

Radiofrequency Thermal Ablation vs. Percutaneous Ethanol Injection for Small Hepatocellular Carcinoma in Cirrhosis: Meta-Analysis of Randomized Controlled Trials

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OBJECTIVES: Radiofrequency thermal ablation (RF) and percutaneous ethanol injection (PEI) have been employed in the treatment of small hepatocellular carcinoma (HCC) as curative treatments. The aim of the study was to review the available evidence comparing RF to PEI for small HCC.

METHODS: Search strategy: Cochrane, MEDLINE, CANCELIT, and ENBASE databases were used. Selection criteria: randomized clinical trials evaluating RF vs. PEI. Data were extracted from each randomized controlled trial (RCT). Primary outcomes were overall survival and local recurrence. Meta-analysis software was used and risk differences (RDs) and their 95% confidence intervals and *Q*-test for heterogeneity were calculated.

RESULTS: Five RCTs were identified including 701 patients. The overall survival was significantly higher in patients treated with RF than in those treated with PEI (RD 0.116, 95% CI 0.173/0.060; heterogeneity not present). Local recurrence rate is significantly higher in patients treated with PEI than in those treated with RF. In the RF group the 1, 2, and 3 years cancer-free survival rates were significantly better than in the PEI-treated patients (respectively: RD 0.098, 95% CI 0.006/0.189; heterogeneity *P*=0.57; RD 0.187, 95% CI 0.082/0.293; heterogeneity *P*=0.98; RD 0.210, 95% CI 0.095/0.325; heterogeneity *P*=0.78). A small number of adverse events were reported in the two treatments.

CONCLUSIONS: RF ablation is superior to PEI in the treatment of small HCC with respect to overall survival, 1, 2, and 3 years survival rates, 1, 2, and 3 cancer-free survival rates, and tumor response. RF shows a significantly smaller risk of local recurrence.

Am J Gastroenterol 2009; 104:514–524; doi:10.1038/ajg.2008.80; published online 13 January 2009

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common malignant diseases in the world with an increasing incidence in industrialized countries (1). The application of surveillance for early detection of small HCC in patients with cirrhosis has increased the number of tumors diagnosed at an early subclinical stage that might better respond to effective treatments such as conventional resection, liver transplanta-

tion, and locoregional procedures (2). However, patients with HCC are often poor candidates for resection because of the lack of reduced hepatic function as a result of coexisting cirrhosis or the presence of multiple tumors (3,4). Nonetheless, orthotopic liver transplantation in small HCC patients is limited, owing to cancer progression and/or death due to underlying liver disease while the patient is on the waiting list. This limitation even applies to countries with a large number of

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Received 17 July 2008; accepted 17 September 2008

available organs (5). Percutaneous ablation under ultrasound guidance is currently the first-line approach in the treatment of early-stage HCC in cirrhotic patients deemed unsuitable for surgery or liver transplantation. Percutaneous ethanol injection (PEI) was the first percutaneous treatment introduced in clinical practice (6,7) and was recommended as the standard ablation treatment for early-stage nonsurgical HCC in the 2001 guidelines of the European Association for the Study of Liver Disease (8). In the mid-1990s radiofrequency thermal ablation (RF) became available for the treatment of small HCC (9,10) being recommended as the standard ablation treatment in addition to PEI in the 2005 (11) guidelines issued by the European Association for the Study of Liver Disease. The results of RF treatment are more predictable than those of PEI and complete ablation of small lesions can often be achieved in a single session (12,13). Five randomized controlled trials (RCTs) comparing the effectiveness of RF vs. PEI in small HCC have been published (14–18).

The aim of these meta-analyses was to review the available evidence to compare the effectiveness and safety of RF and PEI.

METHODS

Literature search and selection of randomized trials

Eligible RCTs were those comparing RF with PEI for the treatment of small HCC in patients with cirrhosis regardless of the cause of liver disease, irrespective of publication status or language.

Small HCC are defined according to the Milano criteria solitary HCC <5 cm or with up to 3 nodules smaller than 3 cm (19).

All other clinical investigations, such as observational studies, cases series, case–control studies, nonrandomized clinical trials, or randomized phase II b studies have been excluded.

Computerized bibliographic search from the year 1999 to June 2008 was performed on MEDLINE, CANCELIT, the Cochrane

Controlled Trials Register, the Cochrane Library, and ENBASE databases using the following keywords: “hepatocellular carcinoma;” “HCC;” “liver cell carcinoma;” “randomized controlled trial (RCT);” “radiofrequency thermal ablation;” “percutaneous ethanol injection;” and “ablation therapy.” The computer search was supplemented with a manual search of reference lists for all available review articles, primary studies, and books to identify other studies not found in the computer search. We have included RCTs published between 1999 and 2008 in which RF was compared with PEI for treating small HCCs in patients with cirrhosis regardless of the etiology of liver disease, publication status, or language.

