

Single-session Percutaneous Ethanol Ablation of Early-stage Hepatocellular Carcinoma with a Multipronged Injection Needle: Results of a Pilot Clinical Study

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PURPOSE: To investigate the feasibility, safety, and efficacy of single-session ethanol ablation with multipronged needles in the treatment of early-stage hepatocellular carcinoma (HCC).

MATERIALS AND METHODS: A pilot clinical study enrolled 20 patients with Child-Pugh A-B cirrhosis (15 men and 5 women 53–84 years old [mean 70.3 years old \pm 8.3, median 72 years old]) and with 25 HCC tumors 1.2–3.8 cm in longest diameter (mean 2.3 cm \pm 0.6) located in unfavorable locations for radiofrequency (RF) ablation. Ethanol ablation was performed under moderate sedation using a multipronged injection needle (Quadra-Fuse; REX Medical, Conshohocken, Pennsylvania) and ultrasound guidance. Follow-up period ranged from 12–24 months (mean 15.9 months \pm 4.6, median 16 months) and included contrast-enhanced computed tomography (CT) or magnetic resonance (MR) imaging performed 1 month after treatment and at 3-month intervals thereafter.

RESULTS: The treatment protocol was successfully completed in all patients (technical success rate 100%). No major complications were observed. A single treatment session with injection of 5–26 mL of ethanol (mean 9.5 mL \pm 5.5) resulted in complete tumor ablation at 1 month CT or MR imaging in 21 (84%) of 25 tumors. A second treatment session increased the number of tumors with complete response (CR) to 23 of 25 (primary effectiveness rate 92%). Tumor progression was observed in three cases during the follow-up period, for a rate of confirmed CR of 80% (20 of 25).

CONCLUSIONS: Ethanol ablation performed with a multipronged injection needle was not associated with any major complications and resulted in a high rate of confirmed CR. This technique offers an alternative to RF ablation for single-session treatment of early-stage HCC.

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Abbreviations: CR = complete response, HCC = hepatocellular carcinoma, RF = radiofrequency

HEPATOCELLULAR carcinoma (HCC) is the sixth most common cause of cancer (1). The incidence is increasing

worldwide because of the dissemination of hepatitis B and C virus infection. Patients with cirrhosis are at the

greatest risk of developing HCC and should be monitored every 6 months to diagnose the tumor at an early, asymptomatic stage (2,3). Patients with early-stage HCC (defined as a single tumor < 5 cm or up to three tumors < 3 cm each) can benefit from curative therapies, including liver transplantation, surgical resection, and percutaneous ablation (2,3). Liver transplantation is the only option that provides cure of the tumor and the underlying chronic liver disease. Transplantation is limited, however, by an inadequate supply of liver donors (4). Surgical resection is the treatment of choice for HCC in noncirrhotic patients,

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who account for about 5% of the cases in Western countries (3). Among patients with cirrhosis, candidates for resection have to be carefully selected to reduce the risk of postoperative liver failure (5).

Image-guided percutaneous ablation is currently recommended in patients with early-stage HCC who are unsuitable for surgical options (2,3). Ethanol ablation has been the first technique used for local ablation of HCC. Conventional ethanol ablation has several drawbacks, however, including long treatment times because of the need to perform multiple sessions and nonnegligible rates of incomplete ablation caused by the difficulty in achieving a complete and homogeneous perfusion of the tumor by using single end-hole needles. Radiofrequency (RF) ablation has emerged as the most effective method for tumor destruction and is currently used as the primary ablative modality at most institutions (6,7). Nevertheless, there are limitations to the use of RF ablation to treat early-stage HCC.

Histologic data from explanted livers in patients who underwent RF ablation as a bridge treatment to transplantation showed that tumor size and the presence of large (≥ 3 mm) abutting vessels—causing heat loss because of perfusion-mediated tissue cooling within the area to be ablated—significantly affect the outcome of the procedure (9). In one study, complete tumor necrosis was shown histologically in less than 50% of perivascular tumors (8). In addition, the treatment of lesions located along the liver surface—especially in proximity to the gastrointestinal tract—or adjacent to the porta hepatis or the gallbladder is associated with an increased risk of complications (9). It has been estimated that 10%–30% of early-stage tumors may be unsuitable for RF ablation because of their unfavorable location (10,11).

