Percutaneous Ethanol Injection under Interventional Radiographic Computed Tomography-Fluoroscopic Guidance for the Treatment of Small Hepatocellular Carcinomas

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Background: Some small hepatocellular carcinoma (HCC) lesions show as tumor stains by dynamic CT, but cannot be detected by ultrasonography. Percutaneous ethanol injection (PEI) is effective for treating small HCC lesions, but lack of adequate visualization of some lesions can limit its use. In this study, interventional radiographic, CT-fluoroscopically–guided PEI was performed as a new method for treating small HCC lesions that were difficult to detect by ultrasonography.

Methods: Interventional radiographic, CT-fluoroscopically–guided PEI was performed on 11 patients (12 lesions) with HCC lesions measuring 2 cm or less in diameter. A thin needle was introduced into each tumor under CT-fluoroscopic guidance, with injection of contrast medium into the dominant hepatic artery. While lesions were observed using CT-fluoroscopy with the arteriogram, absolute ethanol was injected into the tumors. The ethanol injection rate and volume were monitored by observation of loss of tumor staining during real-time CT angiography.

Results: Needle introduction was successful in all 12 lesions, and disappearance of tumor staining was immediately observed on CT images after ethanol injection. Complications noted after treatment were local abdominal pain in all 11 patients, a slight fever in 9 patients, pneumothorax, right pleural effusion, and ascites, each in 1 patient. No other serious complications were observed.

Conclusions: Interventional radiographic, CT-fluoroscopically–guided PEI is effective in the treatment of small HCC lesions, which are difficult to show by ultrasonography and treat by conventional PEI.

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Key words: hepatocellular carcinoma, interventional radiography, CT fluoroscopy, ethanol injection therapy

INTRODUCTION

Percutaneous ethanol injection (PEI) under sonographic guidance (conventional PEI) has been found to be effective for the treatment of small hepatocellular carcinoma (HCC) lesions, particularly in patients with 3 or fewer early-stage HCC lesions measuring 3 cm or less in diameter.[1–4] However, this technique requires that the entire tumor can be clearly shown by ultrasonography. Although CT and angiography detect small lesions by showing tumor staining, ultrasonography may fail to visualize them in some cases, making it difficult to select the optimal therapeutic method. In recent years, CT-guided PEI has also been used, but in conventional CT systems, the puncture is essentially performed "blind," which may make it difficult to target small tumors accurately.

Recently, a CT-fluoroscopy system has been developed that permits CT images to be acquired in real time.[5] This system has been combined with an angiography system to create an interventional radiographic-CT/Angio system, making it possible to observe small HCC lesions repeatedly in real time in the same way as in ultrasonography. As a result, it is possible to introduce a fine needle into the target lesion under real-time CT guidance.

Interventional radiographic, CT-fluoroscopically guided PEI is expected to become a new alternative for the treatment of these small HCC lesions that are difficult to visualize by ultrasonography. The objective of this study was to assess the feasibility of this therapeutic technique. We investigated the accuracy of needle guidance, using CT-fluoroscopy, for treating small tumors measuring 2 cm or less in diameter by noting changes in tumor staining caused by ethanol injection,

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and recorded the complications associated with interventional radiographic-CT PEI procedures.

PATIENTS AND METHODS

Patients

Between March 1995 and September 1996, interventional radiographic-CT PEI was used to treat 11 patients with HCC (12 lesions) that were not visualized by ultrasonography, but were depicted as high-density areas on early-phase, dynamic CT images and also observed as tumor staining in angiographic images. Patient characteristics are shown in Table 1. Informed consent was obtained from all patients treated.

The diameter of tumors treated ranged from 1.0 to 2.0 cm (average, 1.5 cm). Two lesions were located in the caudate lobe (S1); 1 was in the lateral superior segment (S2), 1 was in the medial segment (S4); 1 was located in the anterior inferior segment (S5); 3 were in the posterior superior segment (S7); and 4 were in the anterior superior segment (S8) (Table 2). Ultrasonography had failed to show these lesions for a number of reasons. The echogenicity of the lesion was thought to be similar to that of the surrounding hepatic parenchyma in 5 lesions in S1, S2, S4, and S5. One lesion in S7, and 3 lesions in S8, were difficult to visualize because they were located immediately below the diaphragm, and the other 2 lesions in S7, and 1 lesion in S8, were considered difficult to depict because they were on the surface of the liver.

Table 1. Characteristics of patients with hepatocellular carcinoma, treated by interventional radiographic-CT percutaneous ethanol injection.

