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Acetic acid versus radiofrequency ablation for the treatment of hepatocellular carcinoma: A randomized controlled trial

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KEYWORDS
Hepatocellular carcinoma;
Radiofrequency ablation;
Acetic acid ablation;
Randomized studies;
Percutaneous treatment

Abstract
Purpose: The purpose of this prospective study was to compare the efficacy of percutaneous acetic acid (PAAI) to that of radiofrequency ablation (RFA) in the treatment of small (≤ 5 cm) hepatocellular carcinoma (HCC) using a randomized trial.
Material and methods: Consecutive patients with small HCC underwent clinical, biochemical, and imaging evaluation. Those fulfilling the inclusion criteria (Child's A/B cirrhosis, less than 5 HCC nodules, HCC nodules ≤ 5 cm diameter, no extrahepatic disease, patent portal vein, normal coagulation profile with informed consent) were randomly assigned to receive RFA or PAAI. Tumor response and survival rate were estimated. Non-inferiority margin of 10% difference was taken for effectivity of PAAI compared to RFA.
Results: Of the 86 patients screened, 55 patients with 67 HCC nodules were included. There were 40 men and 15 women with a mean age of 54.3 ± 10.5 (SD) years (range: 28—71 years). Of these, 26 patients had PAAI and 29 had RFA. The clinical, demographic and imaging profiles of the two groups were similar. Complete response was non-inferior to RFA [PAAI 75% and RFA 83.3%, difference 8.3% CI (−12.5% to 29.2%)]. Lower limit of this 95% CI (−12.5%) was lower than the 10% non-inferiority margin difference (8.3%). Survival rates were similar at 12 months (PAAI, 81.6% vs. RFA, 71.9%; $P = 0.68$) and at 30 months (PAAI, 54.4% vs. RFA, 52%; $P = 0.50$).
Conclusion: PAAI and RFA have similar efficacy in treating small HCC. PAAI could thus be a cost-effective alternative in situations where RFA is either unavailable or unaffordable.

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Abbreviations

HCC	hepatocellular carcinoma
RFA	radiofrequency ablation
PEI	percutaneous ethanol injection
PAAI	percutaneous acetic acid injection
CT	computed tomography
MRI	magnetic resonance imaging
kV	Kilovolts
mAs	millilampere
TRUFI	true fast imaging
VIBE	volumetric interpolated breath-hold examination
BCLC	Barcelona Clinic Liver Cancer
mRECIST	modified response evaluation criteria in solid tumors
HBV	hepatitis B virus
TACE	transarterial chemoembolization
SD	standard deviation

Introduction

Hepatocellular carcinoma (HCC) is the third leading cause of death due to cancer with about 700,000 deaths each year worldwide [1]. Interventional radiology-based treatment accounts for a large proportion of the treatment options for HCC [2], of which ablation is the recommended treatment for early HCC. Amongst the ablative techniques, radiofrequency ablation (RFA) is the most established and widely used treatment [3]. Due to similar survival outcome of RFA by comparison with surgical resection, RFA is the first line therapy for HCC less than 3 cm in diameter [4]. HCC prevalence is high in the developing world and access to RFA is limited due to high cost, infrastructure requirement and lack of skilled expertise. Thus, there is a need for an alternative ablative option in resource constraint settings.

Prior to RFA, percutaneous ethanol injection (PEI) was the standard of care for small HCC [5–7]. However, it had limitations of long treatment time, limited effect on the extra-capsular cancerous spread and high local recurrence rates [8–10]. Acetic acid, another chemical agent, has also been used percutaneously for the treatment of HCC [11]. Data on efficacy of percutaneous acetic acid injection (PAAI) in ablating HCC is scarce. Just two randomized controlled trials are available comparing PAAI with PEI [12,13], and only one comparing PAAI plus PEI with the gold standard technique of RFA [14].

Availability of RFA in India is limited to a few tertiary care centers only. In addition, high cost of disposable electrodes further limits its usage. On the opposite, acetic acid is easily available, inexpensive, and requires no costly infrastructure for the procedure. However, to date, no studies have compared the efficacy of PAAI to that of RFA. Should PAAI show results that are non-inferior to those of RFA, PAAI could then be used as an alternate option to RFA for treating HCC.

The purpose of this prospective study was to compare the efficacy of PAAI to that of RFA in the treatment of small ($\leq$ 5 cm) HCC using a randomized controlled trial.

Materials and methods

Participants

Institutional ethic committee approval was obtained for this prospective study. Trial was registered at http://www.clinicaltrials.gov/ (number NCT01438437). Informed written consent was obtained from all patients. Between January 2001 to June 2015, consecutive patients with HCC underwent detailed clinical, biological examinations, endoscopy and multiphasic computed tomography (CT) or magnetic resonance imaging (MRI) of the liver. The inclusion criteria was the following:

- Child A or B cirrhosis;
- HCC nodules $\leq$ 5 cm in diameter;
- $\leq$ 5 nodules of HCC;
- patent main portal vein;
- normal coagulation profile;
- no extrahepatic disease;
- providing written informed consent.