A multipronged injection needle has been developed to enable single-session ethanol ablation treatment and to ensure a more homogeneous ethanol perfusion throughout the whole tumor mass. The purpose of this pilot clinical study was to investigate feasibility, safety, and efficacy of ethanol ablation performed with a multipronged injection needle in the treatment of early-stage HCC in a location unfavorable for RF ablation.

MATERIALS AND METHODS

Study Design

This study was designed as a prospective, intention-to-treat, single-arm, single-institution pilot clinical trial. The primary endpoints of the study were safety and tumor response. Inclusion criteria for the study were as follows: (a) adult patient with HCC diagnosed according to noninvasive criteria or biopsy (3); (b) patient scheduled to undergo percutaneous ablation after multidisciplinary assessment; (c) tumor in unfavorable location for RF ablation (ie, ≤ 1 cm distance with respect to large [≥ 3 mm in diameter] vessels; the gallbladder; the main, right, or left bile duct; the diaphragm; or the liver surface in proximity to the gastrointestinal tract or the ureter); (d) uninodular tumor measuring 4 cm or less in diameter or early multinodular HCC (up to three lesions, each measuring < 3 cm in maximum diameter); (e) Child-Pugh A or B; (f) Eastern Cooperative Oncology Group score of 0–1; (g) American Society of Anesthesiologists score of 3 or less; (h) prothrombin time ratio greater than 50%; (i) platelet count greater than $50 \times 10^9/L$; and (j) written informed consent.

Exclusion criteria included (a) patient eligible for liver resection or transplantation; (b) presence of macroscopic vascular invasion or extrahepatic metastases; (c) previous treatment for HCC; (d) HCC in transplanted liver; (e) ongoing anticoagulant treatment that cannot be stopped; and (f) pregnancy or child-bearing potential.

Patients

Between May 1, 2006, and June 30, 2007, 20 consecutive patients who met the criteria were enrolled in the study. The patient population comprised 15 men and 5 women 53–84 years old (mean 70.3 years old ± 8.3 , median 72 years old) with 25 HCC tumors 1.2–3.8 cm in longest diameter (mean 2.3 cm ± 0.6). The cause of cirrhosis was related to viral hepatitis in 19 patients (hepatitis B, $n = 2$; hepatitis C, $n = 14$; combined hepatitis B and C, $n = 3$) and to alcohol abuse in 1 patient. Alpha-fetoprotein level was normal (< 20 ng/mL) in 13 patients, was mildly elevated (20–200 ng/mL) in 5 patients,

and was markedly elevated (> 200 ng/mL) in 2 patients. The diagnosis of HCC was established by using noninvasive imaging criteria in 16 patients and by biopsy in 4 patients (3).

Treatment Protocol

Ethanol ablation treatment was administered under real-time ultrasound guidance. Dedicated 3.5-MHz probes for ultrasound-guided interventions or guidance devices were used. A multipronged injection needle (Quadra-Fuse; Rex-Medical, Conshohocken, Pennsylvania) was used for ethanol injection. The device consists of an 18-gauge puncture needle 20 cm in length and a skin patch with 30-degree and 60-degree reference chart. The needle has three retractable prongs, each with four terminal side-holes and a connector with extension tubing clamp. The prongs are deployed from the lateral wall of the needle (1.5 cm proximal to the needle tip), and the deployment distance (maximum 5 cm) required is guided by an indicator on the device window.

The procedures were performed under moderate sedation with standard cardiac, pressure, and oxygen monitoring. The needle was introduced percutaneously into the center of the tumor nodule, and the needle tip was positioned at the deepest margin of the target tumor. The prongs were deployed to the margin of tumor. The three prongs were deployed initially to their maximum length and gradually withdrawn at 1-cm intervals. There was no predefined dose of ethanol to administer. Ethanol was injected until repeated leaks outside the target were seen on the ultrasound scans. An injection-rotation-injection maneuver was used. In tumors 3 cm or less in diameter, after injection of the maximal volume of the ethanol, the prongs were completely retracted into the needle, then a 60-degree rotation of the needle was performed, followed by repeat deployment of the prongs and injection of additional ethanol. In tumors 3.1–4 cm in diameter, two rounds of injection-rotation-injection were performed, the first one with the needle positioned in the deepest portion of the tumor and the second after withdrawal of the needle by 1–2 cm. During any treatment pause, 0.5–1 mL of heparinized saline solution was im-

