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Percutaneous ultrasound-guided radiofrequency ablation of hepatocellular carcinoma with artificially induced pleural effusion and ascites

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Background. Ultrasound-guided procedures are sometimes of limited use because the tumor is located under the diaphragm or near the surface of the liver. We investigated the safety and efficacy of radiofrequency ablation (RFA) with artificial pleural effusion and/or artificial ascites. ***Methods.*** Between January 2002 and May 2006, 43 lesions in 36 patients with hepatocellular carcinoma (HCC) were treated by RFA with artificial pleural effusion and/or artificial ascites. ***Results.*** Artificial pleural effusion allowed visualization of the whole tumor for 36 (83.7%) of the 43 lesions that were otherwise not detectable or poorly visible. Artificial ascites was also helpful in visualizing whole tumors that could not be visualized with only artificial pleural effusion. In all lesions, artificial pleural effusion and/or artificial ascites were helpful in performing percutaneous RFA. Artificial ascites was useful for creating a space between the liver's surface and the skin or diaphragm to avoid burns. Adverse effects after the induction of artificial pleural effusion included pneumonia in one patient and temporary atelectasis in another patient. Severe side effects were not observed. Complete necrosis after RFA was obtained in 43 (100%) of the 43 lesions. During a mean follow-up period of 31.8 ± 5.8 months, local recurrence at the ablation site was found in none of the 43 lesions. ***Conclusions.*** Percutaneous RFA with artificial pleural effusion and/or artificial ascites was a safe and useful treatment that resulted in good local control of HCC.

Key words: artificial pleural effusion, artificial ascites, radiofrequency ablation

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Introduction

The recent widespread use of percutaneous radiofrequency ablation (RFA) has yielded good results in the treatment of hepatocellular carcinoma (HCC).[1–3] However, when the tumor is located under the hepatic dome, it is difficult to visualize on ultrasound (US) owing to the presence of pulmonary air; thus, percutaneous tumor ablation (PTA) using thoracoscopic[4] or computed tomography (CT)-guided[5] approaches is used to overcome this limitation. As well, a laparoscopic approach has been used for tumors located near the liver's surface.[6] However, these approaches are much more invasive or complicated than PTA with artificial pleural effusion or artificial ascites. Although PTA with artificial pleural effusion[7–9] or artificial ascites[10–11] has been previously reported, there are no reports of PTA done with the combination of artificial pleural effusion and artificial ascites. Therefore, in this paper, we report our experience with and the impact of RFA for HCC done using artificial pleural effusion and artificial ascites, both separately and in combination.

Subjects and methods

Patients

Between January 2002 and May 2006, 29 men and 7 women with HCC (43 HCC lesions) were enrolled for RFA treatment with artificial pleural effusion and/or artificial ascites (Table 1). During the same period, we treated 118 patients with 263 HCC lesions by conventional RFA without combination effusion. We generally perform RFA with artificial pleural effusion or artificial ascites if the HCC nodules are located at the liver's surface, or near the diaphragm, intestine, gall bladder, stomach, or heart). Median patient age was 70.5 years (range, 48 to 89 years). All patients had longstanding

Table 1. Summary of results in patients treated by radiofrequency ablation with artificial pleural effusion and/or artificial ascites

	Age (years) median ± SD	Sex M:F	Average size (mm) mean ± SD	Number of nodules	Visualization good:poor	Complete necrosis	Local recurrence	Complications
Pleural effusion only	69.3 ± 5.9	15:2	17.3 ± 6.7	21	2:19	21	0/21	2/21 Pneumonia, 1 Liver abscess, 1
Pleural effusion and ascites	71.6 ± 4.1	11:5	13.0 ± 1.0	19	0:19	19	0/19	1/19 Atelectasis
Ascites only	69.5 ± 0.5	3:0	16.8 ± 4.8	3	3:0	3	0/3	0/3
Total	70.5 ± 4.7	29:7	16.9 ± 5.5	43	5:38	43	0/43	3/43