Patients with Child C cirrhosis, peripheral HCC nodule or adjacent to major organs (like gallbladder, diaphragm, hepatic hilum), exophytic HCC or previously treated HCC, were excluded.

Stratified randomization was done for treatment allocation (*i.e.*, PAAI or RFA). Child A and B cirrhosis strata were taken; each further divided into sub-strata, of solitary or multiple HCC nodules. Sequences were generated by a statistician in permuted blocks of four each. Random allocation of treatment codes (PAAI-A, RFA-B) were written on a paper and kept in serially numbered opaque sealed envelopes. On work-up completion and obtaining consent, the research staff blinded to the contents, opened the envelope for allotment. Investigators performing intervention were not blinded to the treatment as the two ablative procedures were different.

Taking success rates of 95% for RFA and 85% for PAAI, at 90% power, for detecting an equivalence difference of 5% between the two procedures, 67 participants for each arm were estimated. As the trial progressed, there was paucity of patients in the early years. Thus, sample size revision was done in 2010. Recalculated sample size was based on 10% equivalence difference, success rates of 95% for RFA and 85% for PAAI, at 80% power, 27 participants were estimated for each arm. Recruitment was stopped on completion of sample size.

Ablative procedure details

Oral antibiotic was started the day before ablative procedures and thighs properly shaven before RFA. Procedures were performed with aseptic precautions, using local anesthesia and ultrasound guidance. Five procedures were done under CT guidance because HCCs were not seen on ultrasound. Two operators (M.S.G. and S.R.G.) with 10- and 7-years of experience, respectively in interventional radiology, performed ablation procedures.

PAAI

Total calculated dose of acetic acid for PAAI was three times the diameter of HCC [15,16]. Of this, 1.5–2 mL of 40%

glacial acetic acid (one session/week) was injected percutaneously into each HCC nodule. For minimizing pain, 4—5 mL Sensorcaine® (Bupivacaine HC1 Injection, USP) was injected into the HCC and needle tract while withdrawing the same needle.

RFA

RFA was performed using two devices. Before 2006, 17 patients underwent RFA using Radionics RFA system having continuous ice cold perfusion system, cool tip electrodes (single/cluster), generator, grounding pads and chilled saline. End temperature > 60 °C was achieved post-ablation. Needle tract was cauterized by withdrawing the electrode while hot. Tightly applied thigh grounding pads were observed for any heat/burns during RFA. From 2006 and after, Celon RFA machine (Celon AG Medical Instruments), which is a bipolar system was used. For each nodule, 40 KJ energy was deposited and needle tract ablated by intermittent power deposition during electrode withdrawal.

CT and MRI protocols

CT was performed on Somatom Sensation® 40 (Siemens Healthineers) unit. First, unenhanced CT images of the liver were obtained. Subsequently, enhanced axial CT images were obtained at 120 kV, 30—50 mAs and 5-mm slice thickness after intravenous administration of non-ionic iodinated contrast material (80 mL, Iohexol, Omnipaque® 300, GE Healthcare) at 25 s (arterial phase), 60 s (portal-venous phase) and 3 min (delayed-phase) after the start of contrast material injection Coronal CT images were also obtained.

MRI examinations were done on 1.5-Tesla (Magnetom Avanto®, Siemens Healthineers) unit. Two-dimensional T2-weighted turbo spin-echo, true fast imaging (TRUFI) and T1-weighted (with in-phase and out-of-phase) sequences were obtained. After intravenous administration of 0.1 mmol/kg of gadolinium chelate (Gadobenate dimeglumine, Multihance®, Bracco), 3D volumetric interpolated breath-hold (VIBE) sequences were obtained in the axial and coronal planes during the arterial phase (18—20 s), portal-venous phase (45—60 s) and delayed-phase (3 min). Diffusion-weighted MRI sequences were also obtained.

Three investigators (M.S.G., S.B.P. and S.R.G.) who had 16-, 14-, and 12-years of experience, respectively performed image interpretation. Investigators were not blinded to the type of ablative technique performed because they result in differences in imaging appearance. Final result was obtained by consensus readings.

Definitions

HCC was diagnosed using the modified European Association for Study of Liver criteria [16,17]. Barcelona Clinic Liver Cancer (BCLC) staging classification was used for staging HCC [17]. Small HCC was defined as a HCC nodule ≤ 5 cm in size. Cirrhosis was diagnosed on the basis of clinical, biological and upper endoscopy findings.

Tumor response was assessed using CT/MRI of the liver. Complete response was diagnosed when a homogenous, well-defined, hypo-attenuating ablative zone was seen at the tumor site with no enhancing tissue within/at periphery during the arterial or venous phase. End point of ablation was achieved when the tumor developed complete response. Incomplete ablation or partial response was diagnosed when a nodular enhancement at the periphery or within the hypo- attenuating ablative defect was present on arterial phase images with washout on portovenous or delayed-phase images on CT/MRI. After RFA, focal nodularity (asymmetric thickness) of the concentric enhancing ring around the hypo-attenuating ablative zone on arterial phase images, also suggested incomplete ablation.

