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Lipiodol Retention and Massive Necrosis After Lipiodol-Chemoembolization of Hepatocellular Carcinoma: Correlation Between Computed Tomography and Histopathology

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Abstract. This retrospective study examined the computed tomography (CT) criteria for judging the effectiveness of transcatheter arterial Lipiodol-chemoembolization (Lp-chemo-TAE) in 35 cases with hepatocellular carcinoma (HCC). Massive necrosis, defined as involving 97% or more of the HCC nodule, was observed in 15 cases after Lp-chemo-TAE, whereas nonmassive necrosis, defined as involving ≤96% of the HCC nodule, was observed in the remaining 20 cases. In 12 of 15 cases (80%) with massive necrosis, uniform dense retention of Lipiodol (Lp) was observed throughout the HCC nodule on CT images 3–4 weeks after Lp-chemo-TAE as opposed to only one (5%) of 20 cases with nonmassive necrosis ($p < 0.01$). Eight of nine cases (89%) with massive necrosis had tumor attentuation values of 365 Hounsfield units (HU) or greater on CT images 3–4 weeks after embolization, as opposed to only four (27%) of 15 cases with nonmassive necrosis ($p < 0.01$). We conclude that the effectiveness of the Lp-chemo-TAE can be judged on CT from the degree and duration of Lp retention in the HCC nodule and the measurement of the attenuation value of the HCC nodule.

Key words: Lipiodol-chemoembolization—Hepatocellular carcinoma—Lipiodol retention—Massive necrosis—CT

Transcatheter arterial Lipiodol chemoembolization (Lp-chemo-TAE) produces an excellent anticancer effect and prolongs life in patients with inoperable hepatocellular carcinoma (HCC), compared to chemotherapy alone or chemo-TAE without Lipiodol (Lp) [1]. In all likelihood this is the result of longer drug retention with Lp inside the tumor [2].

For this reason, Lp-chemo-TAE therapy is now being used by many medical institutions. The Lp-chemo-TAE therapy has also been performed in preoperative cases in order to reduce tumor viability, tumor size, and recurrence, thereby rendering operations both easier and safer. Lp retention in the HCC nodules can be detected on computed tomography (CT) image as high-density areas. Thereafter, however, any necrotic change in the HCC nodule cannot be detected by CT due to Lp retention.

In this study, we compared the degree and duration of Lp retention in the HCC nodule after Lp-chemo-TAE on follow-up CT to the degree of tumor necrosis found at surgery or at autopsy.

Materals and Methods

This retrospective analysis consists of an autopsied group and an operated group, totaling 35 patients. Autopsies were performed in 12 patients with HCC, 11 men and one woman, ranging in age from 45–69 years (mean 57 years), with the size of the HCC nodule ranging from 2.7–15.0 cm in diameter (mean 6.5 cm). Surgical resections were performed in 23 patients with HCC, 17 men and six women, ranging in age from 40–75 years (mean 57 years), with the size of the HCC nodule ranging from 1.3–10.0 cm in diameter (mean 3.5 cm). All patients had undergone Lp-chemo-TAE therapy between April 1989 and October 1991 at Gifu University Hospital. The noncancerous liver tissue showed cirrhosis in 34 patients and fibrosis in one patient.

For Lp-chemotherapeutic drug emulsion, 5–10 ml of Lipiodol (Lipiodol Ultra Fluid, Andre-Gelbe Laboratories, France) was mixed with 20 mg of epirubicin hydrochloride (Kyowa Hakko