Decisions on which trials to include were taken independently by two reviewers (A.O. and M.O.). Disagreements were solved by discussion. Only one trial was excluded (12) because it was not randomized. Five RCTs, all published as full papers (14–18), fulfilled the inclusion criteria and were included in the meta-analysis. An intention-to-treat analysis was declared only in one study (18); in the other studies, the intention-to-treat was not reported although the authors stated that there was no interruption of treatment and consequently the intention-to-treat and analysis per protocol should coincide.

Three trials compared RF with PEI (14,16,18). Two studies considered a third arm: one trial (17) was conducted to compare RF, PEI, and percutaneous acetic acid injection, the other study (15) considered PEI, RF, and another group in which higher-dose PEI was performed. In the meta-analysis we considered only conventional PEI arms.

Measures of primary outcome were overall survival, survival at 1, 2, and 3 years, and local recurrence. Measures of secondary outcomes were cancer-free survival at 1, 2, and 3 years and tumor response. The definitions of tumor response, local recurrence, and new lesions adopted in the five studies are reported in **Table 1**.

Side effects associated with the treatment and the emerging of new lesions were also assessed.

Table 1. Outcome definitions used in the studies included in this meta-analysis

Study characteristics	Lencioni <i>et al.</i> (14)	Lin <i>et al.</i> (15)	Shiina <i>et al.</i> (16)	Lin <i>et al.</i> (17)	Brunello <i>et al.</i> (18)
Tumor complete response (RF and PEI)	Hypoattenuating non-enhancing area in both arterial and venous phases on phase spiral CT	Persistent hypoattenuation of the tumor on CT scan after 4 months after the most recent ablation therapy	Persistent hypoattenuation of the tumor on CT scan	Persistent hypoattenuation of the tumor on CT scan 4 months after the most recent ablation therapy	CT/MR detection of a non-enhanced area of necrosis/scar at the site of every lesion defined as HCC at baseline
Local recurrence	Recurrence within or around the treated tumor	Presence of an enhanced tumor on CT corresponding to the initial target tumor	Appearance of viable cancer tissue touching the original lesion	Presence of enhanced tumor on CT corresponding to the initial target tumor	Arterialized lesions with wash out and hypodensity in the late phases within or around the treated tumor
New lesion	The emergence of new tumor remote from the treated lesion	Development of an enhanced tumor on CT in a different segment from the original tumor	Appearance of new lesion away from the original one	Development of an enhanced tumor on CT in a different segment from the original tumor	Arterialized lesions with wash out and hypodensity in the late phases >1 cm distant from the treatment site

PEI, percutaneous ethanol injection; RF, radiofrequency.

Trials review and data extraction

The methodological quality of the trials was assessed by four major criteria previously validated (20–26): adequate generation of the randomization sequence, adequate concealment of treatment allocation, blinded outcome assessment, and intention-to-treat analysis. Each quality component was rated as yes, unclear, or no. The quality of trials was reported according to each separate component (22).

Data concerning trials, patient characteristics, technical methods, and treatment outcome (Tables 1–4) was abstracted by two independent reviewers (A.O. and M.O.) and discrepancies were resolved by discussion.

Statistical methods

Statistical tests for heterogeneity of risk differences were performed using the Cochrane Q-test with a cutoff level of $P < 0.10$. Pooled risk differences (95% confidence intervals) were calculated using either the fixed effects model or random effects model. Publication bias assessment (PBA), calculated using the Klein *et al.* (27) method, expresses how many unpublished studies with negative or null results are needed to influence the results of the meta-analysis. Number needed to treat (NnT) was also calculated as $1/\text{pooled risk difference}$. Peto method or DerSimonian-Laird method was used for odds calculation (28).

All procedures and calculations were made following the methodology reported elsewhere (28).

Source of support

This meta-analysis was not supported by any company or private individual or with grants. The entire cost of the meta-analysis was borne by the authors' respective institutions.

RESULTS

The five RCTs included a total of 701 patients: 354 treated with RF and 347 treated with PEI.

The quality of trials was acceptable and homogeneous according to the considered items: three main items were completely respected in all five trials. The only item not respected was the blinding which was impossible in these trials comparing two different invasive procedures.

The clinical and methodological characteristics of the five RCTs are shown in Table 2 and the patient characteristics are shown in Table 3. The control treatment was PEI in all trials. The criteria for inclusion were uniform in all five trials.