Recurrence was diagnosed when local tumor progression was seen as a new enhancing tumor at the treated tumor site on CT/MRI. New lesions were those which appeared as new enhancing tumors in a different segment other than the original tumor on CT. Tumor response assessment criteria was changed to modified response evaluation criteria in solid tumors (mRECIST) criteria which came up in 2010. It categorized tumor response into complete or partial response, stable or progressive disease (Fig. 2) [18].

Follow-up and outcome measures

Four weeks after ablation procedure, patients had clinical examination, and biological tests. Tumor response was assessed using CT. MRI was performed when CT was inconclusive or unavailable.

Patients with complete response and normal liver function were followed up at 3-, 6- and 12-months and thereafter every six months. For patients with partial response, repeat ablation was undertaken. Patients with progressive disease were offered an alternative therapy depending on their BCLC stage. Follow-up was done till the study end (April 30, 2016), disease progression or death.

Primary outcome was tumor response and secondary outcome was the survival rate. Adverse effects were recorded.

Statistical analyses

Clinical, biochemical and imaging data, ablative procedure details and adverse events were collected by the study coordinator (S.B.P.). Statistical analysis was performed using Stata 12.1 (Stata Corp). Continuous data were expressed as mean ± standard deviation (SD) and ranges and compared among groups using Student *t*-test or Wilcoxon's rank sum. Categorical data were expressed as proportions and percentages and compared using Chi^2 test or Fisher exact test. Significance was set at $P < 0.05$. Cumulative progression free survival and overall survival probabilities were estimated using Kaplan—Meier survival curves.

Results

Patients

Eighty-six patients with HCC were initially evaluated. Of these, 31 did not fulfill the inclusion criteria: 26 patients had a HCC in an unsuitable location for percutaneous treatment and 5 refused treatment. Thus, 55

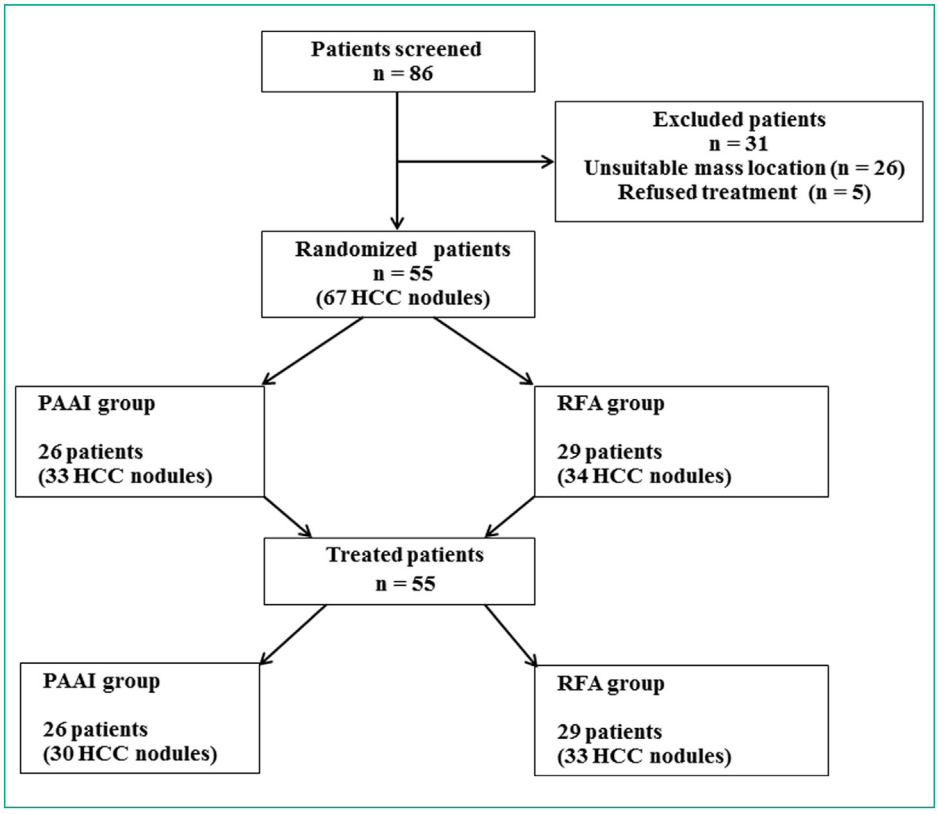

Figure 1. Flow chart diagram of patient inclusion into the study.

patients with a total of 67 HCC nodules were randomly assigned to PAAI group (26 patients) or RFA group (29 patients) (Fig. 1). There were 40 men and 15 women with a mean age of 54.3 ± 10.5 (SD) years (range: 28–71 years).

HCC was due to hepatitis B virus (HBV) in 29/55 patients (53%). Clinical and demographic data and imaging characteristics were similar in patients who underwent PAAI and those who underwent RFA, including HCC nodule size (Table 1).

