

TECHNICAL NOTE

Percutaneous Ethanol Injection via an Artificially Induced Right Hydrothorax for Hepatocellular Carcinoma in the Hepatic Dome

Akimichi Kume, Yuji Nimura, Junichi Kamiya, Masato Nagino, Yasushi Kito

Division of Surgical Oncology, Department of Surgery, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya, 466-8550, Japan,

Abstract

To evaluate the efficacy of sonographically (US) guided percutaneous ethanol injection (PEI) via an artificially induced right hydrothorax (transthoracic PEI) to treat US-invisible hepatocellular carcinoma (HCC) in the hepatic dome. Five cirrhotic patients with US-invisible HCC in the hepatic dome, who were poor surgical candidates, underwent transthoracic PEI. An artificial right hydrothorax was created by instilling 500 ml saline, and absolute ethanol was injected transhydrothoracically into the hepatic dome lesion under local anesthesia. The success and complications were assessed radiologically. The patients were followed up serologically and radiologically for 12–44 (mean 28.4) months. Twenty-five hydrothoraces were induced. All hydrothoraces enabled US visualization of the entire hepatic dome. Eight of the nine small lesions were treated successfully by the treatment. Two of the three local recurrences were eradicated by repeat transthoracic PEI. One large lesion was treated by a combination of transthoracic and regular PEI. The only complication was one clinically insignificant pneumothorax. Induction of a right hydrothorax is feasible and safe. The hydrothorax enables US visualization of the entire hepatic dome and permits US-guided PEI for HCC in the hepatic dome that otherwise would not be possible.

Key words: Hepatic dome—Hepatocellular carcinoma—Ultrasound guided—Percutaneous ethanol injection—Pleural space—Hydrothorax

Percutaneous ethanol injection (PEI) is one of the major treatments for small hepatocellular carcinoma (HCC) [1–5]. Because PEI is commonly performed under ultrasound (US) guidance, an HCC which is not detectable by US is not easily treatable with PEI [5]. Acoustic shadowing caused by air in the right lung makes US visualization of the entire hepatic dome difficult [6]. Consequently, HCCs in the hepatic dome have sometimes been unsatisfactorily treated by PEI [4, 5]. Although segmental or subsegmental transcatheter arterial chemoembolization (TACE) has been reported to be effective for such lesions [7–9], it is not always possible. Matsui

et al. [9] reported that they restricted the indication for subsegmental TACE to patients with fewer than three hepatic lesions.

To overcome these limitations, we artificially induced a right hydrothorax [10]. The therapeutic hydrothorax acted as an acoustic window and provided clear US images of the entire hepatic dome, thus enabling PEI to be performed transhydrothoracically (transthoracic PEI) for HCC in the hepatic dome [10]. In this report we describe the method of transthoracic PEI as well as its follow-up results.

Materials and Methods

Patients

From December 1997 to August 2001, five patients with HCC in the hepatic dome that was incompletely visualized by routine US underwent transthoracic PEI (Table 1). One patient (patient 1) had been followed at our outpatient clinic after partial hepatectomy and had received four PEI treatments to treat HCC with concomitant liver cirrhosis. The other four patients were referred to our clinic specifically for the treatment of US-invisible HCC in the hepatic dome associated with severe hepatic dysfunction due to liver cirrhosis. All patients were considered poor surgical candidates. Anti-hepatitis C virus antibody was positive in the sera of all patients. In two patients (patients 3 and 5) with extremely severe hepatic dysfunction (plasma indocyanine green disappearance rate [11] < 0.05), only transthoracic (and regular) PEI was selected, whereas in the remaining three patients, TACE was occasionally performed in addition. One patient (patient 4) had a history of upper lobectomy of the right lung 46 years previously. Results of a pulmonary function test (vital capacity and forced expiratory volume in 1 s [12]) were within normal limit in all patients. Informed consent was obtained from all patients prior to transthoracic PEI treatment, which was approved by the human research review committee of Nagoya University Hospital.

Transthoracic PEI

Transthoracic PEI was administered as a single- or multi-session treatment. We defined a single-session transthoracic PEI treatment as a combination of primary hydrothorax induction, transhydrothoracic ethanol injection, hydrothorax evacuation, and catheter removal. A multi-session transthoracic PEI treatment was defined as a combination of a single-session transthoracic PEI without catheter removal, repeated sessions of transhydrothoracic ethanol injection under secondary hydrothorax induction with subsequent hydrothorax evacuation, and final catheter removal. In every case commercially available physiologic saline preheated to 37°C was used to induce the hydrothorax.