chronic liver disease. Three patients were positive for hepatitis B surface antigen, 30 were positive for hepatitis C virus, and three had cryptogenic hepatitis. Twenty-nine patients had Child-Pugh class A, and seven had Child-Pugh class B liver cirrhosis. Patients with Child-Pugh class C liver cirrhosis, bleeding tendency, chronic heart disease, or chronic pulmonary disease were excluded from this study. The diameter of the HCC ranged from 5 to 36 mm (mean ± standard deviation, 16.9 ± 5.5 mm) on dynamic CT (Light Speed Ultra 16, GE Yokogawa Medical Systems, Tokyo, Japan) or US (SSD 5500, Aloka, Tokyo, Japan). The ethics committee of our university approved the study protocol, and written informed consent was obtained from all patients before treatment. This study's observation period was 31.8 ± 5.8 months (range, 17.7–50.4 months).

Of the 43 lesions, 11 lesions were new and 32 were recurrent. The diagnosis of HCC was based on the presence of enhancement on CT hepatic arteriography and a perfusion defect on CT arterial portography during angiography (Integris BV 3000, Philips, Tokyo, Japan); histological findings of the percutaneous liver biopsy; and increased levels of tumor markers, such as α-fetoprotein or des-γ-carboxyprothrombin.

When a hypervascular tumor was noted on angiography, it was mandatory to perform transcatheter arterial embolization (TAE) before RFA therapy by injecting iodized oil (lipiodol, Guerbet, Paris, France) with a gelatin sponge (Gelfoam, Upjohn, Kalamazoo, MI, USA) into the segmental branch or the subsegmental branch of the hepatic artery. In this study, TAE was attempted in 31 (72.1%) of the 43 lesions.

When the tumors were located under the hepatic dome and could not be visualized or were only partly detected on US, though not on CT, US was performed again with artificial pleural effusion.

Artificial pleural effusion and artificial ascites

All patients were premedicated with an intramuscular injection of 25 mg of hydroxyzine and 15 mg of pentazocine while conscious. During each procedure, oxygen saturation and other vital signs were observed regularly.

To produce the artificial pleural effusion, the location of the pleural cavity was first determined. In practice, we identified the region considered to be the pleural cavity on US as the area where the liver could be observed on deep expiration but could not be observed on deep inspiration because of pulmonary air. This area was usually located between the right anterior and the right posterior axillary lines. After local anesthesia was given, a 21-gauge needle was inserted gently through the chest wall. When the tip of the needle was just in front of the surface of the liver, 5 to 10 ml of 5% glucose sterile solution at 37°C was injected. The needle was considered to be correctly inserted into the pleural cavity when no resistance was noted during the test injection. After approximately 5 mm of fluid space was observed on US, 50 to 100 ml of 5% glucose was injected. The needle was then changed to a 14-gauge needle (Daimon needle, Silux, Kawaguchi, Japan), and 5% glucose was rapidly injected to produce an artificial pleural effusion. After injecting a sufficient amount of 5% glucose, we attempted to observe the tumor on US with the patient in a semisitting position. More 5% glucose was added until the tumor or the needle tract was visualized clearly (Fig. 1).

Artificial ascites was produced by first establishing local anesthesia and then inserting a 21-gauge needle just in front of the surface of the liver to inject 5% glucose. RFA therapy was started as soon as the fluid space was made, before the fluid could escape into the rest of the abdomen (Fig. 2).

Radiofrequency ablation

After these procedures were completed, RFA was performed. The locations of the 43 lesions and their treatments were as follows: for 19 (8 in segment 7 and 11 in segment 8) that were located under the hepatic dome but deeper than 5 mm from the liver surface and not