Variable	No. of patients
Sex	
Male	11
Female	0
Age (years, mean ± SD)	60.3 ± 7.8
Viral markers	
HBsAg (–), HCVAb (+)	11
Associated chronic liver disease	
Liver cirrhosis	11
Child's classification	
A	6
B	5
Previous treatment	
Hepatectomy	6
PEI	2
TAE + PEI	1
none	2
Alpha-fetoprotein (ng/mL)	
< 20 (normal)	5
≥ 20, ≤ 100	5
> 100	1
No. of tumors	
1	10
2	1

HBsAg, hepatitis B surface antigen; HCVAb, hepatitis C virus antibody; TAE, transcatheter arterial embolization; PEI, percutaneous ethanol injection.

Interventional Radiographic-CT/Angio System and CT Fluoroscopy

The diagnostic imaging system used in this study was an interventional radiographic-CT/Angio system (Toshiba, Tokyo, Japan). This system combines an Xpress/SX CT system, with real-time continuous CT (CT-fluoroscopy) and helical scanning capabilities, and a DFP-2000A angiography system, in a collinear arrangement (Fig. 1). The same patient examining couch is used for both CT and angiographic examinations. It slides longitudinally to permit a rapid switching between the 2 modalities.

CT-fluoroscopic images were acquired by scanning the same section continuously, at a rate of 1 rotation per second. Image data were updated every 60° to reconstruct images to a total of 360° of data continuously. Images are therefore generated at a rate of 6 images per second (1 image every 0.17 seconds), which permits observation in near real time. In addition, the system permits the observation of tumor staining on CT-fluoroscopy with arteriography in real time.

Treatment Methods

Interventional radiographic-CT PEI was performed as follows. First, digital subtraction angiography was performed selectively in the celiac, proper hepatic artery, and in other arteries to the liver, such as the right inferior phrenic artery and left gastric artery. CT arteriography was used to visualize the dominant arteries supplying the HCC lesion, and to confirm the presence of tumor staining. Based on the CT arteriogram, an entry point and direction for the puncture needle were determined. During injection of the contrast medium (Iopamilon; Schering, Berlin, Germany) at a rate of approximately 1 mL/sec via the dominant artery, the lesion was observed using CT-fluoroscopy, and 1 or 2 needles were introduced into the tumor. A 22G, 15-cm Chiba needle (Top, Tokyo, Japan) was employed for puncture. The needle was advanced through the pleura for 5 of the 12 lesions (Table 2).

After the entry of the needle into the tumor was confirmed, absolute (99.5%) ethanol was injected at a slow rate through each needle, using an extension tube and a 10-mL syringe. Two to 5 mL of ethanol was injected during real-time CT angiography, simultaneously with the observation of the loss of tumor staining during injection of the contrast medium via the dominant artery. Ethanol injection and confirmation of tumor staining were performed repeatedly, as needed. The needle was withdrawn when the tumor staining disappeared. CT arteriography was then performed again. If residual tumor staining was seen, the process

Table 2. Characteristics of 12 hepatocellular carcinoma lesions treated by percutaneous ethanol injection under interventional radiographic CT-fluoroscopic guidance.

Tumor no.	Tumor site	Tumor size (cm)	Number of punctures	Transpleural needle puncture	Volume of ethanol (mL)
1	S1	1.5	2	–	10
2	S2	2.0	4	+	16
3	S1	1.5	4	–	21
4	S8	1.5	2	+	11
5	S5	1.0	1	–	8
6	S8	1.8	3	+	17
7	S7	1.8	3	+	20
8	S8	2.0	2	–	19
9	S2	1.0	1	–	12
10	S4	1.2	1	–	19
11	S7	2.0	2	–	18
12	S7	1.2	2	+	15

S1, caudate lobe; S2, lateral superior segment; S4, medial segment; S5, anterior inferior segment; S7, posterior superior segment; S8, anterior superior segment.

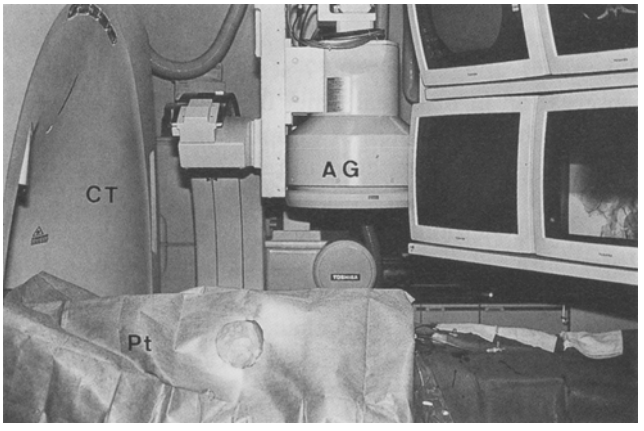

Fig. 1. Interventional radiographic-CT/Angio system. This system combines a CT and an angiography system (AG) in a collinear arrangement. Pt, Patient.

was repeated. Treatment was terminated after disappearance of tumor staining was confirmed.

