Diffuse intrahepatic recurrence after percutaneous radiofrequency ablation for solitary and small hepatocellular carcinoma

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Abstract Two patients developed segmental, diffuse intrahepatic recurrence after percutaneous radiofrequency ablation (RFA) to treat a primary, solitary, and small (2.5 cm) hepatocellular carcinoma (HCC). Despite the size of the HCC, levels of the tumor markers (α -fetoprotein, α -fetoprotein-L3%, and des- γ -carboxyprothrombin) were all elevated before RFA, and tumors in both patients were contiguous with a major branch of the portal vein. Tumor biopsies of both patients revealed moderately differentiated HCC but diagnostic imaging showed an area of reduced tumor blood flow, suggesting a poorly differentiated component. Since early detection of post-RFA malignancies by standard ultrasonography and contrast-enhanced computed tomography was difficult, the most sensitive indicator of recurrence in these two patients was the elevated tumor markers. The diffuse intrahepatic recurrence was thought to be caused by increased intratumoral pressure during RFA, resulting in the dissemination of cancer cells through the contiguous portal vein. The clinical course of these tumors indicate that the choice of RFA should be carefully considered when treating specific subtype of HCC that is adjacent to main portal vein branch and involves a possible poorly differentiated component and that surgical resection or combinations of RFA with other treatment modalities such as transcatheter arterial chemoembolization should be considered as alternative treatment strategies.

Keywords Hepatocellular carcinoma · Radiofrequency ablation · Dissemination · Diffuse recurrence

Introduction

Percutaneous radiofrequency ablation (RFA) is a minimally invasive and highly curative local treatment for hepatocellular carcinoma (HCC) with a diameter 3 cm or less. It can be applied to multiple lesions and repeatedly performed for recurrent lesions [1, 2]. The procedure was approved in Japan as a local therapy for liver cancer in April 2004 and it is presently the main curative therapy for patients with cirrhosis and with small HCC and for those who are not good candidates for surgical resection [3]. According to the Japanese Guidelines for the Treatment of Liver Cancer, RFA is indicated for tumors with a diameter of 3 cm or less and also for up to three lesions [4]. However, problems related to RFA therapy include rapid recurrence and cancer cell dissemination [5–10].

We describe two patients who underwent curative RFA according to the indication criteria of the Japanese Guidelines for the Treatment of Liver Cancer to treat primary and solitary small HCC accompanied by high tumor marker levels. They both developed subsequent segmental, diffuse, intrahepatic recurrence around the treated lesions. The diffuse recurrence did not form tumors, which differed from nodular recurrence. Cancer cell dispersion through the portal vein during RFA might have been responsible for the recurrence in these patients. Thus, the potential for serious complications of RFA should be carefully considered before establishing a strategy to treat highly malignant HCC, as illustrated by our experience with these two patients.