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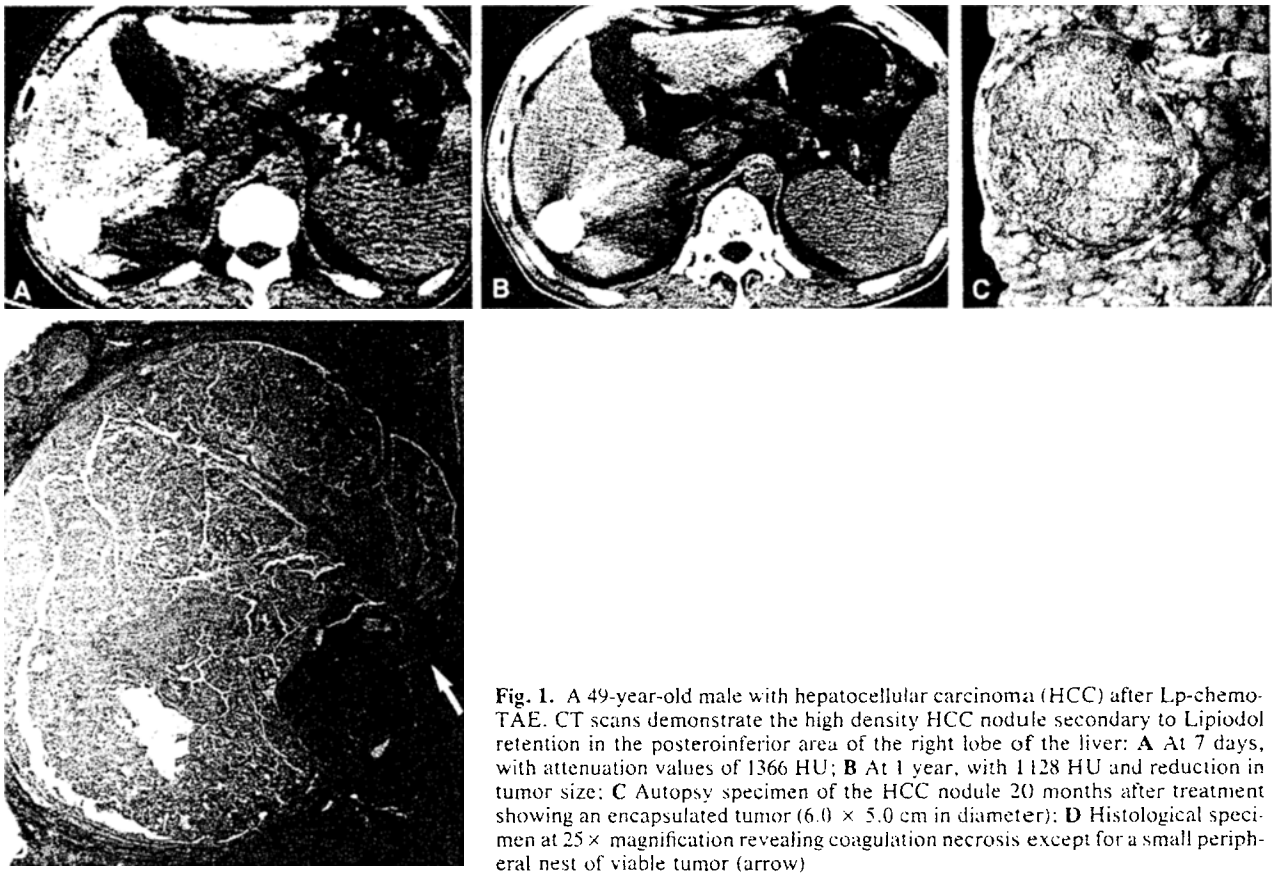

Fig. 1. A 49-year-old male with hepatocellular carcinoma (HCC) after Lp-chemo-TAE. CT scans demonstrate the high density HCC nodule secondary to Lipiodol retention in the posteroinferior area of the right lobe of the liver: **A** At 7 days, with attenuation values of 1366 HU; **B** At 1 year, with 1128 HU and reduction in tumor size; **C** Autopsy specimen of the HCC nodule 20 months after treatment showing an encapsulated tumor (6.0 × 5.0 cm in diameter); **D** Histological specimen at 25× magnification revealing coagulation necrosis except for a small peripheral nest of viable tumor (arrow)

Kogyo, Tokyo, Japan), 10 mg of mitomycin C (Kyowa Hakko Kogyo, Tokyo, Japan), and 3 ml of a non-ionic contrast medium (iohexol, Daiichi Pharmaceutical Co., Tokyo, Japan). The volume of Lp ranged from 5–10 ml, depending on the size of the tumor. We first injected the Lp-chemotherapeutic drug emulsion selectively into the HCC nodule feeding artery (the proper hepatic artery or its distal branches), and then embolized more proximally with gelatin sponge cubes 1–3 mm in diameter (Gelfoam, The Upjohn Co., USA).