Treatment

Amongst the 26 patients (33 HCC nodules) assigned to PAAI, two patients with 2 and 4 HCC nodules, could not complete treatment. New lesions developed in both patients after treatment of one and two HCC nodules respectively, and thus transarterial chemoembolization (TACE) was undertaken. PAAI was therefore performed on 30 HCC nodules in 26 patients.

In the 29 patients (34 HCC nodules) assigned to RFA, one patient with 3 HCC nodules had undergone RFA for 2 HCC nodules only, and died of variceal bleeding leaving the third nodule untreated. Thus RFA could be done on 33 HCC nodules in 29 patients (Table 2).

More ablative sessions were required for patients who underwent PAAI (total, 61 sessions in 26 patients; mean, 1.9 ± 1.3 [SD]) than for those who underwent RFA (total, 44 sessions in 29 patients; mean, 1.3 ± 0.5 [SD]) ($P = 0.003$).

Outcome measures

Tumor response post-PAAI

One month post-PAAI, two patients with single HCC each did not undergo CT. Thus, 24 patients with 28 HCC nodules who underwent PAAI were evaluated. Complete response was observed in 21/28 (75%) HCC nodules in 19 patients while 7/28 (25%) HCC nodules in 7 patients had partial response (Table 2) (Fig. 2).

Of the 21 HCC nodules (19 patients) that developed complete response earlier, 16/21 (76%) HCC nodules in 15 patients continued to be disease-free while 6 patients developed progressive disease in terms of new lesions or lung metastases on follow-up evaluation. Recurrence developed in 6 HCC nodules (at 4.1-, 6.4- and 7.9-months in three HCC nodules, at 12.5- and 15.9-months in 2 HCC nodules and 29.1-months in one HCC nodule) leading to a recurrence rate of 3/21 (14%), 5/21 (24%) and 6/21 (29% at 1-, 2- and 3-years, respectively). Recurrence at 4.1-months was completely treated by repeat PAAI.

Of the 7 patients (with a single HCC nodule each) with partial response earlier, two continued to have partial response (one died, the other could not be completely treated by 3 PAAI sessions and TACE was performed). The remaining 5 patients developed new HCC lesions during the course of treatment. Hence, a total of 13/26 (50%) patients who underwent PAAI developed progressive disease. At the end of follow-up, 5 deaths occurred in the PAAI group. Three

Table 1 Clinical profile and biochemical parameters of patients in PAAI and RFA groups.

Variable	PNAI ($n=26$)	RFA ($n=29$)	*P*-value
Age (year)	53.5 ± 10.5 [35—71]	54.5 ± 11.1 [28—70]	0.75
Sex			
Male	20/26 (47%)	20/29 (69%)	
Female	6 (23%)	9/29 (31%)	0.51
Diabetes	2/26 (8%)	5 (17%)	0.29
Alcohol consumption	6/26 (23%)	11 (40%)	0.23
Presenting symptoms			
Weight loss	5/26 (19%)	10/29 (34%)	0.20
Anorexia	3/26 (11%)	9/29 (31%)	0.08
Abdominal pain	7/26 (27%)	12/29 (41%)	0.26
Abdominal mass	1/26 (4%)	0/29 (0%)	0.29
Abdominal distension	11/26 (42%)	9/29 (31%)	0.39
Fever	4/26 (15%)	2/29 (7%)	0.31
Jaundice	3/26 (11%)	4/29 (14%)	0.80
Gastrointestinal bleeding	2/26 (8%)	2/29 (7%)	0.91
Biochemical parameters (mean ± SD) [range]			
AST (IU/dL)	81 ± 76 [29—154]	86.0 ± 56 [27—233]	0.77
ALT (IU/dL)	66 ± 8 [24—416]	66.0 ± 40 [28—193]	0.99
SAP (IU/dL)	215 ± 178 [66—369]	303 ± 207 [69—456]	0.10
Total protein (mg/dL)	8 ± 0.9 [6.0—8.5]	11 ± 17 [6.3—8.6]	0.38
Serum albumin (mg/dL)	4 ± 0 [2—5]	7 ± 18 [2—5]	0.37
AFP (ng/mL)	($n=25$)[a] 306 ± 942 [2.6—4688]	($n=28$)[a] 1365 ± 5544 [2—29324]	0.35
PST score			
0	13/26 (50%)	21/29 (72%)	
1	9/26 (35%)	6/29 (21%)	
2	4/26 (15%)	2/29 (7.0%)	0.22
Child's status			
A	19/26 (73%)	18/29 (62%)	
B	7/26 (27%)	11/29 (38%)	0.38
Etiology of HCC			
HBV	14/26 (54%)	15/29 (52%)	
HCV	9/26 (35%)	9/29 (31%)	
HBV + HCV	2/26 (8%)	0/29 (0%)	
Alcohol	1/26 (4%)	3/29 (10%)	
NASH	0/26 (0%)	2/29 (7%)	0.30
HCC nodule distribution (per patient)	26 (33 nodules)	29 (34 nodules)	
One nodule	21/26 (21 nodules)	26/29 (26 nodules)	
Two nodules	4/26 (8 nodules)	1/29 (2 nodules)	
Three nodules	0/26 (0 nodule)	2/29 (6 nodules)	
Four nodules	1/26 (4 nodules)	0/29 (0 nodule)	0.16
BCLC stage of HCC			
A	22/26 (85%)	24/29 (83%)	
B	4/26 (15%)	5/29 (17%)	0.85

