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Intra-arterial alcoholization of advanced hepatocellular carcinoma

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Abstract. For the purpose of achieving emergency hemostasis of a ruptured hepatocellular carcinoma (HCC) or prevention of such rupture, we applied a new method of transcatheter therapy: intra-arterial alcoholization. Five patients with a ruptured HCC and 42 with an impending rupture were treated by intra-arterial injection of absolute ethanol mixed with an equal volume of iodized oil, Lipiodol (EtOH-Lp). The tumor size ranged from 4 to 26 cm (mean 7.8 cm) in diameter. The catheter tip was placed in the segmental branch or a more distal position of the hepatic artery, and 2–40 (mean 10.6) ml of EtOH-Lp was infused under fluoroscopic guidance. Infiltration of ethanol into the HCC mass was recognized as a dense deposition of Lipiodol on plain abdominal X-rays and computed-tomography. In all five cases of ruptured HCC, hemostasis was achieved. In all 42 cases of impending rupture, tumor rupture was prevented, and all except 3 patients could be discharged. No significant complication of the gastrointestinal tract or biliary tract was seen. The incidence and severity of postembolization syndrome were markedly lower than those seen in cases treated with Gelfoam embolization.

Introduction

Tumor rupture and consequent intraperitoneal bleeding is one of the most important prognostic factors in patients with advanced hepatocellular carcinoma (HCC) [18]. A recent report of the Liver Cancer Study Group of Japan estimated tumor rupture as the cause of death in 10% of 2,487 patients with HCC in Japan between 1982 and 1985 [9]. Therefore, emergency hemostasis and prevention of tumor rupture are essential for improving the survival of these patients.

Although transcatheter arterial embolization (TAE) has been well accepted as a method of treatment for unresectable HCC [23], no standard method of embolization has been established [15], even for huge tumors that have ruptured [6, 16] or are at high risk of rupture. With the objective of achieving emergency hemostasis of ruptured HCC or prevention of rupture, we applied a new method of transcatheter therapy: intra-arterial alcoholization.

Patients and methods

From February 1983 to January 1993, 316 fresh cases of HCC underwent TAE in Shizuoka General Hospital. In all, 11 patients (3.5%) had a complication of spontaneous rupture and intraperitoneal hemorrhage of the HCC, and 75 were regarded as being at high risk of tumor rupture (impending-rupture cases). We defined impending rupture as a clinical entity of HCC that is associated with either severe abdominal pain suggestive of increased intratumoral pressure and/or subcapsular hemorrhage, intratumoral hematoma, or a huge bulging tumor with necrosis as revealed on computerized tomography (CT) scans, any of which strongly suggests a high risk of rupture. Until July 1989, we applied standard Gelfoam embolization for six ruptured cases, but the results were unsatisfactory, with no case of 1-year survival being recorded.

From August 1989 to November 1992, 5 patients with a ruptured HCC with active intraperitoneal bleeding and 42 patients with an impending rupture were treated by intra-arterial injection of absolute ethanol mixed with an equal volume of iodized oil (EtOH-Lp, Lipiodol Ultra Fluide; Lab. Antré Guerbet, Aulnay-sous-Bois, France).

A total of 41 men and 6 women were aged 18–76 years. All five patients with HCC rupture manifested a clinically severe condition, presenting with either sudden onset of abdominal pain with shock, marked abdominal distension, rapidly progressive anemia, or bloody ascites. In all 42 patients with impending rupture, the findings on CT scans were compatible with those described above; 18 of these subjects had severe right-upper-quadrant pain. The serum total bilirubin value was less than 3.5 mg/dl in all cases because, in our opinion, obvious

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jaundice should contraindicate any type of catheter intervention [16]. On the CT scans, the tumors ranged in size from 4 to 26 (mean, 7.8) cm in diameter.

After the clinical diagnosis of tumor rupture or impending rupture, emergency angiography was performed, including celiac angiograms, transarterial portograms, and superselective hepatic angiograms. In all cases, precise angiographic observation was also done by cine-mode digital-subtraction angiography (cine-DSA) at 4–8 frames/s to determine the feeding artery of the tumor and to evaluate the presence and extent of any portal-vein tumor thrombus.

