosis of all the daughter nodules found with accumulated lipiodol (Fig. 2).

The cumulative survival rates were compared between the Lp-TAE and GS-TAE groups. The 1-year, 2-year and 3-year cumulative survival rates were 60.4%, 42.9% and 28.0%, respectively, in the Lp-TAE group, compared with survival rates of 44.0%, 26.0% and 15.0% rates, respectively, in the GS-TAE group (Fig. 4). The survival rate, calculated by the direct method in the 31 hepatocellular carcinoma patients who lived for more than 3 years after Lp-TAE, was 6.8% in the GS-TAE group and 20.8% in the Lp-TAE group. A high 1-year cumulative survival rate (81.8%) was obtained in the 15 patients treated by ACA-Lp-TAE.

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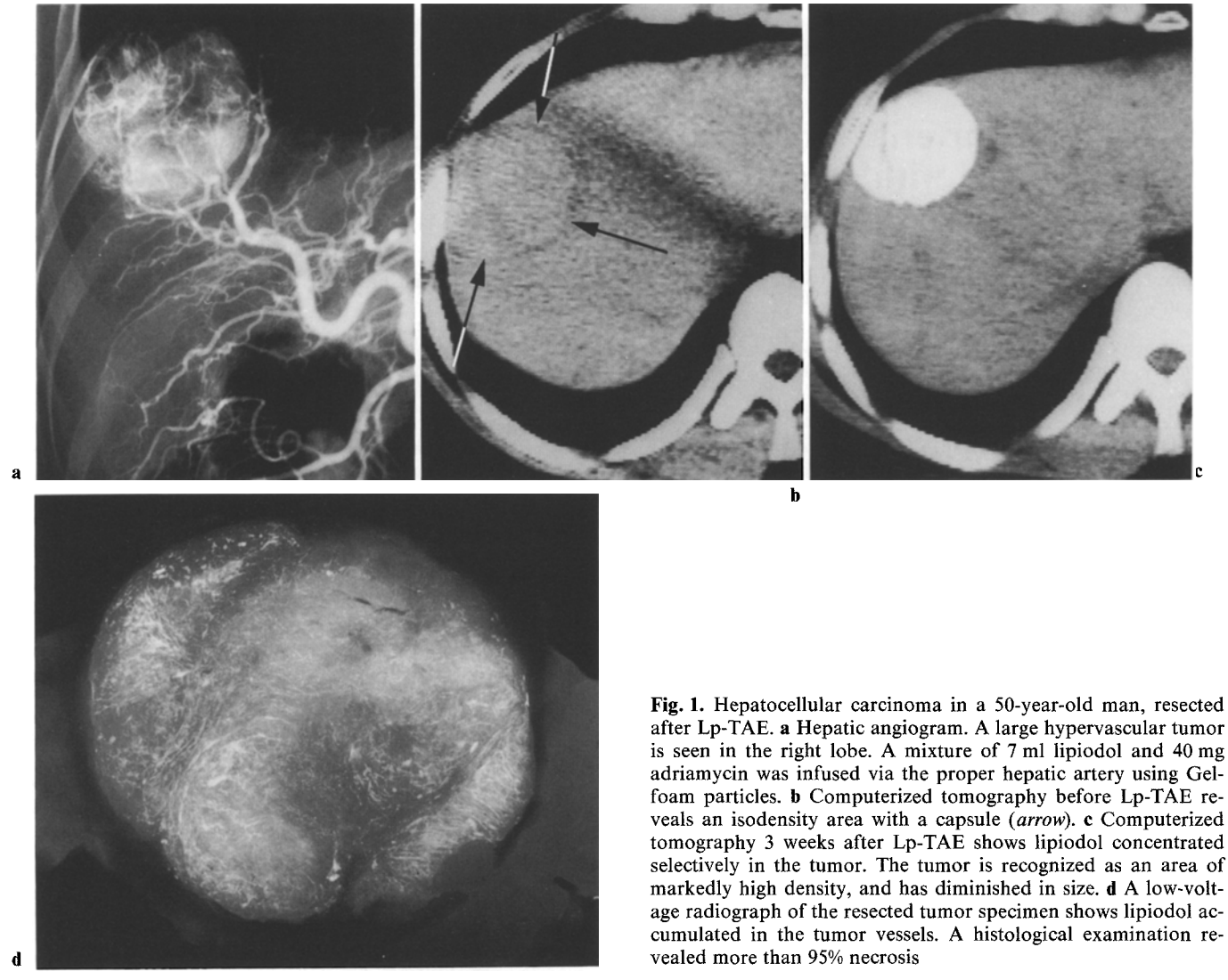