Table 1. Transthoracic PEI (percutaneous ethanol injection via an artificially induced right hydrothorax)

Patient			HCC no.	Diameter (mm)	Sessions of transthoracic PEI treatment ^{b,c}			Additional TACE ^{c,d}	Total ethanol (ml)	Outcome ^{e,f}
No.	Age/sex	kICG ^a			1st	2nd	3rd			
1	68/M	0.084	1	11	1	2 (15)		18	D2 (29)	
			2	12	1					
2	62/F	0.092	3	16	1			6	D1 (43)	
			4	12	1					
			5	16	1					1 (3)
3	49/M	0.040	6	23	4			50	D1 (20)	
			7	15	2					
4	66/M	0.060	8	13	0 ^g	2 (3)	1 (6)	1 (4)	32	D2T (11)
			9	8	1					
5	65/F	0.035	10	61	4	6 (3)		261 ^h	R2 (9)	

^akICG, plasma indocyanine green disappearance rate

^bOne transthoracic PEI treatment includes a primary hydrothorax induction and one- or multi-session ethanol injections

^cNumbers in parentheses are time since the previous treatment (months)

^dTACE, transcatheter arterial chemoembolization

^eDE1, died after one transthoracic PEI; D2, died after repeat transthoracic PEI; D2T, died after repeat transthoracic PEI treatment with additional TACE; R2, recurred after repeat treatment of transthoracic with concomitant and regular PEI

^fNumbers in parentheses are time from the last treatment to the final CT/MRI (months)

^gEthanol was not injected

^hCombination of two transthoracic PEI treatments and eight separate regular PEI sessions were performed

The patient was placed in the supine position and an intravenous catheter was placed. Then, a primary right hydrothorax was induced under local anesthesia by either a two-step or a one-step method. The two-step method was used initially in two instances before it was replaced by the one-step method.

The two-step method of inducing a primary right hydrothorax was performed as follows: First, a 23 gauge needle connected to a three-way stopcock attached to a 5 ml syringe was inserted into the right 6th intercostal space in the midaxillary line. The needle was advanced gently until there was a loss of resistance, which indicated that the needle tip had entered the pleural space. Then, 200 ml of saline was injected slowly into the right pleural space using a 20 ml syringe, and the needle was withdrawn. Subsequently, the pleural space was catheterized at the same insertion site using a commercially available central venous access kit, and an additional 300 ml of saline was instilled through the catheter using an intravenous drip infusion set connected to the intrapleural catheter.

The one-step method of inducing a primary right hydrothorax was performed as follows: First, an 18 gauge Tuohy needle was inserted into the right 6th intercostal space in the midaxillary line under US guidance. After US confirmed that the needle tip was within the intercostal muscles, the stylet was removed, and the needle was connected to an intravenous drip infusion set with a 500 ml saline bottle that was hung about 50 cm above the bed. After the roller clamp of the drip infusion set had been fully opened, the needle was carefully advanced while the drop chamber was observed closely. When saline drops started to enter the chamber, and hence the pleural space, the advance of the needle was stopped, and the needle was held tightly in this position until all 500 ml of saline had been instilled, and the Tuohy needle was withdrawn.

After inducing a primary right hydrothorax, US was performed to examine the hepatic dome via the hydrothorax. When the targeted lesions in the hepatic dome were visualized by US, they were punctured transhydrothoracically using a 20 cm, 21 gauge needle with a closed conical tip and three terminal sideholes (PEIT needle; Hakko, Tokyo, Japan) and absolute (99.5%) ethanol was injected. The volume of ethanol injected into each lesion was estimated before the procedure using the equation proposed by Shiina et al. [3], but the actual volume was usually modified depending on patient compliance, the change in the US appearance of the lesion during ethanol injection, and the response to earlier injections as determined by

contrast-enhanced computed tomography (CT) or contrast-enhanced magnetic resonance imaging (MRI) when multi-session transthoracic PEI was performed [13]. The maximum amount of ethanol was limited to 15 ml per session based on our protocol for a routine single PEI session.