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Case reports

Case 1

Contrast-enhanced computed tomography (CT) revealed a liver tumor of 2.5 cm in diameter adjacent to the posterior branch of the portal vein in segment 6 of a 49-year-old man with liver cirrhosis caused by hepatitis C. Contrast-enhanced ultrasonography and CT angiography revealed a tumor with ring-shaped enhancement (Fig. 1a, b); cholangiocellular carcinoma or metastatic liver cancer was suspected. However, HCC was diagnosed on the basis of elevated tumor markers: α -fetoprotein (AFP), 1,233.7 ng/ml; α -fetoprotein-L3% (AFP-L3), 16.7%; and des- γ -carboxyprothrombin (DCP), 211 mAU/ml. A tumor biopsy specimen showed a moderately differentiated HCC. Liver function was maintained (Child A), but the platelet count was obviously reduced ($5.5 \times 10^4/\text{mm}^3$), and the indocyanine green (ICG) test at 15 min was 29%. Thus, the HCC was judged unresectable, and percutaneous RFA using the Cool-tip RF system (Valleylab, Boulder, CO, USA) was performed. Post-RFA contrast-enhanced CT confirmed total tumor necrosis (Fig. 1c). Although the tumor markers had decreased to within normal ranges 3 months later, AFP level increased again (30.2 ng/ml) 4 months later. The patient had a low titer of hepatitis C virus serotype 2. Accordingly, low-dose interferon was administered for 24 weeks to eliminate the virus, and the hepatitis C virus became continuously negative. AFP level also decreased again to within a normal range during interferon therapy. However, the tumor makers began to increase immediately after the interferon therapy, and HCC recurrence was suspected. However, ultrasonography and contrast-enhanced CT, which were performed every 1–2 months, did not clearly indicate recurrent liver lesions. Contrast-enhanced CT performed 9 months after renewed elevation of the tumor markers showed new expansion of the low-density area in the posterior segment after the portal phase (Fig. 2a). Magnetic resonance imaging (MRI) revealed low-intensity on T1-weighted images and high-intensity on T2-weighted images in the same area of the liver, and a recurrent lesion was diagnosed. Liver function at the time of recurrence was Child A with an ICG value at 15 min of 14%, indicating that liver function had improved compared with that at the onset of the HCC. Thus, surgical resection was considered feasible. Before resection, tumor markers were high (AFP, 10,814 ng/ml; AFP-L3, 34%; and DCP, 256 mAU/ml). The right lobe of the liver was resected and gross inspection revealed that the tumor that developed after RFA was encapsulated, with coagulation necrosis inside. Microscopy revealed the absence of viable tumor cells inside the tumor. However, cancer cells had diffused at

the periphery of the tumor, and tumor thrombus was found both in the right hepatic vein and in the right posterior segment of the portal vein (Fig. 2b, c). Following resection, the patient developed bone, lung, and brain metastases, and died 17 months after surgery.

Fig. 1 **a** Hepatocellular carcinoma in segment 6 is adjacent to posterior branch of portal vein on CT portography (arrow). **b** Ringed enhancement in tumor evident on CT arteriography (arrow). **c** Contrast-enhanced CT shows complete necrosis of hepatocellular carcinoma in segment 6 after percutaneous ultrasound guided radiofrequency ablation (arrows)

Fig. 2 **a** Low-density area during portal phase on contrast-enhanced CT (arrows). **b** Liver parenchyma is replaced with diffused multiple small nodules in resected specimens. Ablated tumor is thickly encapsulated and completely necrotized. **c** Tumor thrombus growing into right hepatic vein

Case 2

A tumor of 2.5 cm in diameter was detected in segment 3 of the liver of a 71-year-old woman with chronic hepatitis C and multiple hepatic cysts. The liver tumor contacted the

P3 branch of the portal vein, and contrast-enhanced ultrasonography and CT arteriography revealed a heterogeneously stained tumor (Fig. 3a, b). Various tumor markers were elevated: AFP, 765.3 ng/ml; AFP-L3, 63.8%; and DCP, 1,598 mAU/ml. The platelet count was obviously reduced ($3.4 \times 10^4/\text{mm}^3$) and liver function parameters

Fig. 3 **a** Hepatocellular carcinoma is adjacent to portal vein branch of segment 3 on CT portography (arrow). **b** Heterogeneously enhanced tumor on CT arteriography (arrow). **c** Complete necrosis of hepatocellular carcinoma in segment 3 on contrast-enhanced CT after combination therapy of percutaneous ethanol injection and radiofrequency ablation (arrow)

were Child B and ICG 15 min of 16%. The surgical risk was high and the patient did not wish to undergo resection. Thus, percutaneous RFA using the Cool-tip RF system (Valleylab) was combined with ethanol injection. Subsequent contrast-enhanced CT confirmed complete tumor necrosis (Fig. 3c). However, serum tumor marker levels did not decrease after treatment and in fact further increased. Thus, recurrence was suspected, and ultrasonography and contrast-enhanced CT were performed every 1–2 months. However, recurrent liver lesions were not clearly indicated. Contrast-enhanced CT at 5 months after RFA revealed extensive diffuse recurrence in segment 3 of the liver (Fig. 4). However, contrast-enhanced ultrasonography with Levovist (SH U 508A; Schering AG, Berlin,

