Well-differentiated hepatocellular carcinoma smaller than 15 mm in diameter totally eradicated with percutaneous ethanol injection instead of radiofrequency ablation

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Received: 14 December 2008 / Accepted: 5 March 2009 / Published online: 21 March 2009
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Abstract We describe three cases of well-differentiated hepatocellular carcinoma (HCC) smaller than 15 mm in diameter completely eradicated with percutaneous ethanol injection (PEI) instead of using radiofrequency ablation (RFA). Ultrasound (US) examination revealed one nodule each in segment 2 (hypoechoic, near bile ducts, 10 mm), in segment 5 (hyperechoic, near the gall bladder, 15 mm), and in segment 7 (hypoechoic, near the diaphragm, 15 mm). Although imaging studies revealed isovascular (case 1) and hypervascular (cases 2 and 3) nodules, histological analysis of US-guided biopsy tissue revealed well-differentiated HCC. In consideration of the location of the nodules, PEI, instead of RFA, was administered and the nodules were rendered necrotic. Although RFA is superior to PEI in the treatment of small HCCs from the viewpoint of treatment

response and long survival, PEI is strongly recommended for HCCs located near bile ducts, the gall bladder, and the diaphragm, especially when the nodules are smaller than 15 mm in diameter.

Keywords Percutaneous ethanol injection · Bile ducts · Gall bladder · Diaphragm · HCC smaller than 15 mm in diameter

Introduction

Hepatocellular carcinoma (HCC) is one of the major malignancies worldwide [1–4]. With recent advances in diagnostic imaging, particularly in ultrasound (US), an increasing number of small or early-stage HCCs have been detected. In patients with early-stage HCC, percutaneous ethanol injection (PEI) is a second choice when surgical techniques have been precluded. Over the past few years, however, several methods of thermal tumor eradication through localized heating or freezing, including radiofrequency ablation (RFA), laser ablation, microwave ablation, and cryoablation, have been developed and clinically tested. Among these, RFA has recently emerged as a real competitor to PEI.

Indeed, RFA is superior to PEI in the treatment of small HCCs from the viewpoint of treatment response and long-term survival [5–7]. It is difficult, however, to apply to tumors located near bile ducts, the gall bladder, and the diaphragm. In contrast, PEI is feasible, efficacious, and very safe.

We describe three cases of well-differentiated HCCs smaller than 15 mm in diameter located near bile ducts, the gall bladder, and the diaphragm, completely eradicated with PEI instead of using RFA.

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Case reports

Case 1

A 73-year-old woman with hepatitis C virus (HCV)-related cirrhosis (Child-Pugh A class) was admitted to Kobe Asahi Hospital for further examination of a 10-mm hyperechoic nodule in segment 2 (S2) near the bile ducts. The levels of tumor markers in March 2007 were as follows: α -fetoprotein (AFP) 26 ng/ml (normal: ≤ 10.0), lens culinaris agglutinin A-reactive fraction of AFP (AFP L3) 4.0% (< 10.0), and protein induced by vitamin K absence (PIVKA-II) 14 mAU/ml (≤ 40). Contrast-enhanced US revealed isovascularity in both the early- and postvascular phases. Contrast-enhanced computed tomography (CT) revealed an isovascular nodule in the early phase and washout in the late phase (Fig. 1a). Histologically, the nodule was a well-differentiated HCC characterized by more than twofold the cellularity of the nontumorous area and mild cell atypia with a thin trabecular pattern (Fig. 1b). PEI was administered (three sessions; twice a week) by 1 to 2 injections of 95% sterile ethyl alcohol (total 10.4 ml) delivered to the nodule with a multiple side-hole 21-gauge needle (Et-hanoject, TSK, Tokyo, Japan). After that, contrast-enhanced CT revealed a low-density area (LDA) (Fig. 1c), and, histologically, US-guided biopsy revealed complete necrosis of the nodule. The levels of tumor markers revealed the following values: AFP 14.4 ng/ml, AFP L3 3.7%, and PIVKA-II 14 mAU/ml. No local recurrence, metachronous tumors, or distant metastases of the original tumor have been observed for 22 months since PEI.