Fig. 1. Hepatocellular carcinoma in a 50-year-old man, resected after Lp-TAE. **a** Hepatic angiogram. A large hypervascular tumor is seen in the right lobe. A mixture of 7 ml lipiodol and 40 mg adriamycin was infused via the proper hepatic artery using Gelfoam particles. **b** Computerized tomography before Lp-TAE reveals an isodensity area with a capsule (*arrow*). **c** Computerized tomography 3 weeks after Lp-TAE shows lipiodol concentrated selectively in the tumor. The tumor is recognized as an area of markedly high density, and has diminished in size. **d** A low-voltage radiograph of the resected tumor specimen shows lipiodol accumulated in the tumor vessels. A histological examination revealed more than 95% necrosis

Discussion

The present analysis of the results of treatment by TAE covered a large number of patients with hepatocellular carcinoma. Lp-TAE, that is, embolization with Gelfoam particles preceded by the infusion of a mixture of lipiodol and an anticancer drug via the proper hepatic artery, produced a significantly higher therapeutic effect as compared with embolization with drug-impregnated Gelfoam particles alone (GS-TAE) [5–7]. The microembolization of the tumor vessels by lipiodol, the long retention of the anticancer drug combined with lipiodol in the tumor, the slow release of the anticancer drug and the occlusion of the hepatic arterial blood flow by Gelfoam particles seemed to exert a synergic action to produce an excellent anti-tumor effect. Radioisotope-labelled L_p-TAE showed that the anticancer drug was retained together with the lipiodol, and maintained its high concentration in the tumor.

Furthermore, lipiodol mixed with the anticancer drug also frequently accumulated in the small daughter nodules that developed from the hepatocellular carcinoma [5–7]. Lp-TAE was also found to have an excellent effect in the treatment of the daughter nodules that had so far failed to respond to conventional GS-TAE. This fact is considered to contribute to the improvement of prognosis after Lp-TAE. The repeated application of TAE results in the occlusion of the main feeding artery and the development of fine collateral vessels. However, a mixture of lipiodol and the anticancer drug, which flows into the recurrent tumors and the daughter nodules through the fine collateral vessels, would be expected to demonstrate a remarkable therapeutic effect [6].

Our recent application of the ACA-Lp-TAE method produced satisfactory results. This suggests the usefulness of multiple chemotherapy for the management of hepatocellular carcinoma. However, a final evaluation of the effect of ACA-Lp-TAE is still premature, because of the insufficiency of data. A pre-evaluation of the various background factors, including the liver functions and tumor morphology, are needed. We intend to increase our clinical application of ACA-Lp-TAE, and to continue long-range studies on its effect.