RESULTS

Illustrative Case

A 57-year-old man with cirrhosis, who had tested positive for hepatitis C virus antibody, was admitted for recurrence of HCC in March 1995. He had undergone partial resection of the S8 area in June 1993. In August 1994, CT showed the recurrence of 3 HCC lesions in S2, the posterior inferior segment (S6), and S8, and transcatheter arterial embolization was performed twice, on 1 September 1994 and 21 October 1994. A good therapeutic response was observed in the S2 lesion, but the others were relatively unaffected, because they were supplied by the right inferior phrenic artery. Therefore, conventional PEI was performed in January and February of 1995, and disappearance of the lesions was confirmed by CT. At the same time, CT showed a lesion 1.5 cm in diameter in S1, which was not visualized by ultrasonography. The patient's liver function was judged to be Child's class A. His serum alpha-fetoprotein level was 8.6 ng/mL (normal range < 9.5 ng/mL). Angiography and CT arteriography revealed tumor staining in S1 from the inferior phrenic artery (Fig. 2A, B). Insertion of a catheter into S1 was considered difficult, and the patient was not considered a candidate for conventional PEI or transcatheter arterial embolization. Interventional radiographic-CT PEI was considered feasible, and informed consent was obtained from the patient.

Under CT-fluoroscopic guidance, with enhancement of the inferior phrenic artery, 2 puncture needles were inserted into the tumor (Fig. 2C). Injection of a total of 10 mL of ethanol (5 mL from each needle) resulted in the disappearance of tumor staining (Fig. 2D). After the procedure, the patient complained of transient local abdominal pain and slight fever, but was discharged 4 days later.

Puncture and Ethanol Injection under CT-Fluoroscopic Guidance

Based on previously acquired CT images, the liver segment and direction for puncture can be determined in advance. The puncture needle can be advanced while observing real-time CT images on the monitor, with the patient holding his or her breath, and with fine adjustment of the patient couch. Table 2 shows the number of punctures and the amount of ethanol injected at the time tumor staining disappeared for each tumor. Each tumor received 1 to 4 punctures. During angiography visualizing the dominant blood vessel, 2 mL to 5 mL of ethanol was injected from each needle, and changes in tumor staining were observed on CT images.

Tumor staining usually started to disappear during the ethanol injection. However, tumor staining did not disap-