CT scans were performed with and without contrast enhancement before Lp-chemo-TAE, and then 7–10 days, 3–4 weeks after treatment, and then once every 1–3 months if necessary. CT scans after treatment were examined for the degree and distribution of Lp retention in the HCC nodules under usual window settings, as well as under a window length of 50–100 and a window width of 1000–1200.

The interval between the Lp-chemo-TAE therapy and autopsy ranged from 65–745 days (mean 308 ± 199 SD). Surgical resections were performed after the posttreatment liver function tests had returned to those prior to treatment. The interval between Lp-chemo-TAE and surgical resection ranged from 17–178 days (mean 46 ± 34 SD). All autopsy and surgical specimens were cut into slices 5–10 mm thick after they were fixed in 10% formalin in the same axis as the CT images.

Histological specimens of the HCC nodule were compared to the degree and the distribution of Lp retention in the HCC nodule on CT images. The percent necrosis of the HCC nodule was determined from the necrotized area on that histological cross-section which corresponded to the largest diameter of the HCC nodule on CT. Massive necrosis was defined as involving 97% or more of the HCC nodule, while nonmassive necrosis was defined as anything less.

Statistical data analysis was carried out by Fisher's direct method. A probability level of $p < 0.05$ was considered significant.

Results

CT scans 7–10 days after Lp-chemo-TAE demonstrated diffuse distribution of Lp, although not uniform, in noncirrhotic and cirrhotic liver parenchyma. Lp was more focally concentrated in and around HCC nodules. Areas of necrosis or fibrosis in the HCC nodule having little or no blood supply on arteriography resulted in uneven Lp distribution or none at all. Lp retained in noncirrhotic and cirrhotic liver parenchyma generally disappeared within 3–4 weeks after treatment; however, in many HCC nodules, Lp was retained for a longer time, and it was often recognized on CT images 1 year or more after treatment. CT images after Lp-chemo-TAE therapy therefore showed the HCC nodules as distinct high-density areas.

Histological examinations of liver specimens showed massive necrosis in seven (58%) of 12 autopsied cases and in eight (35%) of 23 surgically resected cases, and nonmassive necrosis in the remaining 20 cases. There were no significant differences in tumor size between patients with massive necrosis and those with nonmassive necrosis.

In 12 (80%) of 15 cases with massive necrosis, uniform dense retention of Lp was observed throughout the HCC nodule after treatment, as op-