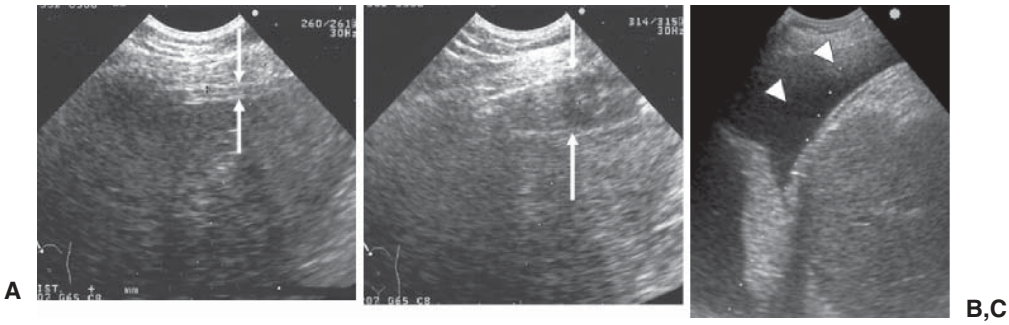

Fig. 1A–C. Production of artificial pleural effusion. **A** We found the pleural cavity (*arrows*) on ultrasound (US). A 21-gauge needle was inserted gently through the chest wall. **B** An approximately 5-mm-wide fluid space (*arrows*) was observed on US, and was followed by injection of 50 to 100 ml of 5% glucose. **C** 5% glucose was added until the tumor or the needle tract was visualized clearly by artificial pleural effusion (*arrowheads*)

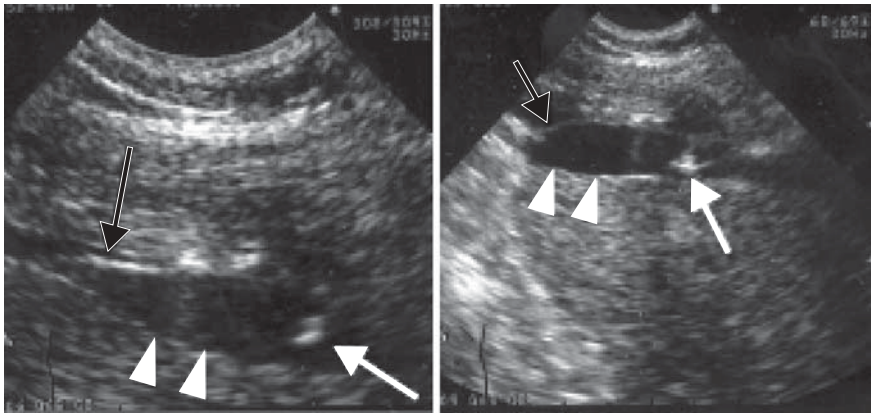

Fig. 2. Production of artificial ascites. Artificial ascites (*white arrowheads*) was produced by insertion of a 21-gauge needle (*white arrow*) into the space between the diaphragm (*black arrow*) and the surface of the liver and injecting 5% glucose. We started radiofrequency ablation therapy as soon as the fluid space was made, so that the fluid would not escape to other spaces in the abdomen

well visualized owing to the presence of pulmonary air, RFA was performed with only artificial pleural effusion being induced; for two that were well visualized on US, artificial pleural effusion was induced to obtain a safe needle tract to avoid injuring the hepatic vein; for three (1 in segment 1, 1 in segment 5, and 1 in segment 6) that were not under the hepatic dome but were located near the liver's surface (within 5 mm), RFA was performed with only artificial ascites; for 17 that were located under the hepatic dome and near the liver's surface (2 in segment 2, 8 in segment 7, and 7 in segment 8), RFA was performed with a combination of artificial pleural effusion and ascites; and for two (both in segment 8) that were not close to the liver's surface but could not be visualized well with only artificial pleural effusion, RFA was performed with a combination of an artificial pleural effusion and artificial ascites. The main factor that necessitated the use of artificial ascites or artificial pleural effusion was the location of the HCC. For HCC close to the surface of the liver, artificial ascites appeared to be better to avoid burning the pleura or peritoneum. By using artificial fluids, pain can be avoided and the HCC can be well visualized, which allows safe and precise RFA treatment.