After ethanol injection, the pleural space was catheterized using a commercially available central venous access kit and the intrapleural saline was aspirated. When an intrapleural catheter had already been placed during the process of inducing a right hydrothorax (two-step method), the catheter was used to aspirate the intrapleural saline. When an adequate volume of ethanol had been injected in one session, the catheter was withdrawn and the treatment finished (single-session transthoracic PEI). If an adequate volume of ethanol could not be injected in one session, the catheter was left in situ and multi-session transthoracic PEI was scheduled.

In multi-session transthoracic PEI, the subsequent session was scheduled for 3–7 days after the previous session. The patient was placed in the supine position and an intravenous catheter was placed. This time, a secondary right hydrothorax was induced using the indwelling catheter without anesthesia. An intravenous drip infusion set was connected to the distal end of the indwelling intrapleural catheter and 500 ml of saline was instilled through the catheter into the right pleural space. After induction of a secondary right hydrothorax, a subsequent session of transhydrothoracic ethanol injection was performed. After ethanol injection, the intrapleural saline was aspirated through the indwelling catheter.

Postprocedurally, a chest radiograph was taken to look for pneumothorax. Vital signs were closely monitored before, during, and for 6 hr after each treatment session. Contrast-enhanced CT and/or MRI were used to evaluate the effect of ethanol injection [13] as well as intrathoracic complications such as lung injury or pleural effusion. In multi-session transthoracic PEI, the indwelling catheter was finally removed after confirming the effect of the treatment by contrast-enhanced CT and/or MRI. In patients with additional tumors outside the hepatic dome, regular PEI was performed concomitantly with transthoracic PEI.

After treatment, one patient who had been followed at our outpatient clinic (patient 1) was followed again at our outpatient clinic, while the remaining four were followed by the former attending physicians who had referred the patients to us. Contrast-enhanced CT and/or MRI were performed at an interval of 3–6 months until the patients developed hepatic failure.

Results

Twenty-five hydrothoraces (11 primary and 14 secondary) were induced. The entire hepatic dome was visualized by US via the right hydrothorax in every case. Vital signs remained completely stable during the procedure. Pneumothorax occurred once after one of the two primary hydrothorax inductions by the two-step method, but was clinically insignificant. Of the 25 transthoracic PEI sessions, four were complicated with five episodes of sporadic fever over 38°C (two sessions on the treatment day, one session on the treatment day and the next day, and one session on the next day). However, no persistent fever occurred. No other adverse effect related to the procedure was noted. Six of the 11 primary hydrothoraces were repeated ones; however, no adhesion related to previous transthoracic PEI was noted in the pleural space. During the study period, 18 examinations of contrast-enhanced CT or MRI were performed to evaluate the results of transthoracic PEI sessions. The time since the previous session was 1–13 (mean 5.4) days. In all examinations, the site of the puncture to induce a hydrothorax was within the domain of the examination field. No lung injury was diagnosed. Pleural effusion was detected on three of 11 examinations performed on the first to fifth day of the previous session and on one of seven examinations performed on the sixth to thirteenth day of the previous treatment session.

Ten HCCs were included in this series. Nine of the 10, in four patients (patients 1–4), were relatively small (less than 30 mm in diameter) and had been invisible by routine US. Nine transthoracic PEI treatments (15 sessions in total) were planned for them. Although US visualized the entire hepatic dome via the hydrothorax in each session, it failed to delineate one lesion (probably because it was isoechoic), which appeared on CT during arterial portography (CTAP) [14] as a negatively enhanced tumor, and treatment had to be abandoned in this case. This lesion became hypervascular on post-contrast CT 3 months later and was clearly delineated by US via the hydrothorax. It was successfully ablated by transthoracic PEI at that time. All other small lesions were clearly visualized by US via the hydrothorax and were successfully treated by transthoracic PEI. Thus, eight of the nine transthoracic PEI attempts on small HCC were successful.

All four patients were alive in August 2001. Radiological follow-up using contrast-enhanced CT and/or MRI was performed. The follow-up period was 12–44 (mean 28.4) months from the initial transthoracic PEI to the latest radiological examination. Three of the nine small HCC recurred locally and transthoracic PEI was repeated. While two of them were eradicated by repeat transthoracic PEI, the remaining lesion recurred again and was treated by TACE (Table 1). No local recurrence was diagnosed thereafter during the radiological follow-up period of 11–43 (mean 26.9) months (Table 1).