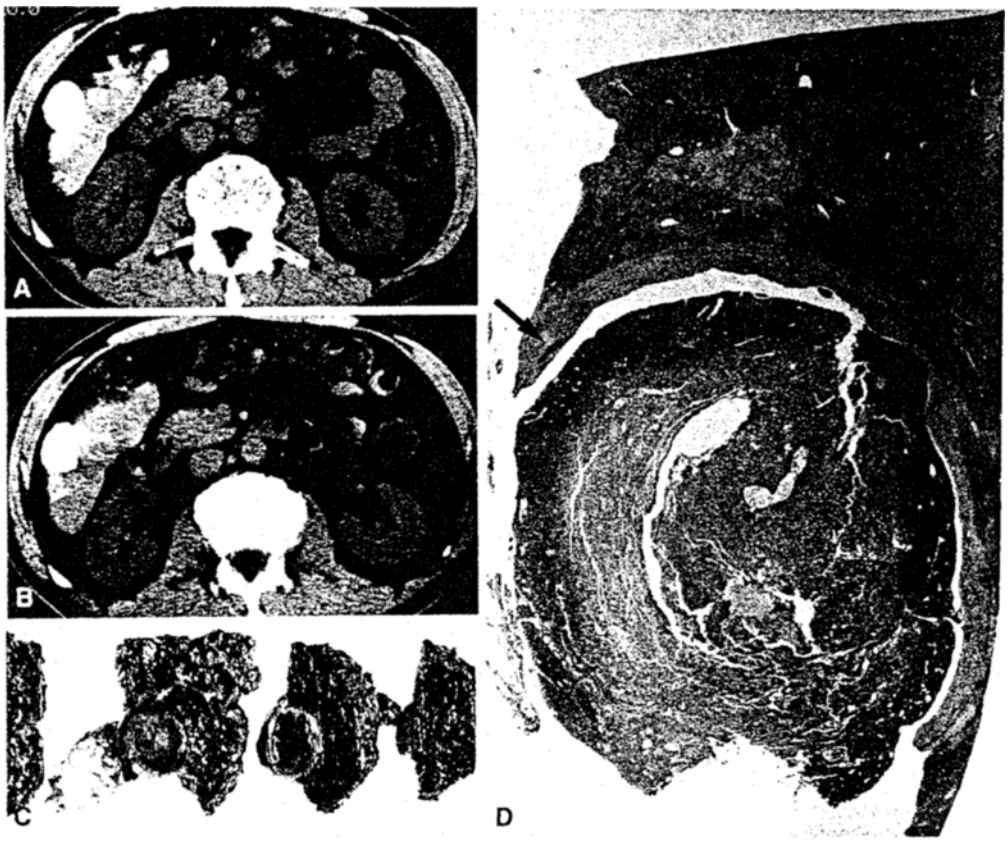

Fig. 2. A 54-year-old male with hepatocellular carcinoma after embolization as in Fig. 1. CT scans: **A** 7 days and **B** 29 days after treatment show the HCC nodule as a markedly high-density spot in the posteroinferior area of the right lobe due to Lipiodol retention, with attenuation values of 412 HU **(A)** and 446 HU **(B)**. Note the reduction in the tumor size between A and B. **C** Surgically resected specimen of the HCC nodule 31 days after embolization shows an encapsulated tumor nodule (3.0 × 2.3 cm in diameter). **D** The histological specimen reveals complete coagulation necrosis in most of the tumor tissue, but a small peripheral nest of viable cancer (arrow).

posed to only one (5%) of 20 cases with nonmassive necrosis ($p < 0.01$).

CT attenuation values were measured on CT scans showing the largest tumor diameter. As the investigation was retrospective, CT studies of only 24 patients (nine with massive necrosis and 15 with nonmassive necrosis) were available on optical disks. When the attenuation cutoff level was set at 365 Hounsfield units (HU) on CT images taken 3–4 weeks after treatment, sensitivity and specificity were 89% and 73%, respectively [i.e., eight (89%) of nine cases with massive necrosis had tumor attenuation values of 365 HU or greater as opposed to only four (27%) of 15 cases with nonmassive necrosis ($p < 0.01$)] (Figs. 1 and 2). In five of eight autopsied cases, there was a prolonged posttreatment period during which an attenuation value of 365 HU or greater persisted in the HCC nodule (Fig. 3). Moreover, in three of these five cases, there was a transient increase in the attenuation value on follow-up CT images. When there was a transient increase in the attenuation value, the HCC nodule was concurrently found to decrease in size. It was thus suspected that the necrotized tissue in the HCC nodule was absorbed and Lp was concentrated. The transient increase in the attenuation values was also observed in five of 16 operated cases. One of nine cases with massive necrosis had low HU, and four of 15 cases with nonmassive necrosis had 365 HU or greater.

Discussion

In 1966, Idezuki et al. [3] injected Lp into the portal vein in patients with metastatic liver cancers, and found that the tumors appeared as radiographic lucencies in the uniformly opacified livers. In 1979, Nakakuma et al. [2] found that Lp stayed longer in the tumor tissue than in the nontumorous areas of the liver, after contrast medium had been injected into the tumor feeding artery. Moreover, they reported that there was a deposition of an Lp-chemotherapeutic drug suspension in hepatic tumors, and