Major exclusion criteria across the five trials were: class C according to Child-Pugh score in five trials; low platelet count and/or high INR in three trials; tumor location near the hepatic hilum in four trials. In one trial lesions greater than 3 cm were excluded (18).

The sample size of each RCT varied and ranged from 102 to 232 patients (14–18). The percentage of men ranged from 63% to 71%.

A total of 487 patients (pts) had a single lesion (PEI 234; RF 253). Tumor size was ≤ 3 cm in 658 pts (PEI 325; RF 333).

Prevalence of HCV infection in enrolled patients ranged from 29% to 81% and that of HBV infection from 4% to 69%. The proportion of patients in class A according to the Child-Pugh score ranged from 56% to 78%.

The outcome definitions and major end-points used in the five studies are shown in Table 1.

Treatment methods

The treatment methods are similar across the five studies and are summarized in Table 4.

Primary outcomes

Overall survival and survival at 1, 2, and 3 years. Overall survival was considered as a primary end-point. The information was retrievable from all the five RCTs considered.

The overall survival was significantly higher in patients treated with RF than in those treated with PEI (five trials reported this data; risk difference 0.116—95% CI 0.173/0.060; heterogeneity not present; PBA=10; NnT=9) (Figure 1). OR = 1.92 (1.35–2.74).

The pooled estimate of differences in the survival rate at 1, 2, and 3 years was higher in the RF group risk difference (RD) 0.049 (95% CI 0.017/0.081; heterogeneity not present; PBA=3; NnT=20), 0.124 (95% CI 0.072/0.176; heterogeneity not present; PBA=18; NnT=8), 0.184 (95% CI 0.113/0.255; heterogeneity $P=0.03$; PBA=17; NnT=5). OR at 1 year = 2.30 (1.27–4.14); OR at 2 years = 2.39 (1.62–3.51); OR at 3 years = 2.32 (1.20–4.48).

The presence of heterogeneity is due to paper by Brunello *et al.* (18) in which the survival is similar at 1, 2, and 3 years in the two groups of therapy. All five studies reported survival at 1 and 2 years and four studies reported survival at 3 years (15–18).

Local recurrence. The pooled estimate of the treatment effect, performed on four trials (14–17), shows that RF has a lower risk of local recurrence compared to PEI (RD -0.129 —95% CI $-0.079/-0.179$; heterogeneity $P=0.41$; PBA=18; NnT=8) (Figure 2). OR = 0.29 (0.18–0.47).

Secondary outcomes

Cancer-free survival at 1, 2, and 3 years. Three studies involving 330 pts reported 1 and 2-year cancer-free survival (14,15,17) and only two studies (228 pts) reported 3-year cancer-free survival (15,17). The weighted differences in cancer-free survival at 1, 2, and 3 years were, respectively, 0.098 (95% CI 0.006/0.189; heterogeneity $P=0.57$; PBA=0; NnT=10), 0.187 (95% CI 0.082/0.293; heterogeneity $P=0.98$; PBA=6; NnT=5), 0.210 (95% CI 0.095/0.325; heterogeneity $P=0.78$; PBA=4; NnT=5). OR at 1 year = 1.69 (1.02–2.76); OR at 2 years = 2.11 (1.36–3.26); OR at 3 years = 2.72 (1.54–4.79).

Tumor response. This information was missing in a single article (16).

RF shows a better performance with respect to PEI in terms of complete necrosis of tumor (four trials; RD 0.091, 95%