Germany) showed no clear inflow of the contrast agent into the tumor after the RFA and no residual tumor blood flow. Segment 3 was enhanced overall in the arterial phase but residual enhancement was observed throughout the delayed phase, indicating that recurrence was unlikely. When recurrence was diagnosed, all serum tumor marker levels were high (AFP, 411,428 ng/ml; AFP-L3, 38.6%; and DCP, 493 mAU/ml). Liver function (Child B and ICG 15 min of 21%) was worse than that at the time of the initial treatment. Resection was not considered an option. Portography revealed P3 portal vein invasion and left hepatic arteriography revealed extensive tumor staining throughout segment 3. Transcatheter arterial chemoembolization (TACE) was performed, but the patient experienced liver failure and died 2 months later.

Fig. 4 **a** Local residual blood flow of the tumor is not evident on arterial phase of contrast-enhanced CT (arrow). New extensive area is slightly enhanced in segment 3. **b** Extensive diffuse recurrence in segment 3 during equilibrium phase of contrast-enhanced CT (arrows)

Discussion

We performed curative RFA on two patients with primary, solitary HCC less than 3 cm in diameter, according to the indication criteria of the Japanese Guidelines for the Treatment of Liver Cancer. However, both patients developed highly advanced, diffuse recurrence that led to poor outcome. Several features of the two patients were similar, including the fact that the primary tumor was in contact with a major portal vein branch. When a tumor is contiguous with a major blood vessel, the cooling effect of blood flow helps to prevent sufficient elevation of the intratumoral temperature and RFA cannot achieve thermocoagulative necrosis of the tumor tissue [11]. Complete necrosis might not have been achieved in our patients because of this effect. However, diagnostic imaging after tumor recurrence in both patients notably revealed no clear post-RFA intratumoral blood flow. Also, the inspection of the resected specimen revealed complete necrosis of the tumor by the RFA in the first patient (Case 1). These findings indicate that recurrence due to incomplete RFA treatment was unlikely.

A second feature shared by both of these cases was that the tumors were not homogeneously stained, which is a finding typical of HCC. Several reports have indicated that moderately differentiated HCC is characterized by abundant arterial blood flow, whereas blood flow becomes reduced with the progression of cancer cell dedifferentiation [12, 13]. Ring-shaped enhancement was evident in the first patient (Case 1), whereas the tumor stain was faint and heterogeneous in the second patient (Case 2). Biopsy performed on tissues from both patients showed moderately differentiated HCC, but tumor staining on contrast-enhanced ultrasonography and on CT arteriography revealed an intratumoral region with decreased blood flow, indicating poorly differentiated cancer cells.

A third feature shared by both patients was that levels of the serum tumor markers AFP, AFP-L3, and DCP were high, although the tumors were quite small. Portal vein invasion correlates with serum AFP-L3 or DCP levels [14, 15]. Furthermore, the histopathological differentiation of HCC with a high AFP-L3 level is low and serum AFP-L3 or DCP levels are significantly higher in diffuse type than in nodular type HCC [16, 17]. Serum AFP-L3 and DCP levels were high in both of our patients, and the imaging findings indicated that poorly differentiated cancer cells were probably already present in the tumor together with microscopic portal invasion before RFA.

Accordingly, although the tumors in our patients were solitary, small HCCs, they appear to have been highly invasive, poorly differentiated, and in contact with portal branches. Ruzzenente et al. [10] reported that the risk factors for rapid growth of HCC after RFA were an elevated serum AFP level and the location of the tumor in the vicinity of a large portal vein. Insertion of a direct current needle into such HCC tumors by RFA results in increased intratumoral pressure [18]. In our patients, cancer cells had probably already invaded the blood vessels and disseminated in massive numbers via the large portal vein branch in contact with the tumors. The segmental distribution of diffusely infiltrated cancer foci also supports this notion.