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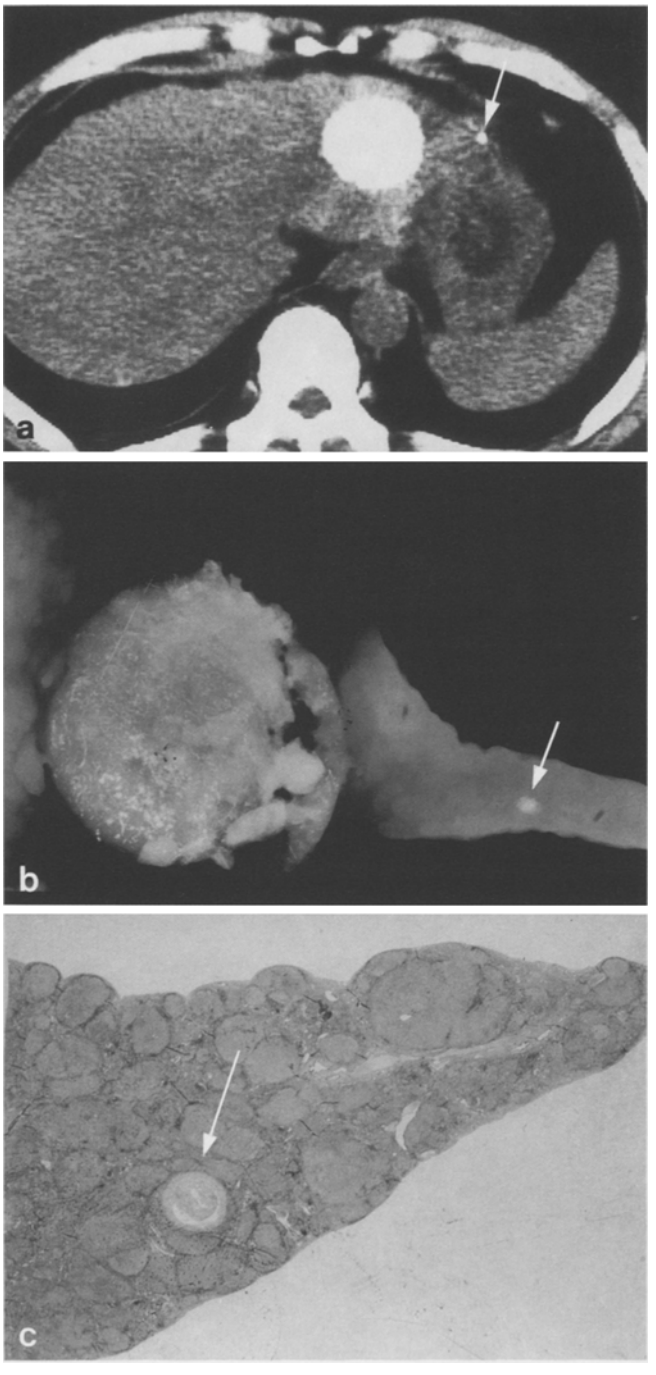

Fig. 2. Hepatocellular carcinoma in a 66-year-old man resected after Lp-TAE. A mixture of 8 ml lipiodol and 20 mg adriamycin and 10 mg mitomycin C was infused via the proper hepatic artery. This was followed by TAE using Gelfoam particles. **a** Computerized tomography 35 days after Lp-TAE: the main tumor is visualized as a markedly high-density area and a small high-density round spot is seen laterally (*arrow*). **b** A low-voltage radiograph of the resected liver specimen: lipiodol has accumulated within the main tumor vessels. A small high-density round spot (*arrow*) is also visible. This conforms to the high-density spot shown in **a**. **c** Microscopical views of the small high-density spot in **a** and **b**. The small high-density spot is identified as a daughter nodule with complete necrosis (*arrow*)

Fig. 3. See next page

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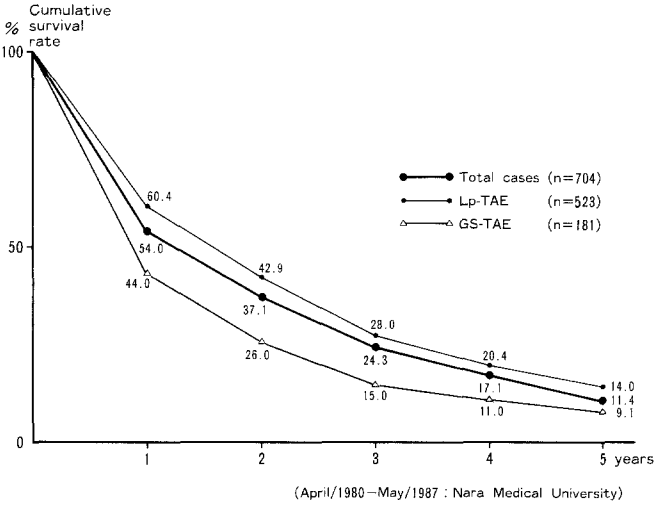

Fig. 4. The cumulative survival rate of patients with hepatocellular carcinoma after hepatic arterial embolization. ——, Comparison between Lp-TAE and GS-TAE