Table 2. Study characteristics of each RCT included in the meta-analysis

Study characteristics	Lencioni <i>et al.</i> (14)	Lin <i>et al.</i> (15)	Shiina <i>et al.</i> (16)	Lin <i>et al.</i> (17)	Brunello <i>et al.</i> (18)
Inclusion criteria	(1) Adult patient with hepatic cirrhosis and either a single HCC ≤5 cm or three HCCs each ≤3 cm, (2) HCCs located at least 1 cm away from the hepatic hilum or the gallbladder, (3) absence of vascular invasion or extrahepatic metastases, (4) hepatic cirrhosis classified as Child-Pugh class A or B, (5) prothrombin time ratio (i.e., normal time divided by patient's time) greater than 50%, (6) platelet count higher than 50,000 per mm ³ (50–109 per l), (7) no previous treatment for HCC, and (8) ineligibility for surgical resection or transplantation	(1) Cirrhotic patients with 1–3 pathology or cytology-proven HCCs for each tumor measuring 1–4 cm in greatest dimension	(1) Histopathologically confirmed carcinoma or a lesion showing characteristic imaging feature of hepatocellular carcinoma, (2) lesions were unresectable or the patient had refused surgery, (3) 3 or fewer lesions ≤3 cm, (4) liver function of Child-Pugh class A or B, (5) no extrahepatic metastasis or vascular invasion, (6) no previous or simultaneous malignancies	(1) Adult patients with 1–3 HCCs measuring ≤3 cm in diameter each, (2) HCC located at least 1 cm away from the hepatic hilum or gall bladder, (3) absence of vascular invasion or extrahepatic metastasis, (4) liver cirrhosis classified as Child-Pugh class A or B, (5) prothrombin time 3 s less than that of control values, (6) platelet count greater than 50,000 per mm ³ , and (7) no previous treatment for HCC	(1) Cirrhotic patients, (2) Child-Pugh class A or B, (3) 1–3 HCC nodes ≤30 mm in diameter
Exclusion criteria	NR	(1) Child-Pugh grade C, (2) previous HCC treatment, (3) tumor located within 5 mm of liver hila or the common bile duct, owing to the risk of injury to the major bile duct following RF ablation	(1) Platelet <50×10 ⁹ per l, (2) prothrombin activity <50%, (3) refractory ascites	(1) Child-Pugh class C, (2) previous HCC treatment, (3) tumor located within 1 cm of the liver hilum or common bile duct	(1) Patients without liver cirrhosis, (2) Child-Pugh class C, (3) platelet <40,000, (4) INR >1.75, (5) PTT >40s, (6) hypovascular HCC, (7) lesions not detectable by US, lesions close (≤1 cm) to the gallbladder, hepatic hilum, colon, or stomach, (8) venous invasion or metastatic disease, (9) lesions of more than 30 mm, (10) patients suitable for liver transplantation, (11) patients suitable for resection
Primary end points	Overall survival	Local tumor progression	Survival	Local recurrence	Complete response (CR) at 1 year after the end of the treatment, consisting of 1–2 cycles of PEI or RFA
Secondary end points	(1) Local recurrence-free survival (2) Event-free survival (i.e., survival free from local recurrence, new HCCs, and extrahepatic metastases)	(1) Overall survival (2) Cancer-free survival	(1) Overall recurrence (2) Local tumor progression	(1) Overall survival (2) Cancer-free survival	(1) Early CR (at 30–50 days after completion of the PEI or RFA treatment) (2) Complications (3) Overall survival (4) Costs
Number of patients screened	NR	NR	232 (of 507 HCC during 21 months)	337 (of 1,200 HCC per year)	NR
Number of patients randomized	104 (RF 52/PEI 50) Two patients had to be excluded before randomization for (inclusion criteria) protocol violation	157 (RF 52/PEI 52/ higher dose PEI 53)	232 (RF 118/PEI 114)	187 (RF 62/PEI 62/PAI 62)	139 (RF 70/PEI 69)

Table 2. Continued

Study characteristics	Lencioni <i>et al.</i> (14)	Lin <i>et al.</i> (15)	Shiina <i>et al.</i> (16)	Lin <i>et al.</i> (17)	Brunello <i>et al.</i> (18)
Generation of randomization list	Computer-generated randomization list that was not available to the treating physician	Computer-generated randomization list that was not available to the treating physician	Computer-generated random numbers	Computer-generated randomization list that was not available to the treating physician	Simple random allocation sequence stratified by unit, produced by the epidemiology unit, using a computerized random number generator with random block sizes. The random sequence could not be predicted by the operators because each received the allocations sealed in closed, sequentially numbered envelopes
Number of patients lost to follow-up evaluation	NR	NR	0	NR	RF 1/PEI 5
Mean follow-up months (RF/PEI)	22.9/22.4	24.5/23.8	37/35	28/26	26.5 (12–59.8)
Surveillance	Measurement of alpha 1 fetoprotein levels and US performed at 3-month intervals and dual-phase spiral CT performed at 6-month intervals	Serum alpha-fetoprotein level, US, and CT scan every 2 months	Helical CT, ultrasonography, alpha1fetoprotein every 4 months	Helical CT, US, alpha-fetoprotein every 2–3 months	US examination every 4 months and a spiral CT/MR every 12 months after the first treatment
Intention-to-treat analysis	NR	NR	NR	NR	Intention-to-treat analysis was carried out for the primary end-point and for overall survival. Per protocol analysis (excluding patients lost to follow-up and those not evaluated for early death or disease progression) was performed to assess early and sustained response
Publication status	Full paper	Full paper	Full paper	Full paper	Full paper
Year of publication	2003	2004	2005	2005	2008

HCC, hepatocellular carcinoma; NR, not reported; PEI, percutaneous ethanol injection; RF, radiofrequency; US, ultrasonography.