A Cool-Tip needle radiofrequency system (Radionics, Burlington, MA, USA) was used in this study. Under US guidance, a 17-gauge monopolar Cool-Tip needle was precisely inserted into the tumor via the 14-gauge needle that was used to induce the artificial pleural effusion. In each lesion, to obtain a safety margin around the viable tumor, we selected a 2-cm or 3-cm ablation-type needle. Each ablation was done for 12 min or for at least four power roll-offs, as recommended by the manufacturer.

Within a week after RFA, dynamic CT was done. In patients in whom the low-density area surrounding the original tumor was considered large enough, "complete necrosis" of the tumor was considered to have been obtained, and no further treatment was given. However, if a low-density area did not completely surround the original tumor area, then additional RFA sessions were given until complete necrosis was achieved. When a residual tumor was easily detected on CT but it was difficult to distinguish the viable area from the original RFA ablation area on conventional gray-scale US, virtual US was used during the additional RFA treatment.

After each RFA treatment with artificial pleural effusion, as much as possible of the fluid in the pleural

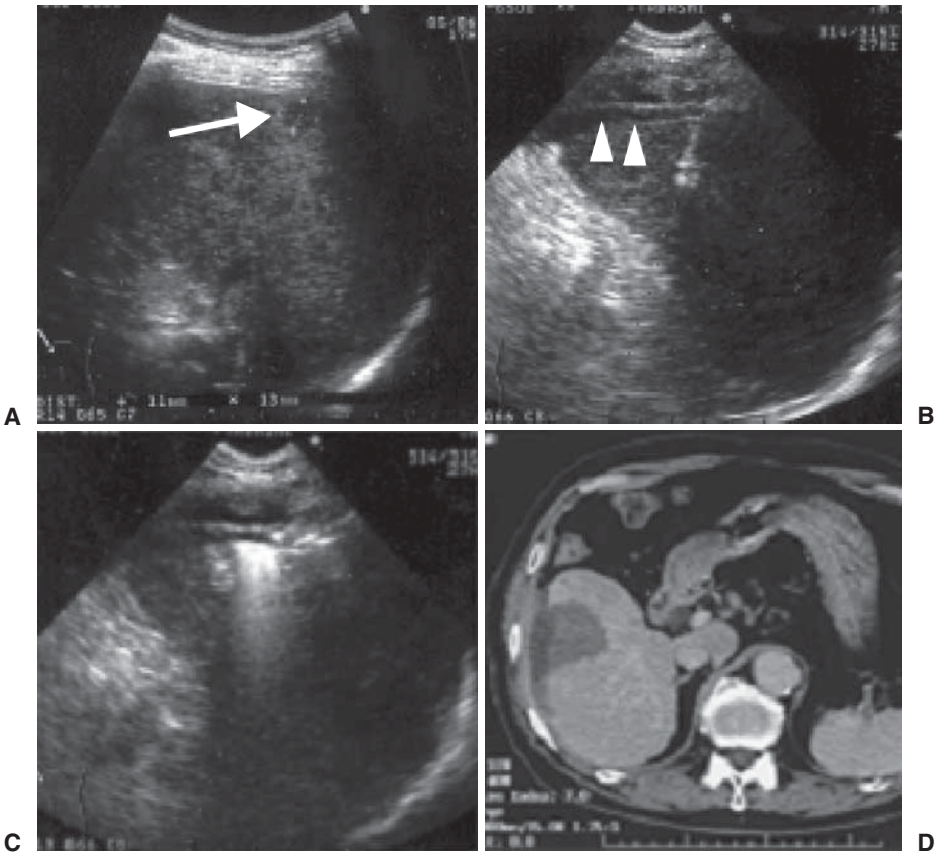

Fig. 3A–D. A 69-year-old man with hepatocellular carcinoma was treated by radiofrequency ablation with artificial ascites. **A** Ultrasonography obtained before treatment showed a hypoechoic nodule (*arrow*). **B** After an injection of 5% glucose to cause the artificial ascites (*arrowheads*), the radiofrequency ablation needle was inserted. **C** Ablation was completed without burning the diaphragm. **D** After the treatment, a computed tomography scan revealed a completely necrotic area

cavity was removed. Chest radiography was done immediately if the patient complained of respiratory symptoms, such as dyspnea or cough.