The catheter tip was placed in the segmental branch or a more distal position of the hepatic artery using a 5-F catheter or a coaxial microcatheter system (Tracker 18 Vascular Access System; Target, San Jose, Calif.). After pretreatment by infusion of 3–5 ml of 1% lidocaine to prevent pain and arterial spasms, 2–40 (mean, 10.6) ml of EtOH-Lp was injected slowly and very carefully under fluoroscopic observation until the flow in the feeding artery had ceased.

To estimate the effect of this procedure, we repeated DSA immediately afterward; plain abdominal X-rays on days 0, 3, 7, and 30; and CT scans on days 7 and 30. Complete blood cell counts, blood chemistry, and determinations of prothrombin time, serum alpha-fetoprotein, and plasma PIVKA-II values were carried out before and at 1, 3, 7, and 14 days after the EtOH-Lp infusion. Also, in 35 patients, upper-gastrointestinal endoscopy was performed within 1 week of the procedure to determine the presence and severity of esophageal varices and to detect any acute ulcer formation due to the ethanol infusion.

Results

Imaging findings

On fluoroscopy during the procedure, rapid accumulation of Lipiodol in the tumor was observed immediately after the injection of EtOH-Lp. On follow-up, plain abdominal X-rays and CT scans revealed dense deposition of Lipiodol in the tumor, just as observed in cases treated by Lipiodol-TAE [15], but the density of Lipiodol tended to be higher in the present cases.

Clinical efficacy

(1) Hemostatic effect. In all five cases of ruptured HCC, hemostasis was achieved immediately after the EtOH-Lp infusion as confirmed by the disappearance of extravasation on the angiogram and from the subsequent clinical course. In three cases of active bleeding during emergency angiography, slight leakage of the EtOH-Lp into the peritoneal cavity was observed, but no serious complication occurred except for transient abdominal pain. All five patients could be discharged within 1 month of this emergency intra-arterial alcoholization.

(2) Preventive effect on rupture. In all 42 cases of impending rupture, the HCC tumor rupture was prevented. In two patients who had a huge mass in the right lobe of the liver but maintained relatively good liver function (Child A cases), hepatectomy was performed at 1–2 months following the intra-arterial alcoholization. In 32 patients who were younger and had retained relatively good liver function (Child A-B cases), standard chemoembolization and/or chemoinfusion via the totally implanted catheter system (reservoir) were added. All except three patients could be discharged at 2–6 weeks following the intra-arterial alcoholization. Three patients died in the hospital due to progressive hepatic failure.

(3) Effect in pain relief. In all of the patients who had experienced abdominal pain at the time of entry to the angiography ward, pain relief was obtained during or within a few hours of the infusion of the EtOH-Lp.

Side effects and complications

The incidence and severity of postembolization syndrome (fever, abdominal discomfort or pain, nausea and vomiting) were markedly lower than those observed in cases treated with conventional Gelfoam embolization. Endoscopy performed at 3–7 days following the intra-arterial alcoholization did not detect any case of acute ulceration that was attributable to the EtOH-Lp infusion. During the clinical follow-up conducted in- and outside the hospital for up to 3 years (mean, 13.5 months), no significant complication of the gastrointestinal or biliary tract was seen.

Pathologic findings of resected or autopsied liver

Gross and microscopic examination of resected (two cases) and autopsied (six cases) liver tissues revealed broad necrosis and thick fibrous scar formation in the treated segment or lobe. However, no case presented findings of infarction in the untreated part of the liver or the bile duct or of gallbladder necrosis.

Case presentation

Case 1. (Fig. 1)

A 72-year-old Korean man with type-C cirrhosis was admitted because of sudden onset of severe upper-abdominal pain. A CT scan showed multiple tumors in the liver (Fig. 1c), and the serum alpha-fetoprotein level was extremely high. A diagnosis of HCC with impending rupture was made, and emergency angiography showed multiple tumor stains measuring up to 6 cm in diameter in both the right and left lobes of the liver, several of which protruded from the liver surface (Fig. 1a).

A tracker 18 catheter was inserted into each of the feeding arteries at the subsegmental level (S8, S6, S7, and S1), and a total of 9 ml of EtOH-Lp was infused into each. Plain abdominal X-rays (Fig. 1b) and a CT scan (Fig. 1c) showed dense deposition of Lipiodol in the tumors. Tumor rupture was avoided, and no pain symptom recurred thereafter. The patient was discharged 3 weeks following the procedure.