AST: aspartate aminotransferase; ALT: alanine aminotransferase; SAP: serum alkaline phosphatise; AFP: alpha fetoprotein; PST: performance status; HBV: hepatitis B virus; HCV: Hepatitis C virus, NASH: non-alcoholic steatohepatitis; BCLC: Barcelona Clinic Liver Cancer; HCC: hepatocellular carcinoma.

[a] Number of patients in whom AFP was measured.

deaths were cancer-related and 2 were due to complications of the underlying chronic liver disease.

Tumor response post-RFA

Twenty-seven patients with 30 HCC nodules were evaluated and 2 were lost to follow-up. One month post-RFA, complete response was obtained in 25/30 (83%) HCC nodules (22 patients) and partial response in 5/30 (17%) HCC nodules (5 patients) (Table 2) (Fig. 3).

On final follow-up, 21/25 (84%) HCC nodules (19 patients) who had complete response earlier, continued to be disease-free. Six patients developed new HCC lesions and one had new HCC nodules and distant metastases, while the primary tumor remained completely treated. Recurrence occurred in 5 HCC nodules (5 patients). One recurrence developed at 18

Table 2 Treatment details and outcome in 26 patients treated with PAAI and 29 patients treated with RFA.

Variable	PAAI		RFA		*P*-value
Randomized (patients)	26 (33 nodules)		29 (34 nodules)		
Treated (patients)	26 (30 nodules)		29 (33 nodules)		
HCC size (cm)					
Mean size ± SD [range]	2.7 ± 1.0 [1.1—5.0]		2.7 ± 1.2 [1.0—5.0]		0.90
1—2 cm	9/30 (30%)		12/33 (36%)		
2.1—3 cm	11/30 (37%)		7/33 (21%)		
3.1—4 cm	8/30 (27%)		9/33 (27%)		
4.1—5 cm	2/30 (7%)		5/33 (15%)		0.50
Total ablative sessions	61		44		0.002
Mean ± SD [range]	1.9 ± 1.3 [1—5]		1.3 ± 0.5 [1—3]		
End point of tumor ablation (one month)	Patients[a]	Nodules	Patients[a]	Nodules	
Complete response	19/24 (79%)	21/28 (75%)	22/27 (81%)	25/30 (83%)	
Partial response	7/24 (29%)	7/28 (25%)	5/27 (18%)	5/30 (17%)	
Not assessed	2/26 (8%)	2/30 (7%)	2/29 (7%)	3/33 (9%)	0.43
Total follow-up (month)	336.3		436.8		
Mean ± SD [range]	13.0 ± 12.0 [0.1—37]		15.1 ± 18.0 [0.3—67.3]		
Median	7.8		7.3		0.61
Final tumor response	Patients[a]	Nodules	Patients[a]	Nodules	
Complete response	15/19 (79%)	16/21 (76%)	19/22 (86%)	21/25 (84%)	
Partial response	1/7 (14%)	2/7 (29%)	2/5 (40%)	2/5 (40%)	0.14
Tumor recurrence	6/24 (25%)	6/21 (29%)	5/29 (17%)	5/25 (20%)	0.49
Patients with progressive disease (new lesions/metastases)	13/26 (50%)		14/27 (48%)		0.68
Recurrence interval (months)					
Mean ± SD [range]	12.7 ± 9.1 [4.1—29.1]		9.1 ± 7.4 [3.2—18.0]		0.50
Median	10.2		4.7		
Cumulative PFS					
At 12 months	12 (41%)		14 (58%)		0.39
At 30 months	3 (32%)		5 (42%)		0.37
Cumulative overall survival					
At 12 months	12 (82%)		14 (72%)		0.68
At 30 months	3 (54%)		5 (52%)		0.50

SD: standard deviation; PFS: progression free survival.
[a] Number of patients are not mutually exclusive due to multiple masses in several patients.

months, which was completely treated by repeat RFA. In the remaining 4 patients (4 HCC nodules), local recurrence with new HCC lesions developed between 3.2- and 18.3-months and TACE was undertaken. Recurrence rate for treated HCC nodules was 3/25 (12%) and 5/25 (20%) at 1- and 2-years, respectively.

Of the 5 patients (with a single HCC nodule each) who had partial response at one month, 3 had progressive disease, while 2 continued to be partially treated (one died and the other was lost to follow-up). In total, 14/27 (48%) patients had disease progression. By the study end, 10 deaths occurred in the RFA group: 3 were cancer-related, 5 due to complications of underlying liver disease and 2 due to both.