CI 0.143/0.038; heterogeneity $P=0.06$; PBA=8; NnT=11) (Figure 3). OR=2.28 (1.46–3.35).

Occurrence of new lesions. No differences were found between the two groups with respect to the appearance of new lesions (RD -0.017 —95% CI 0.052/ -0.087 ; Heterogeneity not present; PBA = -5 ; NnT = 58) (Figure 4). OR=0.92 (0.67–1.25).

Adverse events. Pain is the most frequent adverse event but the evaluation of the degree of severity is variable across the trials and not easily comparable. Brunello did not report pain

as a side effect. In the other studies, few patients reported pain and there were no significant differences between the two arms (15 of 278 5% in the PEI arm and 21 of 284 7% in the RF arm).

The incidence of serious adverse events was no different between the two procedures in four studies (14–16,18). In Lin's study (17) the major complication rate was 4.8% (3 of 62 patients, including 2 patients with hemothorax and 1 with gastric bleeding and perforation) in the RF group and 0% in the PEI group.

Pleural effusion was described in four studies (14,15,17,18) in nine patients (all in the RF group) two of whom developed hemothorax and required chest tube drainage and one patient

Table 3. Characteristics of patients included in each RCTs using PEI/RF included in the meta-analysis

Patient characteristics	Lencioni <i>et al.</i> (14)	Lin <i>et al.</i> (15)	Shiina <i>et al.</i> (16)	Lin <i>et al.</i> (17)	Brunello <i>et al.</i> (18)
Number randomized	50/52	52/52	114/118	62/62	69/70
Age (year)					
Mean	69/67	59/62	—	60/61	70/69
≤65 years	—	—	41/44	—	—
>65 years	—	—	73/74	—	—
Male sex	36/30	34/35	87/79	39/40	45/43
Mean follow-up (months)	22.4/22.9	23.8/24.5	35/37	26/28	25.3/26.1 ^b
HCV patients	32/35 ^a	14/16	98/90	19/20	47/44
HBV patients	21/19 ^a	37/35	11/18	42/41	0/6
Other aetiology	9/11	1/1	5/10	1/1	22/20
Child A	35/45	39/41	85/85	47/46	39/39
Child B	15/7	12/11	29/33	15/16	30/31
Serum albumin (g/dl)					
≤3.5	20/10	—	49/60	—	—
>3.5	30/42	—	65/58	—	—
Mean	3.7/4.1	3.8/3.7	—	3.9/4	3.42/3.45
Platelet count (×1,000 per mm ³)					
Mean	—	8.6/8.4	—	9.1/9.4	96.90/108.17
≤01 (11)	—	—	61/55	—	—
>10 (11)	—	—	53/63	—	—
Alfa 1 fetoprotein (ng/ml)					
Median	54/27	—	—	—	16.5/22
<100	—	19/17	89/93	24/23	—
100–200	—	10/12	—	13/14	—
201–400	—	14/15	18/19	16/15	—
>400	—	9/8	7/6	9/10	—
Patients with 1 lesion	31/40	40/38	60/72	49/49	54/54
Patients with 2 lesions	15/7	9/11	34/26	12/10	—
Patients with 3 lesions	4/5	3/3	16/17	1/3	—
Patients with >3 lesions	—	—	4/3	—	—
Tumor size ≤3 cm	42/46	38/37	114/118	62/62	69/70
Tumor size >3–<4 cm	8/6	14/15	0/0	0/0	0/0

^a12 coinfection B and C in PEI group and 13 in RF group. ^bValue express as median.

needed urgent thoracotomy. The other cases of pleural effusion resolved spontaneously.

In a single study (18) two patients developed hemoperitoneum, one in the RF arm and one in the PEI arm.

Only 1 study reported an increase in the transaminase level of up to 2–4 times compared to the baseline level

during the first 3 days after therapy in most patients (15). Other adverse effects were reported in Shiina's study (16): transient jaundice (1 case), skin burn (1), hepatic infarction (1) and seeding of malignant cells (3) in the RF arm whereas liver abscess (1) and neoplastic seeding were reported (2) in the PEI arm.