Case 2. (Fig. 2)

A 56-year-old man was admitted to a local hospital because of "acute abdomen". The initial workup, including sono-

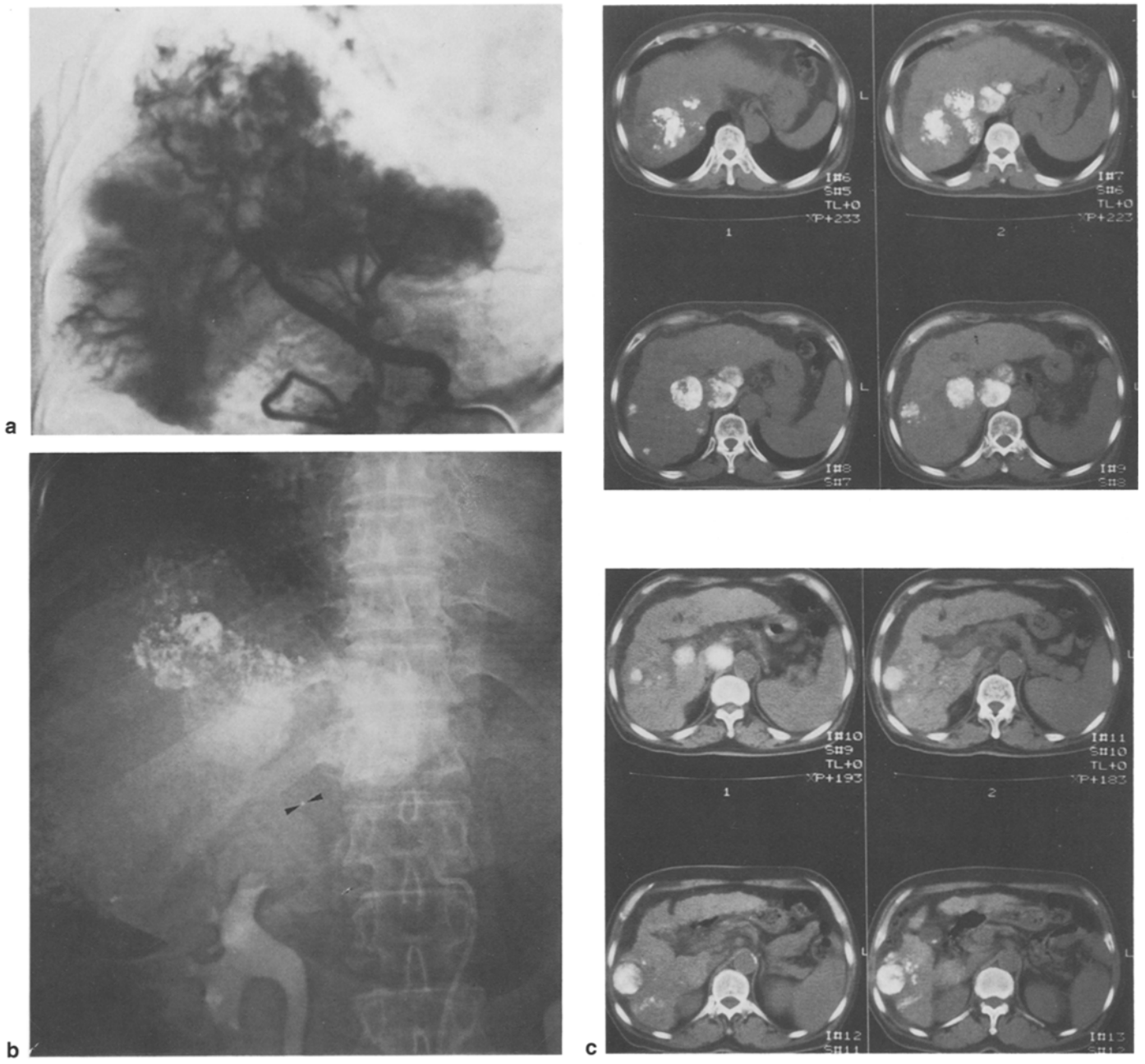

Fig. 1. A 72-year-old man with an impending rupture of HCC. **a** This emergency hepatic angiogram shows multiple tumor stains of up to 6 cm in diameter protruding from the liver surface. **b** A plain abdominal X-ray taken immediately after the infusion of 9 ml of EtOH-Lp into each of the subsegmental feeding arteries. Dense deposition of Lipiodol in the tumors and the platinum ring at the tip of the microcatheter (*arrowhead*) are visible. **c** This CT scan taken 1 week after the procedure shows dense accumulation of Lipiodol in each of the tumor nodules