During three transthoracic PEI treatments, regular PEI was performed concomitantly for HCC located outside the hepatic dome. One patient (patient 1) developed multiple new hepatic lesions (without a local recurrence) in July 2001 and underwent TACE.

The remaining HCC (in patient 5) was a large tumor (61 mm in diameter) in the right anterior segment of the liver and was associated with two daughter lesions located outside the hepatic dome (an 11 mm lesion in the left lateral segment and a 10 mm lesion in the right anterior segment). Although the caudal two-thirds of the main tumor was within the domain of routine US, its cranial one-third was in the hepatic dome and was invisible by routine US.

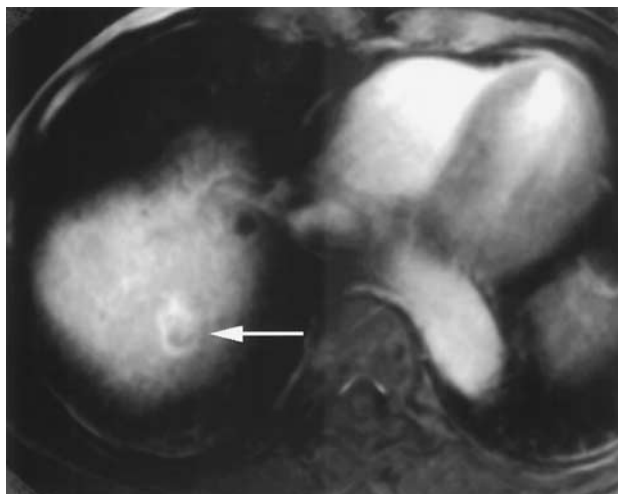


Figure 1. Contrast-enhanced magnetic resonance image in the arterial phase showing a hypervascular lesion (arrow) in the hepatic dome.

Hepatic function (plasma indocyanine green disappearance rate: 0.035) prohibited TACE [15], so combination treatment of transthoracic and regular PEI was conducted as an alternative treatment. After four sessions of transthoracic PEI (for the main lesion) with concomitant regular PEI (for the daughter lesions) had been performed, the intrapleural catheter became occluded and was removed. Post-contrast CT at that time suggested that the two lesions outside the hepatic dome had been completely ablated, whereas several scattered areas of the main tumor remained viable. Eight separate PEI sessions were applied to treat the caudal two-thirds of the main tumor and another six-session transthoracic PEI treatment was used for the cranial one-third of the lesion. Ablation required at total of 261 ml of ethanol. In June 2000, the patient was diagnosed as having a local recurrence together with multiple new HCCs in both lobes of the liver. Further treatment was abandoned, and the patient died of hepatic failure in February 2001, 20 months after the initiation of transthoracic PEI.

Case Presentation (Patient 1)

A 68-year-old man, who had undergone partial hepatectomy for HCC in the right anterior segment of the liver and four PEI treatments to treat other HCCs, was diagnosed as having a new HCC lesion in the hepatic dome on contrast-enhanced MRI (Fig. 1). Since the lesion could not be seen by routine US (Fig. 2), transthoracic PEI was performed in December 1997. US clearly visualized the lesion via the hydrothorax (Fig. 3) and permitted successful ethanol injection. Contrast-enhanced MRI performed 8 days after treatment showed no enhancement of the lesion during the arterial phase (Fig. 4), which suggested necrosis of the lesion [13]. The patient was followed at our outpatient clinic and underwent four PEI treatments to treat new HCCs that developed outside the hepatic dome. In March 1999, 15 months after the first transthoracic PEI treatment, the patient was diagnosed as having a local recurrence of the lesion treated with transthoracic PEI in addition to two other new HCCs located outside the hepatic dome. Two sessions of transthoracic PEI with concomitant regular PEI resulted in complete necrosis of all three lesions, suggested by contrast-enhanced MRI [13]. The patient continued to be followed at our outpatient



Figure 2. Right intercostal view during routine ultrasound. The view of the hepatic dome is obstructed by acoustic shadowing produced by air in the lung.