Table 4. Treatment methods

	Lencioni <i>et al.</i> (14)	Lin <i>et al.</i> (15)	Shiina <i>et al.</i> (16)	Lin <i>et al.</i> (17)	Brunello <i>et al.</i> (18)
PEI					
Needle type	22-Gauge non-cutting needle 21-Gauge needle with a closed conical tip and multiple terminal side holes	22 gauge	21 gauge	22 gauge	21 gauge (multihole)
No. of needle	1	1	2–3	1	1
Alcohol (%)	95	99.5	NR	99.5	95
Dose/session	2–10ml	4.5ml (2–10ml)	2–8ml	4.8ml (2–10ml)	2–20ml
No. of sessions per week	1–2	2	2	2	NR ^a
No. of sessions	4–8	6–12	NR	6–12	1–4 ^a
Treatment courses per tumors (%) (1/2)	60 (82%)/13 (18%)	47 (84%)/9 (16%)	NR ^b	55 (82%)/12 (18%)	NR ^d
Technical objective	Hyperechoic appearance of tumor at US	Hyperechoic appearance of tumor at US	Complete ethanol tumor filling, judged by operator	Complete hyperechoic change of the tumor at US	Complete ethanol filling of the tumor, judged by operator
Total dose per lesion	20.6 ml (4.5–75.0ml)	15.4±5.2ml (4.5–56.2ml)	NR	Calculated by equation: $V(\text{ml}) = 4/3 \pi r^2(c+1)^3$ 13.6±4.7 ml (4.3–52.2ml)	NR
Average of session	5.4±1.6	6.5±1.6	6.4±2.6	4.9±1.3	NR
Hospital stay after starting therapy (days)	NR	1.6±0.3 (2–3)	26.1±9.9 ^e	1.7±0.4 (2–3) ^c	NR
RF					
Electrode type	15-Gauge expandable electrode needle with four retractable lateral exit curved electrodes on the tip and a large dispersive electrode	LeVeen 15 gauge, 15cm	18-Gauge cooled-tip electrode with a 2- or 3-cm exposed tip (Radionics, Burlington, MA)	LeVeen 15 gauge; 12–15 cm	(1) Internally cooled electrode (Cool-Tip with 20 or 30mm exposed tip; Radionics) (2) Multitined expandable electrode (StarBurst and StarBurst XL; RITA Medical Systems, Mountain View, CA)
No of hooks	5	10	NR	10	NR
Diameter of necrosis	NR	3.5cm	NR	2–3.5cm	NR
Generator	50 W RF generator, model 500 L; Rita Medical Systems	RF 2000; RadioTherapeutics, Sunnyvale, CA	CC-1 Cosman Coagulator; Radionics	RF 2000; Radio-Therapeutics	(1) CC-1 200W-RFA generator (Radionics) (2) 150 RFA generator (RITA Medical Systems)
Treatment courses per tumors (%) (1/2)	63 (91%)/6 (9%)	51 (80%)/13 (20%)	NR ^b	62 (83%)/13 (17%)	NR ^d
Temperature	95°C	NR	NR	NR	NR
Average of session	1.1±0.5	1.6±0.4	2.1±1.3	1.3±0.3	NR
Hospital stay after starting therapy (days)	NR	4.4±1.8 (3–15)	10.8±5.5 ^e	4.2±1.9 (3–18)	NR

^aThe majority of patients were treated in a single session. ^bWhen any possible undestroyed portions remained, the therapy was repeated. Patients were hospitalized until CT demonstrated entire tumor necrosis and until any adverse reaction had disappeared. ^cPEI was performed at the outpatient clinic if there were no severe adverse effects after the first PEI during hospitalization. ^dIf needed patients were treated once again with the same technique. ^ePatients remain in hospital until the end of therapy.

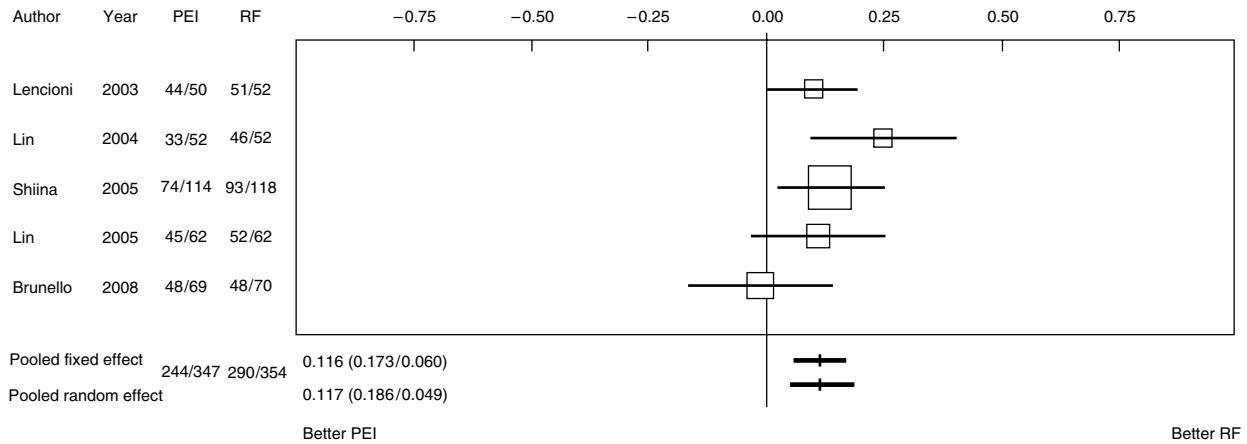


Figure 1. Overall survival.