Case 2

A 55-year-old man with hepatitis B virus-related chronic hepatitis was admitted to Kobe Asahi Hospital for further examination of a 15-mm hyperechoic nodule in segment 5 (S5) near the gall bladder. The levels of tumor markers in May 2007 were as follows: AFP 4.9 ng/ml and PIVKA-II 19 mAU/ml. Contrast-enhanced US revealed hypervascularity in the early phase and defect in the Kupffer phase. Contrast-enhanced CT revealed a ring-shaped enhancement in the early phase (Fig. 2a) and washout in the late phase. Histologically, the nodule was a well-differentiated HCC characterized by more than twofold the cellularity of the nontumorous area and mild cell atypia with a thin trabecular pattern (Fig. 2b). PEI was administered (three sessions; twice a week) by 1 to 2 injections of 95% sterile ethyl alcohol (total 15.5 ml) delivered to the nodule with a multiple side-hole 21-gauge needle (Et-hanoject, TSK, Tokyo, Japan). After that, contrast-enhanced CT revealed an LDA or no enhancement (Fig. 2c), and, histologically, US-guided biopsy revealed complete necrosis of the nodule. The levels

Fig. 1 Before PEI: (a) contrast-enhanced CT revealed washout in the late phase (arrow); (b) well-differentiated HCC was observed. After PEI: (c) contrast-enhanced CT revealed an LDA (arrow)

of tumor markers revealed the following values: AFP 2.9 ng/ml and PIVKA-II 19 mAU/ml. No local recurrence, metachronous tumors, or distant metastases of the original tumor have been observed for 18 months since PEI.

Fig. 2 Before PEI: (a) contrast-enhanced CT revealed a ring-shaped enhancement in the early phase (arrow); (b) well-differentiated HCC was observed. After PEI: (c) contrast-enhanced CT revealed an LDA or no enhancement (arrow)

Case 3

A 71-year-old man with HCV-related cirrhosis (Child-Pugh A class) was admitted to Kobe Asahi Hospital for

further examination of a 15-mm hypoechoic nodule in segment 7 (S7) near the diaphragm. The levels of tumor markers in October 2007 were as follows: AFP 5.3 ng/ml and PIVKA-II 39 mAU/ml. Contrast-enhanced US revealed isovascularity in the early phase and defect in the Kupffer phase. Contrast-enhanced CT and magnetic imaging resonance revealed isovascularity in both the early and late phases. CT during arteriography disclosed slight hypervascularity (Fig. 3a) and CT during arterial portography revealed perfusion defect. Histologically, the nodule was a well-differentiated HCC characterized by more than twofold the cellularity of the nontumorous area and mild cell atypia with a thin trabecular pattern (Fig. 3b). PEI was administered (six sessions; twice a week) by 1 to 2 injections of 95% sterile ethyl alcohol (total 48.0 ml) delivered to the nodule with a multiple side-hole 21-gauge needle (Et-hanoject, TSK, Tokyo, Japan). After that, contrast-enhanced CT revealed an LDA (Fig. 3c), and, histologically, US-guided biopsy revealed complete necrosis of the nodule. The levels of tumor markers revealed the following values: AFP 3.6 ng/ml and PIVKA-II 24 mAU/ml. No local recurrence, metachronous tumors, or distant metastases of the original tumor have been observed for 14 months since PEI.

Discussion

PEI has been the standard therapy since the late 20th century; however, a drastic shift from PEI to RFA has recently been introduced into clinical practice because effective ablation seems more readily attainable with RFA than with PEI or microwave coagulation. Most trials comparing RFA and PEI for the treatment of small HCCs have demonstrated not only local efficacy but also survival in favor of RFA.