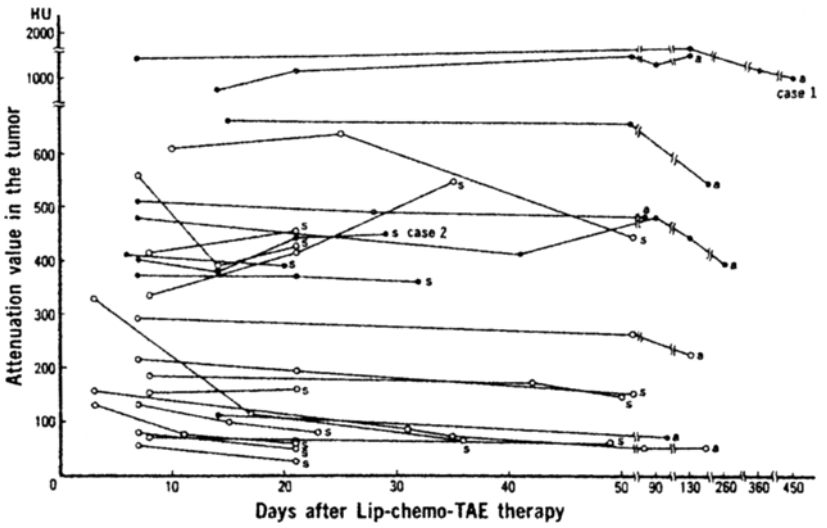

Fig. 3. Changes in CT attenuation values of the tumor area after Lp-chemo-TAE. All CT attenuation values of the HCC nodule before embolization were between 15 HU and 50 HU. ●, Massive necrosis (97% or more of the tumor); ○, nonmassive necrosis (96% or less of the tumor); a, autopsied case; s, operated case.

confirmed its therapeutic effects [4]. It is not yet clear why Lp remains in the HCC nodules after Lp-chemo-TAE.

The site of Lp retention is both in the lumen of the tumor microvasculature and in the extracapillary space. Retention in the tumor microvasculature is believed to be related to the viscosity, surface tension, etc., of Lp as well as to the number, diameter, and architecture of the tumor vessels [5–7]. The reason for Lp retention in the extracapillary space is believed to be slow decomposition and absorption of Lp due to the lack of a reticuloendothelial or lymphatic system in the HCC tissue [5–7]. Other factors affecting Lp retention in the tumors include site, volume, and frequency of arterial injection, as well as tumor size, histological type of HCC (less Lp retention in the case of fibrotic or sclerotic types), and degree of tumor vascularity [6]. A study on the biodistribution of radiolabeled lipids shows that bile is the major route by which Lp is excreted from the liver parenchyma [7].

In an experimental study, gelatin sponge cubes were retained in second- and third-order hepatic artery branches 4 weeks after embolization [8]. In clinical studies, gelatin sponge cubes were retained in the fibrous capsules around the tumor and even in the cirrhotic liver parenchyma between 11 and 50 days after embolization and almost always lodged within arteries of 50–500 micron diameters [9, 10]. When gelatin sponge cubes alone were used, arterial collaterals developed rapidly as the 1–3 mm cubes obstructed arteries proximal to the level of arterioportal communications [11].

Lp as a liquid can embolize distal to the arterioportal communications and is deposited inside the tumor vessels [5]. This type of embolization is more effective in preventing the development of collateral circulation.

It has been estimated that the hepatic artery supplies the liver with 25% of its blood volume and 50% of its oxygen under normal conditions, while the portal vein provides 75% of blood volume and 50% of oxygen [12]. Histopathological specimens obtained after Lp-chemo-TAE showed accordingly that nontumorous tissues were not significantly damaged unless there was tumor thrombus in the portal vein [13]. However, preoperative TAE with mitomycin C was shown to have severe inhibitory effects on hepatic regeneration after partial hepatectomy [14]. It has also been reported that after TAE therapy, a high degree of necrosis is found in the tumor when the tumor is hypervascular, has a dense fibrous capsule, has a diameter of 5 cm or less, and is histologically of the trabecular type [6, 15, 16].

However, since small HCC nodules and the daughter nodules less than 0.5 cm in diameter are fed not only by the artery but also by the portal vein [17, 18], TAE therapy is less effective for these nodules.

In cases where Lp is retained on the CT images densely and uniformly throughout the HCC nodule for 1 month or longer, the tumor is found to have undergone necrosis in many of these cases [19]. After Lp-chemo-TAE, the necrotized tissue in the tumor nodule is slowly absorbed and eliminated. It is presumed that the slow absorption and elimination are due to embolic occlusion of the tumor microvasculature and of small arteries around the tumor [20].

This study discloses the new finding that massive necrosis is present in those cases where the tumor has an attenuation value of 365 HU or greater on

CT images taken 3–4 weeks after Lp-chemo-TAE. Therefore, we conclude that it is possible to evaluate the effectiveness of the Lp-chemo-TAE on CT from the degree and duration of Lp retention in the HCC nodule, and the measurements of attenuation values of the HCC nodule.

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