Results

Artificial pleural effusions were successfully induced in all patients; the volume (mean ± SD) of the injected pleural effusion was 514 ± 106 ml. Artificial pleural effusion allowed the visualization of the whole tumor on US in 36 (83.7%) of the 43 lesions located under the hepatic dome that were not previously detectable or were poorly visible on US. Oxygen inhalation was needed during the procedure in 5 (12.2%) of 36 patients. The pleural effusion disappeared within 1 week in 38 (95.0%) of 40 cases; one of the remaining patients developed transient pneumonia, and the other developed temporary atelectasis secondary to the artificially induced pleural effusion. One patient who received RFA with artificial pleural effusion developed a liver abscess that required drainage (Table 1).

In all lesions, artificial ascites induced with 210 ± 86 ml of 5% glucose created a space between the liver surface and skin or diaphragm that helped avoid burns. RFA treatment with artificial ascites alone was done to ablate a tumor located in segment 6 near the surface of the liver in one case; the patient's tumor developed complete necrosis without pain or skin burn (Fig. 3).

The use of artificial pleural effusion and/or artificial ascites was also helpful for visualizing the whole tumor and the needle tract in five lesions in which the conventional route was blocked by the hepatic vein. Overall, artificial pleural effusion and/or artificial ascites played a role in performing percutaneous RFA in 38 (88.4%) of the 43 lesions. In five lesions that were difficult to detect on US, virtual US was used. Among 19 patients who received RFA with artificial pleural effusion and artificial ascites, 12 patients (63.2%) experienced no pain; slight pain was reported by six patients (31.6%), and only one patient (5.2%) experience a moderate level of pain and needed analgesics. Finally, there was no lesion for which ablation had to be discontinued owing to intolerable pain. No side effects were observed in patients in whom both artificial pleural effusion and artificial ascites were induced.

Complete necrosis after RFA was obtained in 43 (100%) of the 43 lesions. Local recurrence at the ablation site was found in 0 (0%) of the 43 lesions. There were no cases of seeding in either the pleural or abdominal cavity.

During the observation period, two patients (5.5%) died from recurrent HCC and liver failure that was not related to the RFA treatment.

Discussion

When using PTA in patients with HCC, the tumor must be clearly visualized on US to avoid complications and to treat the tumor successfully.[12] Recently, percutaneous RFA has become widely used in HCC patients owing to its safety and efficacy.[1–3] However, RFA is difficult when the tumor is located under the hepatic dome or near the surface of the liver, since the tumor is then poorly visible on US, or adjacent structures, such as the diaphragm or skin, can be burned. Several approaches, such as PTA assisted by thoracoscopy[4] or laparoscopy[5] under general anesthesia, can be used to overcome these limitations and obtain good results. As well, the use of noninvasive methods, such as artificial pleural effusion[7–9] and artificial ascites,[10–11] has been reported. However, previously these methods have been used separately. In this study, the safety and local efficacy of RFA with both artificial pleural effusion and ascites was evaluated.

When performing PTA, it is also important that the needle tract be visualized clearly on US without any structures, such as the hepatic or portal vein, intervening. We induced artificial pleural effusion when the tumor or the needle tract could not be visualized clearly on US because the tumor was located under the hepatic dome or the hepatic vein blocked the view. Artificial ascites was induced in lesions in which the tumor or the needle tract was not clearly visible on US after artificial pleural effusion was induced; artificial ascites was also induced when the tumor was located near the surface of the liver to avoid thermal injury to adjacent structures. Using these procedures, we succeeded in overcoming some of the limitations of percutaneous, US-guided RFA, and the treatment was performed safely in all patients. However, in patients with a past history of a pulmonary or abdominal operation, which can cause intra-abdominal adhesions, the use of this method may be limited, although we did not experience any such difficulties.