Comparison of efficacy of PAAI and RFA

In treated HCC nodules, complete response rate following PAAI was 21/28 (75% [95% CI: 55.1—89.3%]) and 25/30 (83% [95% CI: 65.3—94.4%]) following RFA, yielding an 8.3% difference (95% CI: −12.5 to 29.2%). The lower limit of the 95% CI of the difference (12.5%) was much lower than the 10% non-inferiority margin difference of 8.3% between both techniques, indicating that PAAI was not inferior to RFA.

Cumulative overall survival following PAAI and RFA were similar at 12-months (81.6% vs. 77.9%, respectively; $P = 0.68$) and at 30-months (54.4% vs. 52.0%, respectively; $P = 0.50$) (Fig. 4).

Adverse events

Mild fever and pain was noted after 6/61 (9.8%) and 4/61 (6%) PAAI procedures, respectively. Fever was of moderate intensity after the first session while subsequent sessions were better tolerated. Two deaths (3%) occurred in the PAAI group. Six hours after the procedure, one patient developed left lobe hepatic necrosis, which led to hepatic failure and death on day 6. In another patient, the procedure was

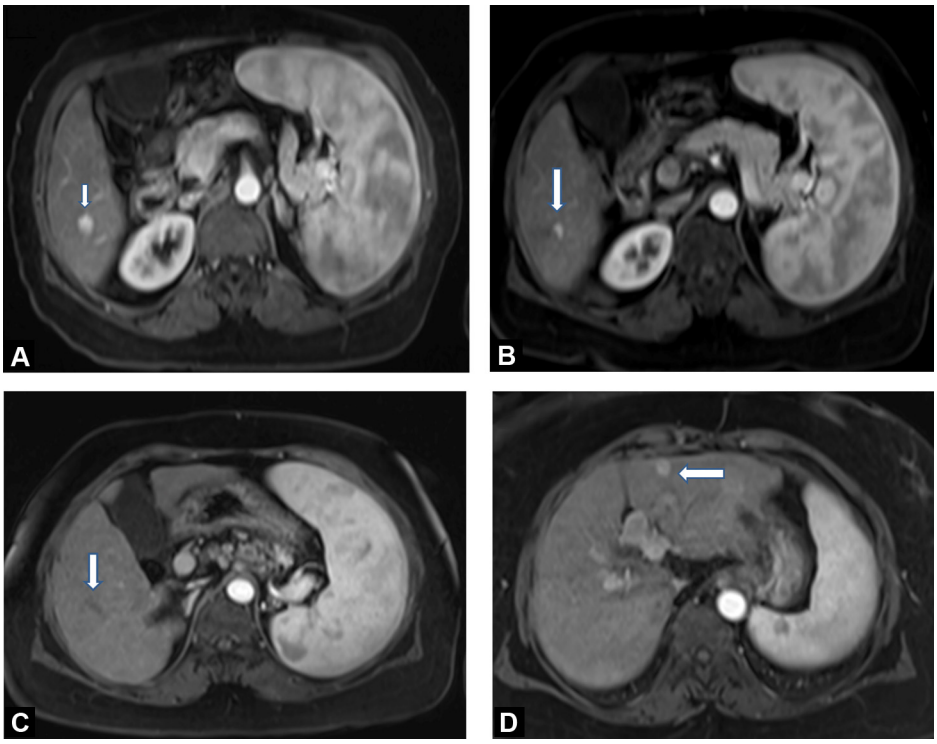

Figure 2. A 41-year-old woman with hepatitis C-related cirrhosis and hypervascular hepatocellular carcinoma (HCC) of 1.5 cm in segment 6 of the liver: A: MR image of the liver in the axial plane obtained during the arterial phase following intravenous administration of gadolinium chelate reveals hypervascular HCC nodule (arrow). The tumor was treated percutaneously using 2 mL of 40% acetic acid; B: four weeks after percutaneous acetic acid injection (PAAI), MR image of the liver in the axial plane obtained during the arterial phase following intravenous administration of gadolinium chelate shows a small, residual enhancing area (1×0.5 cm) in the treated HCC nodule suggestive of partial response. Repeat PAAI was performed; C: follow-up MRI at two years, shows reduction in size and absence of enhancement in the treated HCC during the arterial phase (arrow); D: however, a newly developed, subcapsular small HCC is detected in the left lobe of the liver (arrow), for which PAAI was subsequently performed and complete response was achieved.