graphy and a CT scan, revealed huge liver tumors in the right lobe. The patient was said to be "untreatable" by the attending physician, but his family decided to transfer him to our hospital. His liver function was well preserved and consistent with Child's grade A. A CT scan showed multiple confluent tumors in the right lobe, and a subcapsular low-density region was also recognized within the tumor (Fig. 2a). A hepatic angiogram showed huge hypervascular tumors in the posterior part of the right lobe along with multiple daughter nodules (Fig. 2b).

A total of 12 ml of EtOH-Lp was infused into the right hepatic artery distal to the branch to the gallbladder. A CT scan performed 10 days after the procedure showed dense deposition of Lipiodol in the tumors (Fig. 2c). Extended right hepatectomy was successfully performed at 6 weeks after the intra-arterial alcoholization (Fig. 2d), and the patient was discharged 3 weeks thereafter.

Case 3. (Fig. 3)

A 58-year-old man was referred from the Department of Nuerosurgery. He had been admitted because of low-back pain and gait disturbance and was later diagnosed as having

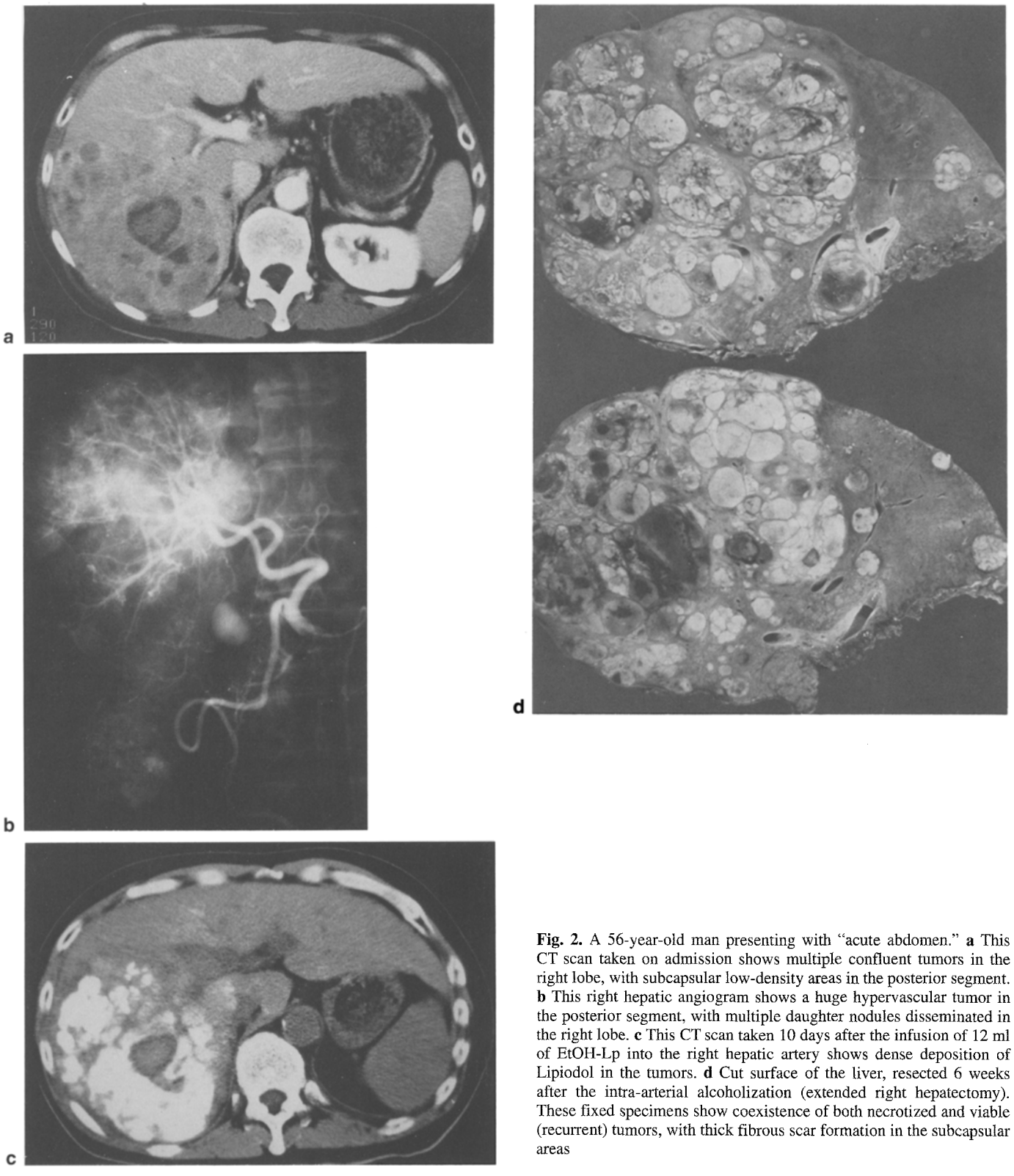

Fig. 2. A 56-year-old man presenting with "acute abdomen." **a** This CT scan taken on admission shows multiple confluent tumors in the right lobe, with subcapsular low-density areas in the posterior segment. **b** This right hepatic angiogram shows a huge hypervascular tumor in the posterior segment, with multiple daughter nodules disseminated in the right lobe. **c** This CT scan taken 10 days after the infusion of 12 ml of EtOH-Lp into the right hepatic artery shows dense deposition of Lipiodol in the tumors. **d** Cut surface of the liver, resected 6 weeks after the intra-arterial alcoholization (extended right hepatectomy). These fixed specimens show coexistence of both necrotized and viable (recurrent) tumors, with thick fibrous scar formation in the subcapsular areas