In this study, the combination of artificial pleural effusion and artificial ascites was used in patients having lesions under the hepatic dome and near the surface of the liver. If the tumor had been ablated without inducing artificial ascites in these patients, all of the tumor might not have been ablated owing to pain. Adhesions between the liver and the diaphragm might also have occurred as a result of a diaphragm burn. Of note, intra-abdominal adhesions limit the ability to successfully treat HCC patients noninvasively. Indeed, most patients with artificial ascites showed decreased pain during ablation. All but one patient could be ablated completely without severe pain. The induction of artificial ascites did not cause ablation to be discontinued in any patients. Since HCC patients can be expected to have recurrences, the initial choice of method should take into account the treatment of the next recurrence. Koda et al.[7] reported that percutaneous RFA with artificial pleural effusion was useful, and, although they did not mention the possible complication of adhesions developing between the liver and diaphragm, they did report difficulty in inducing artificial ascites in the subphrenic space. To overcome this difficulty, we began ablating the tumor as soon as the space between the liver and the diaphragm became visible on US, before the fluid could escape into the abdominal cavity. At present, RFA with the combination of artificial pleural effusion and artificial ascites is still not an established method. However, we identified advantages of performing RFA with this combination instead of a artificial pleural effusion or artificial ascites, and we were able to perform the treatment safely.

Complications due to RFA done with artificial pleural effusion and/or artificial ascites were seen in 3 of 43 HCC lesions (7.0%). Pneumonia occurred in one patient and atelectasis in another; both resolved within a week. A liver abscess was observed in one patient and was treated successfully with antibiotics and drainage. The pneumonia and atelectasis were likely secondary to the artificial pleural effusion, and the liver abscess might have been a result of the RFA. These patients with complications were among the first we treated using this approach; more recently, we have found no such complications. In contrast, with conventional RFA, 21 (8.0%) of 263 treated HCC lesions were associated with complications.[13–17] Thoracic complications were seen in six patients (thoracic cavity bleeding in one, pleural effusion in three, atelectasis in two), abdominal bleeding in four, liver infarction in three, and a biloma developed in eight patients. The mortality rate related to conventional RFA has been reported to range from 0.2% to 0.7%;[18] however, there have been no deaths with our method. Owing to the lack of a prospective control group treated with conventional RFA, we cannot precisely compare the frequency of these complications. Nevertheless, the complications with artificial pleural effusion and/or artificial ascites were not serious and resolved easily.

Although the definition of "safety margins" for local efficacy is controversial in the treatment of HCC, it is important to ablate enough tissue to achieve complete necrosis and thus prevent local recurrence. To achieve this, artificial ascites is useful for creating a space between the liver and adjacent structures, which allows adequate safety margins as determined by CT, without any complications. Accumulation of lipiodol on CT is useful for judging the local efficacy of RFA, since one can distinguish the lipiodol accumulation area from the surrounding treatment area. In this study, all lesions were evaluated as having received adequate ablation by

comparing postablation CT images with CT images obtained before treatment. However, when lipiodol is not injected, it is difficult to tell whether the ablated area completely surrounds the original tumor. In one case, lipiodol was not injected owing to obstruction by the common hepatic artery. In this study, there were no cases of local recurrence (0%).[19–20] The injection of lipiodol into the feeding artery might play an important role in evaluating treatment efficacy in a hypervascular tumor. Although tumor seeding has been reported after PTA,[18] seeding in the pleural cavity or abdominal cavity was not observed in this study.

We previously reported that virtual US was useful in dealing with tumors that were seen faintly on US with the combination of artificial pleural effusion and artificial ascites.[21]

During the observation period of 31.8 ± 5.8 months, two patients died of recurrent HCC and liver failure. The aim of this study was not to evaluate long-term survival; thus, a study evaluating long-term survival with the use of this method needs to be done in the near future.

In conclusion, percutaneous RFA with artificial pleural effusion and/or artificial ascites appears to be a safe and effective treatment for obtaining good local control of HCC.

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