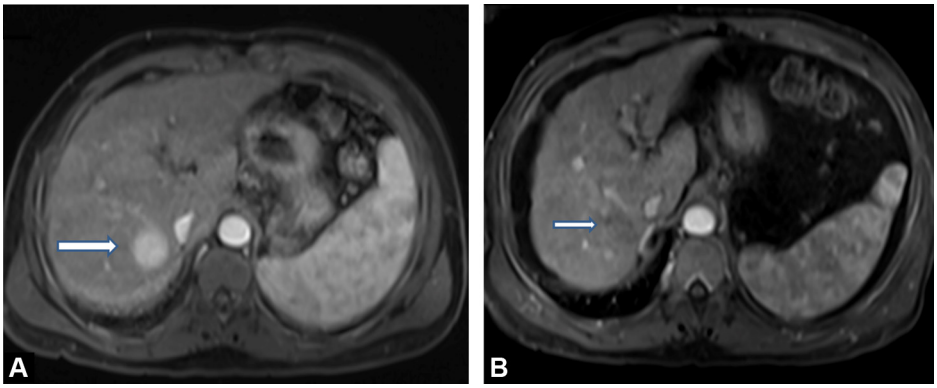

Figure 3. 55-year-old man with hepatitis B-related cirrhosis and hepatocellular carcinoma (HCC) in segment 7 of the liver: A: MR image of the liver in the axial plane obtained during the arterial phase following intravenous administration of gadolinium chelate shows a well-defined, 2.5 cm, homogenous, hypervascular HCC nodule in segment 7 of the liver (arrow). The patient was treated using radiofrequency ablation (RFA); B: four weeks after RFA, MR image of the liver in the axial plane obtained during the arterial phase shows lack of enhancement within the tumor site (arrow) consistent with complete response.

uneventful, however, signs of tumor rupture appeared at 4 hours causing death the next day.

Pain and fever were noted after 5/44 (11%) and 4/44 (9%) RFA procedures, respectively. Transient pleural effusion requiring no intervention occurred after 5/44 (11%) RFA procedures. Two patients developed hydropneumothorax, which improved in 7—10 days with chest tube drainage. Mild hemoperitoneum occurred in one patient which subsided with conservative management.

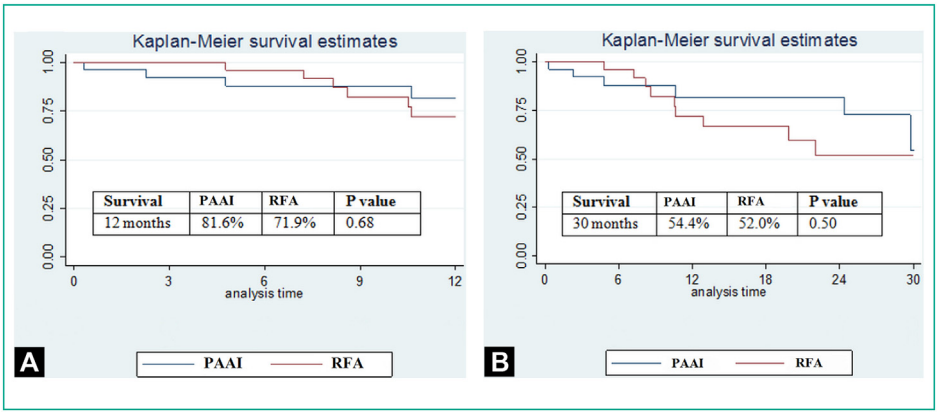

Figure 4. Graphs show Kaplan–Meier survival curves with cumulative overall survivals of patients treated with percutaneous acetic acid injection (PAAI) and radiofrequency ablation (RFA) at 12 months (a) and at 30 months (b).

Discussion

By comparing the efficacy of PAAI to that of RFA for the treatment of small HCC, we found similar cumulative overall survival for PAAI and RFA. In addition, tumor response rate to PAAI was non-inferior to that to RFA. However, we found that the use of PAAI required more sessions than RFA for completing treatment of HCC. Requirement of more treatment sessions with PAAI have also been reported by Lin et al. [14].

Varying concentrations of acetic acid ranging from 15% to 50% have been used for treating HCCs > 3 cm in different studies, showing equal efficacy but requiring less treatment sessions with higher concentrations [19,20]. We used 40% acetic acid after our pilot experience of trying different concentrations. In PAAI, the total estimated dose is instilled in multiple sessions of 1.5–2 mL each because acetic acid takes several hours to solubilize collagen. Researchers showed that larger HCCs are known to require more sessions for achieving complete response (2.4 sessions for 1–2 cm HCC and 3.6 sessions for 2–3 cm HCCs) [12,19]. On the contrary, single high-dose PAAI has also been safely used in HCCs < 4 cm or equal to 3 cm [15,21]. In our study, we needed 1–2 sessions for 1.3 to 1.8 cm HCC nodules, 2–3 sessions for 2.2 to 3 cm HCC nodules, and 3–6 sessions for 3.1 to 4 cm HCC nodules.