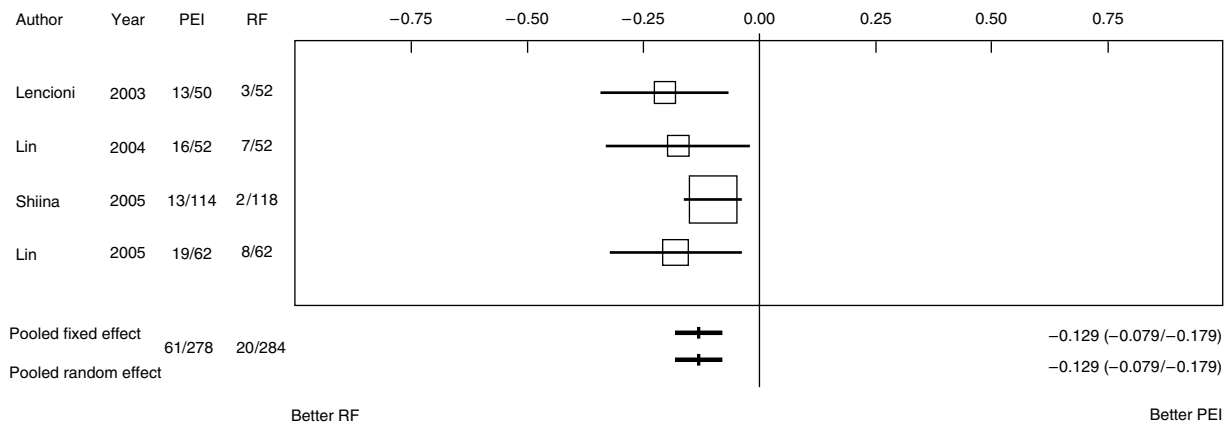


Figure 2. Local recurrence.

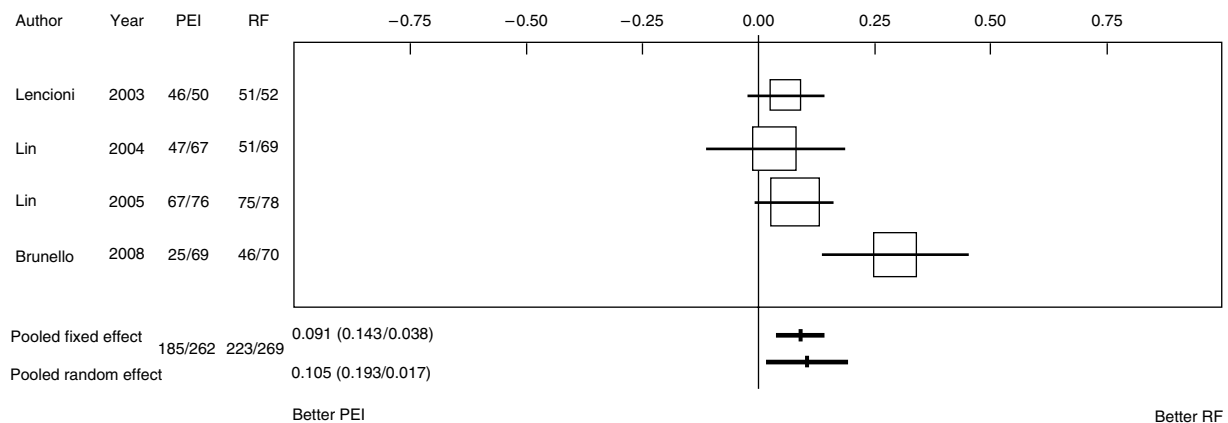


Figure 3. Tumor response.

Three asymptomatic arteriovenous shunts after RF ablation and one chemical thrombosis after PEI were reported in Lencioni's study (14).