The time until post-RFA recurrence differed between our patients. The post-RFA period before the tumor markers started to increase again was quite long (21 months) in the first patient (Case 1), whereas the markers steadily increased after RFA, and diffuse HCC recurrence was diagnosed after 5 months in the second patient (Case 2). This difference probably arose because the first patient (Case 1) received interferon after RFA to eliminate viral infection. Interferon has antitumor effects against HCC and is also effective in preventing HCC recurrence after treatment [19–23]. The possibility of de novo diffuse recurrence cannot be completely denied in the first patient (Case 1). However, AFP level that reincreased after RFA decreased again to within normal range during interferon therapy and became elevated again immediately after the completion of interferon therapy, although the hepatitis C virus was completely eliminated. This finding indicated that residual cancer cell proliferation was suppressed during interferon treatment but continued immediately after release from the antitumor effect of interferon, rather than the possibility of de novo diffuse recurrence in a cirrhotic liver. On the other hand, the tumor markers continued to increase in the second patient (Case 2), who did not receive interferon after RFA. Therefore, the liver of this patient might have harbored small multimetastatic nodules before the RFA procedure. However, the tumors in both patients were histologically encapsulated with neither apparent extracapsule invasion nor portal tumor thrombus

on several images, indicating a low possibility of intrahepatic metastasis before RFA.

Another cause of dissemination might have been the tumor biopsies. Preoperative liver biopsy is associated with a high incidence of tumor recurrence [24], but the risk of seeding with HCC is higher in simple diagnostic biopsies than in biopsies combined with therapeutic procedures [25]. Tumor biopsies were performed immediately before RFA in both patients. Thus, the possibility that the tumor biopsies in these patients elevated the risk of cancer cell seeding is probably quite low, although it cannot be completely ruled out. Nonetheless, considering the presumably high malignant potential of poorly differentiated HCC, indications for puncture of the tumor in needle biopsy or local therapy with a needle should be considered as carefully as possible, especially when patients might have poorly differentiated HCC.

Diffuse HCC recurrence accompanied by vascular invasion is difficult to diagnose at the early stage. Eggel's classification defines diffuse HCC as follows: the entire liver is replaced by innumerable small cancer nodules and differentiation from liver cirrhosis is difficult to determine by gross inspection. Since the lesion appears as individual microscopic cancer nodules, ultrasonographic identification of tumors is difficult. In both of our patients, persistently elevated tumor markers comprised the most sensitive indicator of HCC recurrence, the early detection of which was impossible even by periodic screening with ultrasonography and contrast-enhanced CT every 1–2 months. Early diagnosis of diffuse HCC recurrence is difficult by conventional ultrasonography and contrast-enhanced CT because diagnosis is based on tumor morphology and blood flow. The positive rate of fluorodeoxyglucose–positron emission tomography findings increases with reductions in the histopathological differentiation of HCC, and this diagnostic modality is useful for the early detection of recurrence after liver resection [26]. In addition, superparamagnetic iron oxide-enhanced magnetic resonance imaging (SPIO-MRI) provides information about the number of Kupffer cells and its capacity to detect tumors increase with decreasing levels of histological HCC differentiation [27, 28]. Furthermore, contrast-enhanced MRI with gadoxetic acid, a hepatocyte-specific contrast medium, is superior to contrast-enhanced CT for differentiating lesions [29, 30]. These procedures should be considered as diagnostic options when recurrent lesions are undetectable by ultrasonography and/or contrast-enhanced CT in the presence of steadily increasing levels of post-RFA serum tumor markers.

Based on analyses of circulating AFP messenger RNA after surgical resection of HCC, resection does not apparently increase the risk of cancer cell dissemination [31]. If resectable, consideration should be given to systematic resection of the liver as the treatment of choice for specific

subtype of HCC that is adjacent to major portal vein branch and involves a possible poorly differentiated component that may have microscopic vascular invasion, because the risk of dissemination via the circulation is likely to be high after RFA. Conversely, intervention that involves only minor invasiveness should be considered when tumors are unresectable and careful planning is required to prevent cancer cell dissemination via the blood. In particular, RFA should only be applied after tumor blood flow has been totally stopped by performing TACE. However, further study and analysis are required to determine whether this approach actually helps prevent diffuse HCC recurrence after RFA.

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