In a comparison of PEI and RFA on 86 patients with 112 HCCs [5], complete response was reached in 90.3% by RFA and 80% by PEI, with an average of 1.2 and 4.8 sessions, respectively. In a study of 232 patients (118 treated with RFA and 114 treated with PEI), the 4-year survival rate was 74% (95% confidence interval [CI] 65–84) for RFA and 57% (95% CI 45–71) for PEI, with a 46% smaller risk of death (adjusted relative risk, 0.54 [95% CI 0.33–0.89], $P = 0.02$), a 43% smaller risk of overall recurrence (adjusted relative risk, 0.57 [95% CI 0.41–0.80], $P = 0.0009$), and an 88% smaller risk of local tumor progression (relative risk, 0.12 [95% CI 0.03–0.55], $P = 0.006$) with RFA than with PEI [6]. Similarly, longer survival has also been suggested by the analysis of a subgroup trial in Taiwan [7], and Cho et al. [8] have reported that RFA demonstrates significantly improved 3-year survival status by the meta-analysis of four randomized

Fig. 3 Before PEI: (a) CTA revealed slight hypervascularity (arrow); (b) well-differentiated HCC was observed. After PEI: (c) contrast-enhanced CT revealed an LDA (arrow)

controlled trials. Moreover, RFA requires shorter hospitalization than PEI, which improves the quality of life.

Between January 1999 and May 2002, a total of 3,891 RFAs carried out percutaneously on 2,542 patients, laparoscopically on 23 patients, and surgically on 49 patients (total 2,614 patients) has demonstrated severe complications such as hemothorax, intraperitoneal bleeding, liver abscess, and liver infarction compared with none after PEI in 207 of the 2,614 patients (7.9%) and 9 (0.3%) deaths within 3 months after RFA: 3 from liver failure, 3 from rapid progression and sarcomatous changes, and 1 each from biliary injury, gastrointestinal bleeding, and acute myocardial infarction [9].

Notably, when RFA is done on HCCs near bile ducts, the gall bladder, and the diaphragm, the incidence of complications is more frequent. Twenty-five cases of biliary injury and biloma have been described among 2,614 cases [9], and three cases of late-onset diaphragmatic hernia after RFA of HCC have resulted in death [10, 11]. In our cases, the HCCs were located near bile ducts (case 1), the gall bladder (case 2), and the diaphragm (case 3).

According to extensive clinical and pathological studies on early-stage small HCCs in the past two decades, it has become evident that the majority of small HCCs up to around 20 mm in diameter are composed of well-differentiated cancerous tissues that lack the remarkable cellular and structural atypia seen in classical HCCs [4, 12–16]. Pathological studies on HCCs have shown, however, that tumor size is crucial in microscopic portal invasion and local metastasis. Strictly speaking, the difference in the size of tumors between 15 and 16–20 mm in diameter is significant.

The frequency of portal invasion is significantly lower in 11–15 mm (25%) than in 16–20 mm (40%) HCCs ($P < 0.01$) [17, 18]. Extranodular growth has been found in 5.3% of distinctly nodular tumors <15 mm and in 16.7% of those 16–20 mm in diameter [19]. Accordingly, local ablation therapy for small, distinctly nodular HCCs (16–20 mm) necessitates the ablation of at least a 10-mm wide margin of surrounding tissue to prevent local recurrence from extranodular tumor growth and/or from micrometastasis in the vicinity of the tumor [5]. In general, RFA is superior to PEI for tumor control. PEI, however, can almost totally ablate HCCs 11–15 mm in diameter [20], although the demonstration of complete necrosis by percutaneous core biopsy would not confirm complete tumor necrosis. In conclusion, from the viewpoint of safety, feasibility, and tumor control, we administered PEI, instead of RFA, for well-differentiated HCCs smaller than 15 mm in diameter, located near the bile ducts, the gall bladders, and the diaphragm. Further follow-up is needed to clarify the prognosis of these three cases.

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