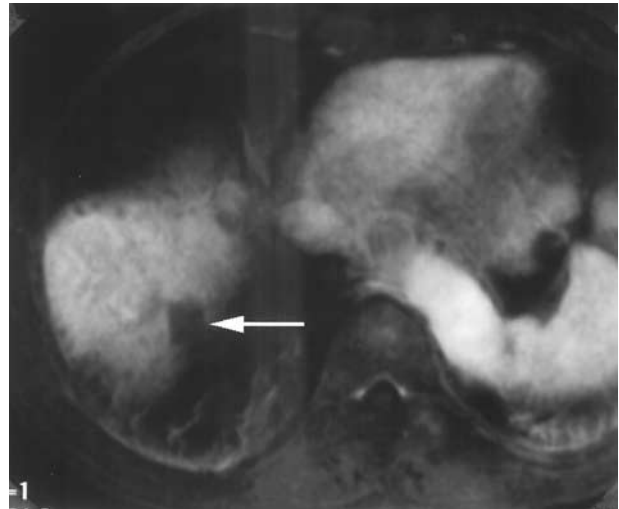


Figure 4. Contrast-enhanced magnetic resonance image in the arterial phase 8 days after percutaneous ethanol injection via a right hydrothorax revealing the treated lesion avascular (arrow).



Figure 3. Right intercostal sonogram via the right hydrothorax visualizing the entire hepatic dome and demonstrating the target lesion (cursors).

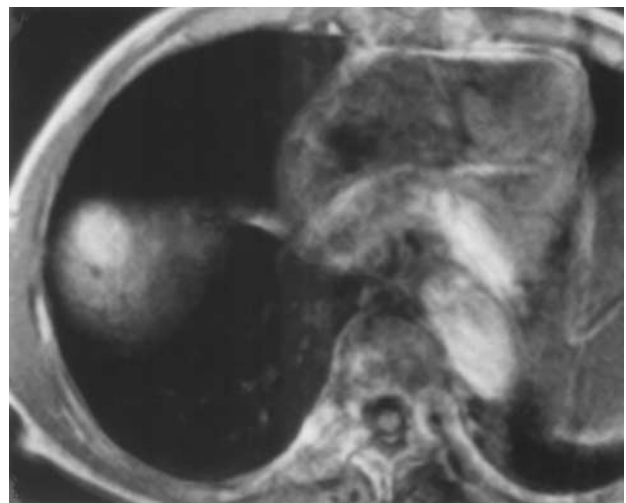


Figure 5. Contrast-enhanced magnetic resonance image in the arterial phase showing a hypervascular lesion in a different part of the hepatic dome.

clinic, and four PEI treatments were performed to treat new lesions outside the hepatic dome. In June 2000, by contrast-enhanced MRI 15 months after the second transthoracic PEI, the patient was diagnosed as having a new US-invisible HCC lesion in a different part of the hepatic dome (Fig. 5). The patient underwent single-session transthoracic PEI for a third time (Fig. 6). No residual lesion was found on a post-contrast CT scan taken in August 2000. In July 2001, multiple new HCC lesions were detected, so TACE was performed. The patient was in a good condition in August 2001.

Discussion

PEI is widely used to treat small HCCs [1–5]. PEI offers several advantages over other forms of treatment, including simplicity,

safety, limited invasiveness, effectiveness, repeatability, low cost, and absence of significant side effects [2]. Because PEI is usually performed under US guidance, HCCs in the hepatic dome, which are sometimes invisible by US due to acoustic shadowing caused by air in the right lung [6], may not be adequately treated by PEI [4], or may not be suitable for PEI at all [5]. Although segmental or subsegmental TACE has been reported to be effective for such lesions [7–9], it is not always possible. Patients who have multiple HCC lesions are not regarded as candidates for subsegmental TACE [9]. In December 1997, we succeeded in transthoracic PEI [10]. Since then, we have treated five inoperable patients with US-invisible HCCs in the hepatic dome. Our success rate with transthoracic PEI for small lesions was 89% (8/9), which is comparable with the reported efficacy of PEI for small HCCs [2, 16].