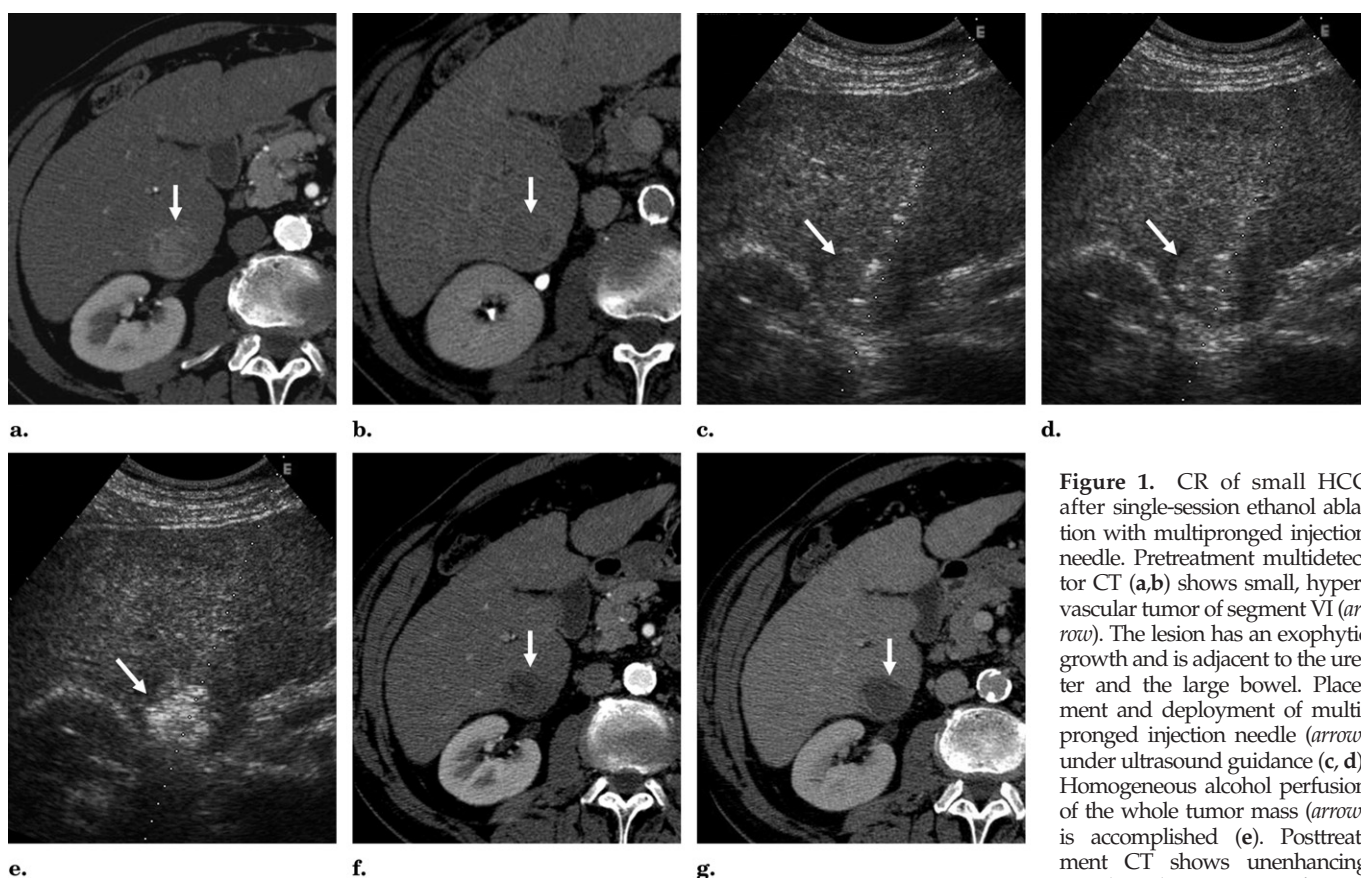


Figure 1. CR of small HCC after single-session ethanol ablation with multipronged injection needle. Pretreatment multidetector CT (a,b) shows small, hypervascular tumor of segment VI (arrow). The lesion has an exophytic growth and is adjacent to the ureter and the large bowel. Placement and deployment of multipronged injection needle (arrow) under ultrasound guidance (c, d). Homogeneous alcohol perfusion of the whole tumor mass (arrow) is accomplished (e). Posttreatment CT shows unenhancing area (arrow) consistent with complete tumor ablation (f,g).

mediately injected into the needle to prevent occlusion of the channels. After the completion of the procedure, the needle was left in the tumor for 1–2 minutes to minimize backward flow along the needle track and then removed.