multiple bone metastases from HCC. He also had type-C cirrhosis, and his liver function had deteriorated as reflected by a serum total bilirubin value of approximately 2.5 mg/dl. A CT scan showed multiple liver tumors, some of which were exophytic on the liver surface with markedly low density, suggestive of spontaneous tumor necrosis (Fig. 3, upper row). A diagnosis of impending rupture of HCC was made, and partial embolization with EtOH-Lp was indicated to prevent rupture and consequent acute mortality.

A total of 7 ml of EtOH-Lp was infusd into the feeding arteries. A CT scan performed at 1 week after the intra-arterial alcoholization demonstrated dense deposition of Lipiodol in each of the tumors (Fig. 3, lower row). The

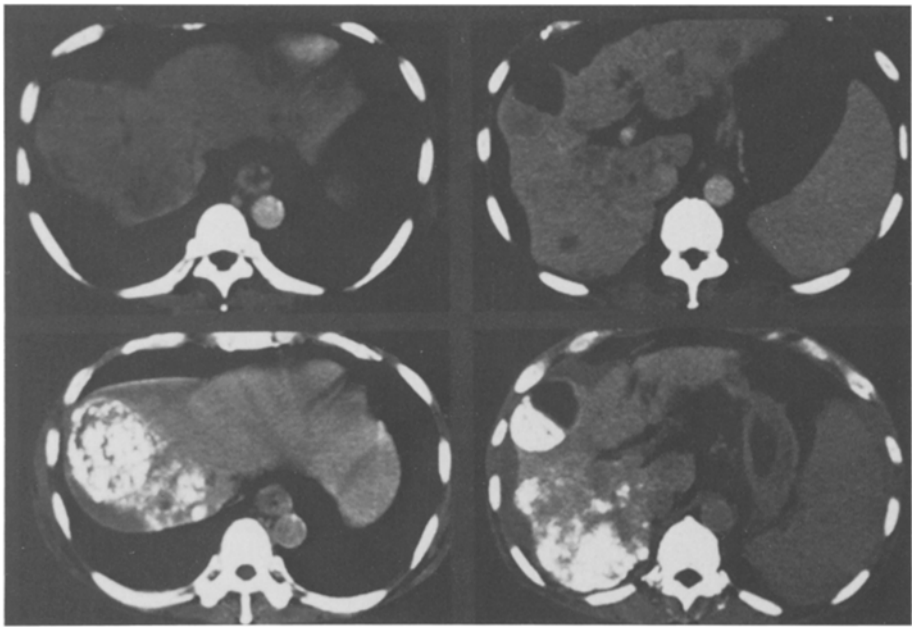

Fig. 3. A 58-year-old man with multiple bone metastases. CT scans taken before (*upper row*) and 1 week after (*lower row*) the intra-arterial alcoholization. Multiple HCC masses are visible disseminated in the liver. Some of the nodules are exophytic on the liver surface and others are of very low density, suggestive of spontaneous tumor necrosis. CT scans in the *lower row* show dense deposition of Lipiodol in the tumors, with a high risk of rupture

patient could not be discharged and died 3 months following the procedure because of progressive liver failure. The autopsy revealed no bleeding in the peritoneal cavity, i.e., the intra-arterial alcoholization had successfully prevented spontaneous tumor rupture.