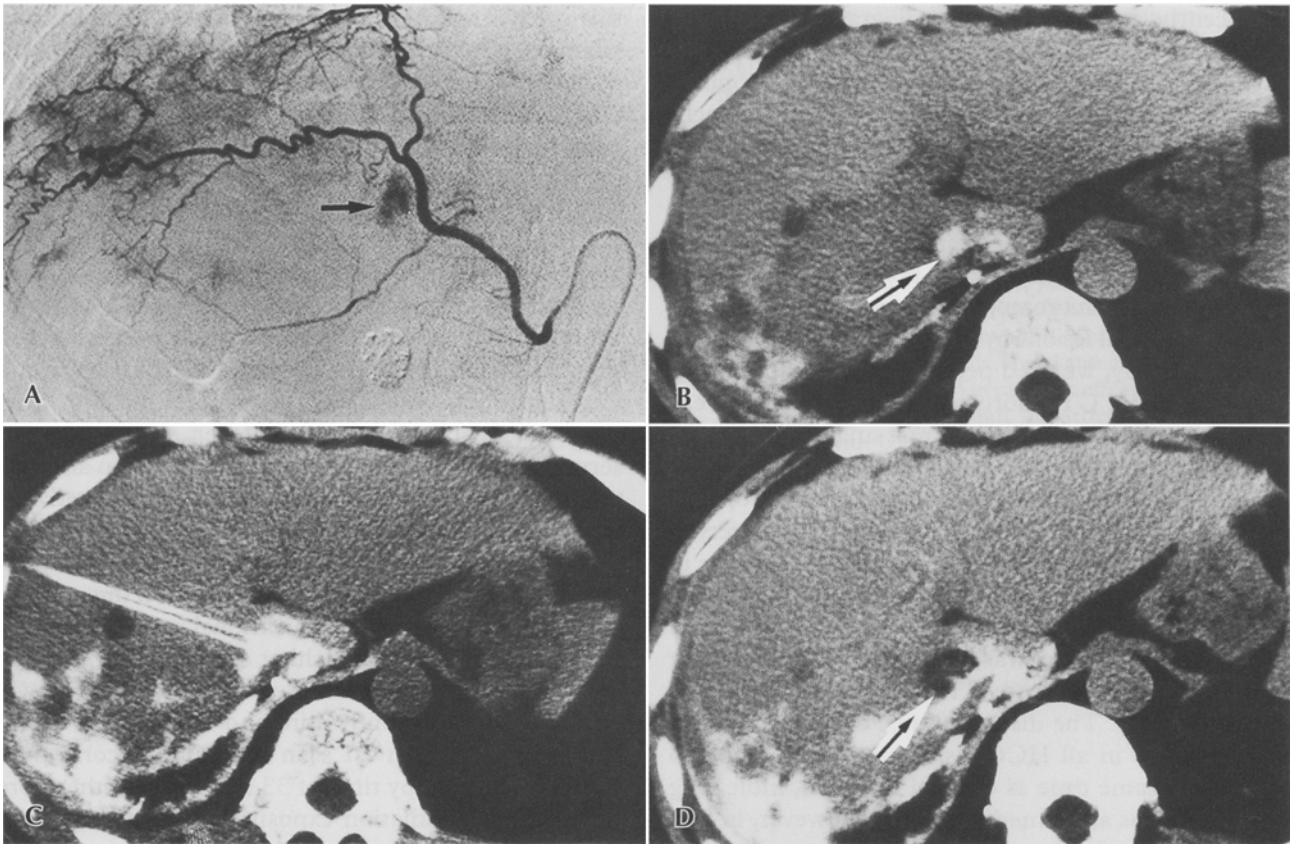

Fig. 2. Images from a patient who underwent percutaneous ethanol injection, under interventional radiographic CT-fluoroscopic guidance, for a hepatocellular carcinoma in the caudate lobe (S1). (**A**) Tumor staining in S1 (arrow), shown on a right, inferior phrenic angiogram. (**B**) CT with right inferior phrenic arteriography, showing a high-density area (arrow). (**C**) Two puncture needles were inserted into the tumor, under CT-fluoroscopic guidance, with enhancement of the right inferior phrenic artery. (**D**) CT with enhancement of the right, inferior phrenic artery after interventional radiographic-CT percutaneous ethanol injection. The tumor staining has disappeared (arrow).

pear during ethanol injection in 4 of 27 punctures (3 of 11 patients), and ethanol injection was stopped before a volume of 5 mL was administered. In these cases, the needle was reintroduced. If changes in tumor staining were observed, more ethanol was injected, up to a total volume of about 10 mL from each needle. All the tumors showed disappearance of tumor staining. The average number of ethanol injections required to eliminate tumor staining was 2.3 (range, 1 to 4), and the average volume of ethanol injected was 15.5 mL (range, 8 mL to 21 mL).

Complications

All patients reported transient local pain, and 9 of 11 patients developed slight fevers. One patient with an HCC lesion in S8, immediately below the diaphragm, developed pneumothorax, but this was successfully treated by placement of a chest tube for 5 days. Another patient developed a right pleural effusion due to ethanol leakage, but this was successfully treated by a single pleurocentesis procedure, in which about 500 mL of fluid was withdrawn. Another patient was found to have ascites by ultrasonography 1 day after the procedure, but this resolved 4 days later with the administration of diuretics. No other serious complications were observed.

DISCUSSION

PEI under sonographic guidance is effective for the treatment of small HCC lesions, and has the advantages that it is minimally invasive, and can be performed safely in patients with impaired liver function.[1–4] However, PEI requires that the entire tumor be delineated, and some lesions immediately below the diaphragm or near the liver surface cannot be visualized by ultrasonography. It was reported that the sonographic detection rate for HCC lesions measuring 3 cm or less in diameter was 84%, and that for HCC lesions less than 1 cm, the rate was as low as 37%.[6] It can therefore be expected that ultrasonography will fail to show some small HCC lesions that are detectable by CT and angiography. Patients with lesions that cannot be visualized by ultrasonography do not undergo conventional PEI.

Recently, an interventional radiographic-CT/Angio system, which combines an angiography system and a helical CT scanner, has been developed. The application of super-high speed image reconstruction techniques has enabled the near real time observation of lesions on CT images. Thus, it has become possible to advance the puncturing needle while observing the target lesion in real time under CT-fluoroscopic guidance.[7] In the liver, it has become possible to puncture a lesion under CT-fluoroscopic guidance, permitting the treatment of small lesions by PEI using CT-fluoroscopy.