The patient was observed in the recovery area for at least 2 hours. Any adverse event was evaluated and recorded. Major complications were defined as complications that, if left untreated, might threaten the patient's life, lead to substantial morbidity and disability, or result in hospital admission or prolonged hospital stay (12). All other complications were considered minor.

Follow-up Protocol

Follow-up was computed starting from the date of the ethanol ablation treatment. The follow-up period ranged from 12–24 months (mean 15.9 months \pm 4.6, median 16 months). The follow-up protocol included contrast-

enhanced triple-phase multidetector CT or dynamic MR imaging studies performed 1 month after treatment and at 3-month intervals thereafter. All studies were performed at the authors' institution by board-certified radiologists with specific skills in liver imaging.

Tumor response was evaluated following the American Association for the Study of Liver Diseases Panel of Experts amendment to Response Evaluation Criteria In Solid Tumors (13). Initial complete response (CR) of the target tumor was defined as the disappearance of any intratumoral enhancement at CT or MR imaging obtained 1 month after treatment. Persistence of viable tumor at 1-month CT or MR imaging (ie, initial treatment failure) was defined as incomplete response. The appearance over follow-up of foci of disease in tumors that were previously considered to be completely ablated (ie, late treatment failure) was defined as local tumor progression. The appear-

ance of new HCC lesions was defined as disease recurrence. Confirmed CR of the target lesion was defined as the absence of any evidence of local tumor progression after initial CR lasting a minimum of 12 months (Figs 1 and 2). Patients with local or distant recurrence were considered for repeat ethanol ablation, depending on overall clinical condition, liver function, and tumor characteristics on imaging. The treatment protocol for patients receiving repeat ethanol ablation was identical to the protocol used for the initial procedure. If additional ethanol ablation treatment was not indicated, patients were considered for transarterial chemoembolization.

RESULTS

The treatment protocol was successfully completed in all patients (technical success rate 100%). No major complication was observed. Fever



Figure 2. Confirmed CR of small HCC treated with multipronged ethanol injection in single session. Pretreatment multidetector CT shows 2-cm HCC (arrow) in segment V (a, b). The tumor is adjacent to the gallbladder. Placement and deployment of needle (arrow) under ultrasound guidance (c). Ultrasound monitoring during alcohol injection in the tumor (arrow) (d) and after the end of the procedure (e). Persistence of ethanol is shown all around the treated tumor (arrow). Follow-up CT obtained 12

months after treatment (f and g) shows shrinkage of necrotic area with absence of enhancement (arrow). Findings are consistent with confirmed CR.

(> 38° C) was the only complication and occurred in five patients.

A single treatment session with injection of 5–26 mL of ethanol (mean 9.5 mL \pm 5.5) resulted in complete tumor ablation at 1-month radiologic imaging of 21 (84%) of 25 tumors (in 16 of 20 patients). A second treatment session performed in the 4 tumors with residual viable neoplastic tissue increased the number of tumors with CR to 23 of 25 (primary effectiveness rate 92%). Three cases of local tumor progression were observed during the follow-up period in patients with initial CR. The rate of confirmed local CR was 80% (20 of 25 tumors). The rate of confirmed CR was 100% in tumors measuring less than 2 cm in longest diameter (8 of 8), 79% in tumors measuring 2–3 cm (11 of 14), and 33% in tumors measuring greater than 3 cm (1 of 3). Patients showing either incomplete response after the second ethanol

ablation treatment or local tumor progression during follow-up were treated with transarterial chemoembolization.

Development of new HCC tumors was observed in five patients, two of whom received additional ethanol ablation treatment. Transarterial chemoembolization was used to treat the remaining three patients with new HCC tumors. At the end of the study, 18 patients were alive, and 2 patients were dead. The cause of death was the emergence of diffuse, infiltrative-type HCC in one patient and the occurrence of liver failure without tumor progression in one patient.

DISCUSSION

Ethanol ablation has been the first technique used for local ablation of HCC. Ethanol induces coagulation necrosis of the lesion as a result of cellu-

lar dehydration, protein denaturation, and chemical occlusion of small tumor vessels. Ethanol ablation has inherent advantages in the low cost and low morbidity. Treatment is usually performed under local anesthesia and does not require patient hospitalization. The schedule includes four to six sessions performed once or twice weekly. The major limitation of ethanol ablation is the high local recurrence rate, which may reach 33% in lesions smaller than 3 cm and 43% in lesions larger than 3 cm (14,15). The injected ethanol does not always accomplish complete tumor necrosis because of its inhomogeneous distribution within the lesion, especially in the presence of intratumoral septa, and the limited effect on extracapsular cancerous spread.