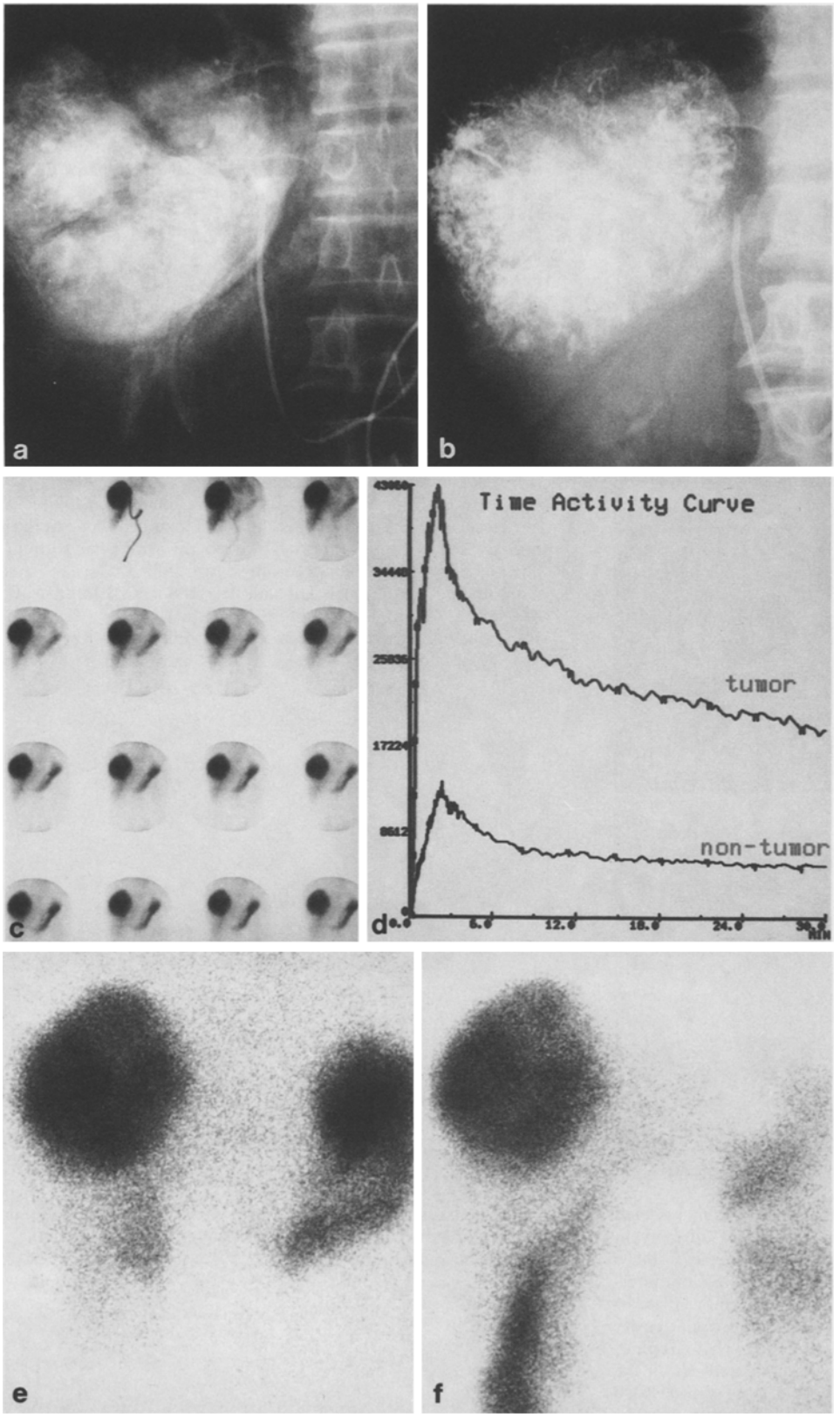

Fig. 3. Hepatocellular carcinoma in a 61-year-old man. Lp-TAE containing $^{99}Tc0_4^-$ was performed. **a** The late phase of a hepatic arteriogram demonstrated tumor vessels in the right lobe. **b** A plain radiogram after Lp-TAE revealed the accumulation of lipiodol in the lesion corresponding to the tumor. **c, d** The dynamic image and the time/activity curve in the tumor and non-tumor of Lp-TAE containing $^{99}Tc0_4^-$ for 30 min. $^{99}Tc0_4^-$ was washed out more quickly in the non-tumor area. However, in the tumor area, the high activity of $^{99}Tc0_4^-$ was retained for 30 min after injection. **e, f** The planer images 4 h (**e**) and 24 h (**f**) after Lp-TAE revealed a high uptake of $^{99}Tc0_4^-$ in the tumor area