In this study, we used percutaneous ethanol injection (PEI) under CT-fluoroscopic guidance (interventional radiographic-CT PEI) to treat small HCC lesions that were difficult to visualize sonographically. We instructed the patient to hold his breath at the appropriate position, adjusted the CT patient couch, and observed the insertion of the puncture needle into the tumor in real time on CT images. In this way, we were able to successfully puncture all small lesions measuring 1 to 2 cm in diameter. Ethanol was slowly injected while tumor staining was observed on CT arteriograms from the dominant artery. The disappearance of tumor staining was confirmed in all HCC lesions, and was found to occur at the same time as ethanol injection, indicating that ethanol has an immediate effect. However, in 3 of 11 patients, no changes in tumor staining were seen, even after the injection of 2 mL to 5 mL of ethanol, probably because ethanol entered the blood vessels, or flowed out of the liver, rather than spreading within the tumor. In these patients, ethanol injection was stopped, and the needle was reintroduced.

Conventional CT, as well as ultrasonography, has been used for guidance in ethanol injection procedures. However, when a conventional CT system is used, punctures are performed blindly after the direction and length of the puncture have been determined. Therefore, it is extremely difficult to accurately target small lesions, and it is not possible to confirm whether ethanol is effectively injected into the lesion. We also discussed techniques in which the puncture is performed under CT-fluoroscopic guidance alone, or under CT-fluoroscopic guidance with tumor staining by the intravenous injection of contrast medium. However, plain CT fails to show small HCC lesions in many patients. When intravenous contrast medium is used, the period of tumor staining is limited to several minutes. Therefore, it is usually difficult to perform PEI under CT-fluoroscopic guidance alone, or with intravenous injection of contrast medium alone. Conversely, interventional radiographic-CT PEI, as performed in this study, permits real-time observation of the treatment process and ensures the safe, accurate treatment of small lesions.

Ebara et al.[8] reports that HCC nodules become avascular after PEI, and that contrast-enhanced CT can correctly depict PEI-induced necrosis in HCC, and is reliable for evaluating the therapeutic effect of PEI. In this study, treatment was terminated when the disappearance of tumor staining was confirmed. The disappearance was immediately observed on CT images after ethanol injection, making it possible to judge the therapeutic effect during the procedure.

We also investigated the complications associated with interventional radiographic-CT PEI. The needle had to be advanced through the pleura for 5 lesions in S7 and S8, and 1 patient developed pneumothorax that was successfully treated by the placement of a chest tube for 5 days. No other serious complications were observed, showing that PEI can be safely performed by this method. Complications associated with ethanol injection were transient local pain and slight fever, which were observed in most patients. Right pleural effusion and mild ascites developed in 1 patient each, but resolved after several days. These complications have also been reported in conventional PEI procedures.

Radiation exposure to the patient and the operator is a major limitation of interventional radiographic-CT PEI procedures. Yamaguchi et al.[9] reports that radiation exposure to the patient's skin surface during CT fluoroscopy is 44.9 mSv/min, and in phantom experiments, a single chest CT scan was found to correspond to a CT fluoroscopy time of 33 seconds. Furthermore, the maximum radiation exposure to the operator was measured at the back of the hand, with a maximum dose of 2.8 mSv (much lower than the dose to the patient) observed in lung needle biopsy procedures performed under CT fluoroscopic guidance. We feel that it is necessary to improve CT systems, to develop associated equipment to reduce voltage and exposure time, and to minimize radiation exposure to the operator's hands, before interventional radiographic-CT PEI can become a widely performed procedure.

Interventional radiographic-CT PEI requires concurrent angiography, and is more troublesome than sonographically guided PEI. Therefore, lesions that can be clearly delineated by ultrasonography should be treated under sonographic guidance. However, in this study, we confirmed that tumors measuring 2 cm or less in diameter, which are difficult to show by ultrasonography, can be safely punctured under CT-fluoroscopic guidance. Using this method, it is possible to completely eliminate the tumor in a single treatment, and its effect can be confirmed immediately. Therefore, it is likely that interventional radiographic-CT PEI will reduce the length of hospital stays, as compared to that necessasry for conventional PEI. To establish the effectiveness of this new therapeutic method, it will be necessary to do long-term studies to investigate recurrence rates and serial changes of cancer markers, such as serum alpha-fetoprotein levels.

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