Discussion

In 1976, Okuda [17] divided patients with HCC into nine clinical types. The "acute abdominal" type in his classification seemed to contain both ruptured and impending-rupture cases. Once the bleeding has started, spontaneous hemostasis is very unusual. Therefore, early detection and correct diagnosis is essential in patients with rupture or a high risk of rupture. On the basis of our clinical experience with more than 400 cases of HCC, we defined the clinical entity of "impending rupture" of HCC according to the symptoms and CT scan findings.

In most cases of rupture, catheter intervention is the only way to prevent a catastrophe [6, 16] because emergency hepatectomy and hepatic artery ligation are associated with high rates of mortality (44%–73%) [2, 13, 14]. Before TAE became applicable to the treatment of HCC, Ong et al. [19] reported an incidence of HCC tumor rupture in 14.5% of their patients in Hong Kong. Although death due to HCC tumor rupture seems to have decreased since TAE has been applied, it remains one of the most important prognostic factors in patients with advanced HCC [9, 18]. Since a standard method of catheter intervention for a rupture or an impending rupture of HCC has not yet been established [6, 16], we applied a new method of emergency transcatheter therapy: intra-arterial alcoholization.

Arterial infusion of absolute ethanol is a standard method of treatment for renal-cell carcinoma (RCC) [5], but it has not been widely applied to the hapatic artery. In the early 1980s, several authors reported experimental data for EtOH infusion into the hepatic artery [3, 20]. However, their results were not very promising because of a high incidence of side effects, although this might have occurred because their experimental systems were rather unnatural: the catheter was tight-wedged or the dose of EtOH was relatively high. At about the same time, several angiographers in Germany applied Ethibloc (Ethicon GmbH; Norderstedt, Germany), an EtOH-containing glue, not only for RCC [8] but also for liver tumors [1, 7]. They reported this agent to be efficacious and safe, which suggested the possibility of using EtOH for the hepatic artery. In their editorial published in 1984, Wallace et al. [22] did not rule out the use of EtOH as an embolic material for the hepatic artery in recognition of the above reasons, and they left the issue open to further investigation and discussion.

In 1989, Park et al. [21] showed the utility of Lipiodol mixed with absolute ethanol as an embolic material for RCC. In 1990, after conducting experiments on rat livers, Matsui et al. [10] showed the safety and efficacy of EtOH mixed with Lipiodol for human minute HCCs [11, 12]. Their major concern was the complete local control and, if possible, the cure (medical segmentectomy) of small HCC by ultraselective catheterization and subsegmental embolization. However, in their report, there was no definite difference in the local control ratio between the conventional Lipiodol-TAE and ethanol-TAE groups.

We had taken note of the sclerosing ability of EtOH on the basis of our experience in the fields of interventional endoscopy, interventional echography, endoscopic injection hemostasis of bleeding ulcers, sclerotherapy of esophageal varices [24], and percutaneous ethanol injection for HCC [4]. We thus surmised that EtOH could be applied for intra-arterial hemostasis and for prevention of bleeding in the treatment of liver cancer. In the present series, 5 patients with a ruptured HCC and 42 patients with an impending rupture were treated by intra-arterial alcoholization in emergency settings. All 5 of the patients with a ruptured HCC could be rescued, bleeding could be prevented in all 42 cases of impending rupture, and 44 of the total of 47

(89.8%) patients could be discharged without serious complications of the gastrointestinal or biliary tract.

In summary, in comparison with chemoembolization using cytotoxic agents, intra-arterial alcoholization is safe and less invasive, is effective in achieving hemostasis and preventing rupture, provides marked efficacy in pain relief, and is less expensive. We conclude that intra-arterial alcoholization is one of the most useful variations of TAE for advanced HCC, especially for large lesions that have ruptured or are about to rupture.

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