RF ablation has been the most widely assessed alternative to ethanol ablation for local ablation of HCC.

Several electrode types are available for clinical RF ablation, including internally cooled electrodes and multi-tined expandable electrodes with or without perfusion (12). In contrast to ethanol ablation, RF ablation enables the creation of a 0.5–1 cm thick ablative margin around the tumor. This cuff ensures that microscopic invasions around the periphery of a tumor have been eradicated. Five randomized trials have consistently shown that RF ablation has a higher anticancer effect than ethanol ablation, leading to a better local control of small tumors (16–20). In addition, two recent meta-analyses confirmed that treatment with RF ablation offers a distinct survival benefit compared with ethanol ablation, establishing RF ablation as the standard percutaneous technique for the treatment of early-stage HCC (21,22).

Nevertheless, even in small tumors, the ability of RF ablation to achieve complete tumor eradication depends on tumor location. Histologic studies performed in liver specimens of patients who underwent RF ablation as bridge treatment to transplantation showed that presence of large (≥ 3 mm) abutting vessels results in a decrease of the rate of complete tumor necrosis to less than 50% because of the heat loss owing to perfusion-mediated tissue cooling within the area to be ablated (8). Several clinical experiences suggested that treatment of HCC tumors in a subcapsular location or adjacent to the gallbladder is associated with an increased risk of incomplete ablation and local tumor progression (23,24). Treatment of tumors in such unfavorable locations has also been shown to result in a significant increase of major complications (25). Although adjunctive measures, such as dextrose water solution injection to displace adjacent structures, have been used in attempts to deal with these limitations, it has been estimated that 10%–30% of HCC tumors of small size may be unsuitable for RF ablation because of their unfavorable location (10,11,26).

In the current study, the use of a multipronged needle for ethanol ablation was shown to be a safe and effective method for single-session treatment of early-stage HCC tumors in locations unfavorable for RF ablation. With this device, ethanol is injected from multi-

ple holes in various directions, which greatly facilitates accomplishment of a homogeneous distribution in the whole tumor mass. Despite the injection of relatively large amounts of ethanol and the inclusion of patients with HCC tumors in unfavorable locations, single-session ethanol ablation with multipronged needles was extremely well tolerated. No major complications were associated with the technique. Fever ($> 38^{\circ}\text{C}$) was the only minor complication and was observed in a few patients. These findings support large amounts of evidence from previous reports regarding the safety profile of ethanol ablation (11).

The rate of confirmed CR of the treated tumors obtained in this study was 80%. To prevent overestimation of treatment effectiveness, we adopted strict criteria for the definition of response, based on careful analysis of lesion enhancement in follow-up CT or MR imaging studies. Confirmed CR of the target lesions was declared only in patients in whom findings at CT or MR imaging were consistent with complete ablation of the treated tumors for a minimum of 1 year after treatment. The confirmed CR rate of 80% compares well with the reported outcomes of RF ablation for tumors located at unfavorable sites (25). The rate of success was affected by tumor size, however: Although none of the eight tumors smaller than 2 cm showed evidence of incomplete response or local tumor progression, two of three tumors larger than 3 cm had evidence of treatment failure.

This study has some limitations. First, the number of patients is small. In most patients who underwent RF ablation during the recruitment period, there were no contraindications to the use of RF ablation. Second, the follow-up period may not have been sufficiently long to identify late recurrences. It has been shown, however, that initial CR to percutaneous ablation is associated with an improved survival in patients with HCC, and it should be considered a relevant endpoint (27). Nevertheless, we acknowledge that after this initial evaluation of efficacy and safety, a large trial with a survival endpoint is warranted to prove unquestionably the clinical benefit of this approach.

Our results confirm, in a Western series, the result of a recent Asian in-

vestigation on the use of a multipronged injection needle for single-session ethanol ablation treatment of HCC (28). The rates of primary effectiveness and local tumor progression observed in that study were similar to those achieved in our series. Despite Asian investigators administering a larger amount of ethanol with respect to the amounts used in our study, the rate of major complications remained below the figures reported in most RF ablation series (9).

In this pilot clinical study, ethanol ablation performed with a multipronged injection needle was not associated with any major complication and resulted in a high rate of confirmed CR on imaging follow-up. The technique offers an alternative to RF ablation for single-session treatment of early-stage HCC.

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