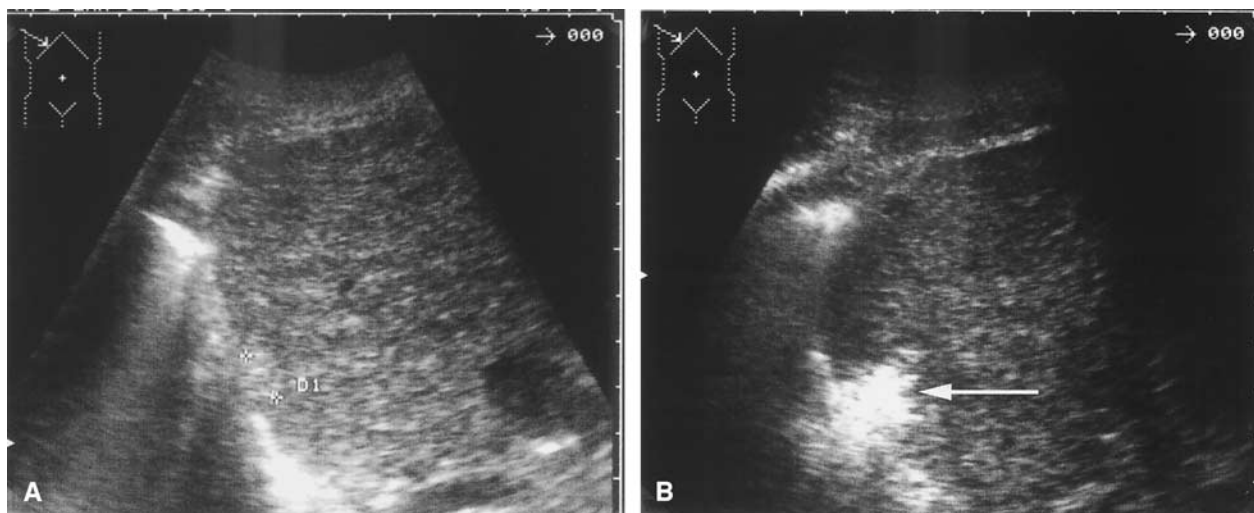


Figure 6. **A, B.** Right intercostal sonogram via the artificial right hydrothorax. **A** A new lesion in a different part of the hepatic dome is demonstrated (cursors). **B** The echotexture of the lesion has changed to a hyperechoic pattern (arrow) following ethanol injection.

Although six of the nine small lesions seemed to be eradicated by a single transthoracic PEI, the actual performance of transthoracic PEI remains unknown, since a histopathologic diagnosis of each lesion had not been obtained before treatment in this study.

Contrast pleurography, which is a combination of inducing an artificial pneumothorax (200–500 ml) and subsequent intrathoracic injection of contrast material, was experimentally developed by Rudy et al. [17] and was clinically established and popularized for various thoracic and lung diseases in the mid-1990s in Japan [18]. Pleural effusion is a common complication after hepatectomy [19], which frequently allows surgeons to perform thoracentesis [19]. In our department, a commercially available central venous access kit is used to evacuate pleural effusion. Sometimes the catheter is left in situ to repeat evacuation. Our technique employed for inducing a therapeutic hydrothorax for this study is a combination of those relatively safe and well-established techniques.

One patient developed a pneumothorax as a complication of two-step primary hydrothorax induction. Interpleural block is a common technique to control unilateral thoraco-abdominal pain and requires placement of a catheter into the pleural space [20, 21]. The incidence of pneumothorax after interpleural block has been reported to be about 2% [21]. Several alternative methods of placing an intrapleural catheter have been proposed to reduce the frequency of pneumothorax associated with interpleural block [22–24]. We modified the method proposed by Scott [24] to improve the way of inducing a primary right hydrothorax (one-step method) during our third transthoracic PEI. No patient developed a pneumothorax subsequently.

We initially placed an intrapleural catheter in the early stage of the process (two-step method) because the effect of a rapid infusion of saline into the pleural space was not well known. We thought that leaving an intrapleural catheter in place during the procedure would increase safety by providing a way to drain the hydrothorax if the patient developed respiratory distress. However, the initial two patients tolerated the infusion of 500 ml of saline so well that we became convinced an indwelling catheter was not necessary. Therefore the intrathoracic catheter was placed in the final stage of the process only to aspirate intrathoracic saline when the one-step method was adopted.