Response rates have a relation with tumor size and location. With RFA, standard wattage and duration of thermal energy is needed for achieving tumor coagulation necrosis (vendor specific, based on tumor size, electrode used). Lower response rates occur in tumors adjoining the bowel (83.3%), gallbladder (86.3%) and major vessels, due to physical limitations of thermal energy deposition in RFA [22]. For HCCs > 5 cm, response rate following RFA is known to drop to 6% [23]. We had 83.3% complete response rate with RFA. With technical advances, availability of better probes/equipment, a higher response rate of 96% for single < 5 cm HCC and 96.7% for three HCCs of 3 cm size, have been reported [24]. Our lower response rate could be explained by the difference in the patient population, which had more patients with larger size and number of HCCs. Additionally, many of them were in difficult to treat, risky locations. Moreover, patients with multifocal HCC are prone to develop progressive disease. We had six patients developing disease progression for which an alternate treatment was provided. This led to an underestimation of RFA outcome. Use of RFA alone for large HCCs is limited. A similar 95% response rate for HCCs < 3 cm with drop to 85% for HCCs > 3.5 cm has been reported by Chen et al. [22].

Tumor response rate following PAAI in our study was 75%. No studies on the exclusive use of PAAI on similar sized HCCs are available in the literature. Better response rates of 100% and 95% in HCCs < 5 cm are reported with a combination of TACE and PAAI [13,20].

Both RFA and PAAI are safe procedures. However, minor and major complications following both are known. Death, though rare, has also been reported [15,21,25,26]. In our study, two patients died following PAAI, possibly due to tumor characteristics rather than the procedure per se. No death was noted in the RFA group.

Recurrence rates at 1- and 2-years following PAAI and RFA were similar in our study. Recurrences have a direct relation with tumor size and a recurrence rate of 2–46%, has been reported in studies on RFA [27–29]. It is largely attributed to the inability to achieve a peritumoral safety margin cuff in larger HCCs. Similar or even higher recurrence rates of 51% and 74% at 1-, 3-years respectively have been shown in HCCs < 5 cm following PAAI [12,13].

In our study, the cumulative survival following PAAI was 82% and 54% at 12 and 30 months respectively. Huo et al. reported a similar survival rate (84% and 51% at 1 and 3 years) in HCCs < 5 cm and less than 4 in number [13]. However, in their study, 50% of the tumors were subjected to TACE prior to PAAI [13]. Better survival (100% and 92% at 1- and 2-years, respectively) has been documented in HCCs < 3 cm [12].

The cumulative survival rates post-RFA were 72% and 52% at 12 months and 30 months respectively in our study. With RFA too, outcomes are better with smaller HCCs. Shiina et al. reported that patients with HCCs < 3 cm have survival rates of 97.2%, 83.8% and 65.1% at 1-, 3- and 5-years'respectively, which dropped to 95%, 71% and 46%, respectively when HCC size -was > 3 cm [30]. In HCCs < 7.5 cm, survival rates of 67%, 32% and 8% respectively at 1-, 3- and 5-years have been reported [31].

Studies comparing outcomes between PAAI and RFA are scarce. A systematic review by Germani et al. [32] found a single randomized controlled trial by Lin et al. that

compared the efficacy of RFA with those of PAAI and PEI in treating HCCs < 3 cm [14]. Lin et al. showed a superiority of RFA in terms of higher complete response rate (96.1%) compared to 92.4% and 88.1% with PAAI and PEI, respectively, lower recurrence rate for RFA (13%) compared to PAAI (29.3%) and PEI (34.5%) and better 1-, 2- and 3-years overall survival rate of 93%, 81% and 74% post-RFA compared to 90%, 67% and 53% with PAAI and 88%, 66% and 51% with PEI. In contrast, major complication rate with RFA was higher (4.8%) compared to 0% each for PAAI and PEI [14].

Our study has several limitations. The sample size was small and it took us an unusually long time to accrue patients with small HCC due to lack of screening program in our country. Additionally, some of our patients could not complete treatment due to natural course of disease progression affecting the outcome measures. Finally, it is worth mentioning that that we used PAAI and RFA alone and not in combination with any immunomodulators, the use of which is known to induce therapeutically effective systemic antitumor immune response [33].

In conclusion, PAAI has similar efficacy than RFA for the treatment of small HCC. Tumor response with PAAI was noninferior to that of RFA (10% non-inferiority margin), similar local recurrence rate (28.6% for PAAI and 20% for RFA) and similar cumulative overall survival at 12 and 30 months. PAAI could thus be a cost-effective alternative technique in situations where RFA is either unavailable or unaffordable.

Human and animal rights

The authors declare that the work described has been carried out in accordance with the Declaration of Helsinki of the World Medical Association revised in 2013 for experiments involving humans.

Informed consent and patient details

The authors declare that this report does not contain any personal information that could lead to the identification of the patient(s).

The authors declare that they obtained a written informed consent from the patients and/or volunteers included in the article. The authors also confirm that the personal details of the patients and/or volunteers have been removed.

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Authors' contributions

SBP — conceptualization; investigation; methodology, data curation; formal analysis, original draft, writing — review.

SKA — conceptualization; methodology; project administration; funding acquisition; resources; supervision; validation review & editing.

VS — software; visualization; data curation; formal analysis; validation, review & editing.

SRG — investigation; methodology; data curation, validation.

Shalimar S — supervision; investigation; methodology.

MSG — investigation; methodology; review.

Disclosure of interest

The authors declare that they have no competing interest.

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