The second patient we treated had three lesions in the hepatic dome. Since we had no idea of multi-session transthoracic PEI using an indwelling catheter at that time, single-session transthoracic PEI was performed for those three lesions injecting 15 ml of ethanol in total, which was the maximum amount permitted in our protocol for a single transthoracic PEI session. One tumor recurred locally 3 months later, requiring another transthoracic PEI treatment. This experience led us to develop multi-session transthoracic PEI to treat our next patient (patient 3), who had two lesions in the hepatic dome. Here, we used contrast-enhanced CT to evaluate the results of the initial two transthoracic PEI sessions, which revealed a residual viable portion in one of the two lesions. Two additional transthoracic PEI sessions were performed immediately. The intrapleural catheter was removed after complete necrosis of the lesion was suggested radiologically.

One of the nine small HCC lesions was not visualized by US via the hydrothorax (probably because it was isoechoic) and transthoracic PEI was abandoned. A CT-guided angled approach [25] had been proposed for puncturing such lesions without traversing the lung; however, the technique seemed too technically challenging to be popularized. Recently CT-guided PEI (traversing the lung) for US-invisible HCC has been reported to be effective with a relatively low incidence of complicating pneumothorax [26–28]. CT-guided PEI can treat not only US-invisible lesions in the hepatic dome, but also tumors whose internal echotexture resembles that of surrounding liver parenchyma [28]. Additionally, CT provides immediate results of ethanol injection, which helps determine the endpoint of the treatment session [26, 28]. Moreover, recent advances in CT technology allow real-time CT fluoroscopy, which eliminates one of the greatest drawbacks to CT-guided PEI [28]. Nevertheless, unless real-time CT fluoroscopy is available, CT-guided PEI seems to be more involved and cumbersome than US-guided transthoracic PEI, which can be available everywhere, can avoid traversing the lung, can be performed even at the bedside, and does not expose the patient to X-rays.

In one patient with a large tumor in the right anterior segment of the liver, combination treatment of transthoracic and regular PEI was used to ablate the tumor. PEI alone is of limited efficacy for large tumors [16, 29] and TACE followed by PEI is recommended

[30]. However, we limited treatment to transthoracic and regular PEI, because the patient's liver functional reserve was severely limited [15]. Single-session PEI under general anesthesia has also been recommended for large HCCs [2]. However, this patient was considered a poor candidate for general anesthesia. In 2000, radio-frequency (RF) ablation therapy became more easily available in Japan. Accordingly good results of percutaneous transhydrothoracic RF ablation for hepatic dome lesions were recently reported [31]. We also successfully treated a case of a hepatic dome metastasis by transthoracic RF ablation in March 2002. Considering the recent results that RF ablation is more reliable than PEI for large HCC [32], RF ablation seems to be more suitable for such a large HCC.

In 18 contrast-enhanced CT or MRI examinations during 25 transthoracic PEI sessions, no lung injury was identified. Pleural effusion, which had been left in situ despite hydrothorax evacuation, seemed mostly to resolve within 5 days after a treatment session. We have encountered only sporadic fever within 2 days of a treatment session. However, if persistent fever had occurred and pleural effusion was simultaneously detected, effusion should have been examined bacteriologically to rule out empyema. Since no adhesion in the pleural space was encountered in our six repeated primary hydrothorax inductions, we think no severe pleuritis had been complicated by transthoracic PEI. In our limited series, no intrathoracic tumor seeding was encountered; however, given the fact that intra-abdominal tumor seeding after PEI is not very rare [33, 34] and that the results of local resection of the seedings are fairly good [34], the patients should be monitored closely during follow-up.

Some contraindications to transthoracic PEI exist. One patient had undergone right upper lobectomy of the lung. Transthoracic PEI was performed without complication; however, extensive intrapleural adhesions may disturb successful induction of a hydrothorax. Limited pulmonary functional reserve may also be a contraindication to transthoracic PEI. Multi-session transthoracic PEI has some unique problems. The indwelling intrapleural catheter must be managed carefully so that it does not become a source of intrapleural infection. Moreover its accidental occlusion or dislocation will require induction of another primary right hydrothorax.

In conclusion, our results suggest that induction of a right hydrothorax is feasible and safe, and that US via the right hydrothorax permits examination of the entire hepatic dome. Furthermore, US-guided transthoracic PEI is effective for treating conventional US-invisible HCCs in the hepatic dome. Transthoracic PEI is a promising method for using PEI to treat US-invisible HCCs in the hepatic dome; notwithstanding a slight increase in technical complexity, it has the same advantages as conventional PEI.

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