Fever was reported only in two studies: in a study (16) a temperature higher than 38.5°C was observed in five patients after PEI; in the other (18) no difference between the two arms

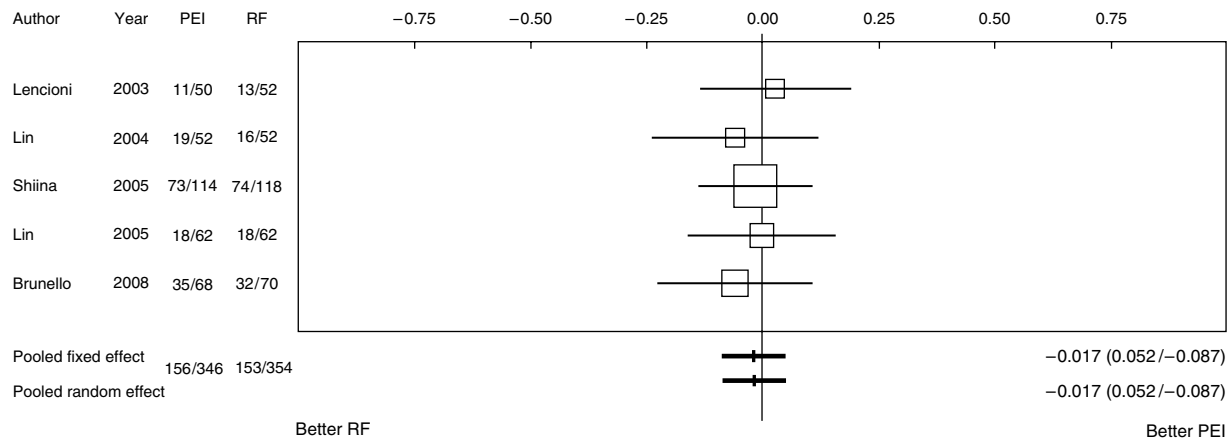


Figure 4. New lesion appearance.

Table 5. Cause of death in PEI/RF arms

Study	Progression	Hepatic failure	Variceal bleeding	Others	Total PEI/RF
Lencioni <i>et al.</i> (14)	2/0	2/0	1/0	0/1 ^a	5/1
Lin <i>et al.</i> (15)	11/3	7/2	1/1	-/-	19/6
Shiina <i>et al.</i> (16)	26/16	8/5	2/1	4/3 ^b	40/25
Lin <i>et al.</i> (17)	10/4	4/3	2/2	1 ^c /1 ^a	17/10
Brunello <i>et al.</i> (18)	NR	NR	NR	NR	28/26
Total PEI/RF	47/23	23/10	6/4	5/5	

NR, not reported.
^aRenal failure. ^bNot reported. ^cSpontaneous bacterial peritonitis.

in the appearance of continual fever of 37.5°C or higher for 3 days or longer were observed.

In all trials, only one procedure-related death was observed in the PEI arm (bowel infarction); the fatality was considered to be possibly related to PEI (18).

Cause of death. The causes of death in all five studies are synthesized in Table 5. The two major causes of death were progression of neoplastic disease and hepatic failure.

DISCUSSION

The Guidelines of American Association for the Study of Liver Disease (11) consider percutaneous ablation as a curative treatment in patients with HCC (according to the Milano criteria (19)) in cirrhosis and well-preserved hepatic function. The effectiveness of these procedures is comparable with hepatic resection.

According to our knowledge this is the first meta-analysis comparing RF vs. PEI in patients with small HCC. The results of the meta-analysis show that in patients with small HCC the treatment with RF is superior to treatment with PEI. Treat-

ment with RF is correlated to a better survival both in terms of overall survival, survival at 1, 2, and 3 years, and cancer-free survival at 1, 2, and 3 years. The advantage of RF treatment on patient survival is statistically significant in the evaluation at 2 and 3 years. This statement may be explained by considering the better performance of RF in terms of complete necrosis of HCC and the low percentage of local recurrence. The effects on survival are homogeneous across the four studies (14–17); only one trial (18) shows nearly equivalent survival with the two treatments; however, in this study the number of patients with Child-Pugh class B cirrhosis was distinctively higher than in the other trials. Furthermore, in Brunello's study there was no correlation between the rate of tumor response and the survival rate. The findings of Brunello's study seem to indicate that patients in Child-Pugh A class are the better candidates for RF.

The better local results of RF could be explained by the stronger and larger coagulation effect of thermal ablation on the HCC nodules and probably on the tumor microsatellites in the surrounding liver tissue compared to the chemical damage induced by ethanol (18,29). Several studies (15,30) demonstrate that complete necrosis of HCC lesions is an important objective

to achieve because it is correlated with a better prognosis. In this setting RF seems to be more effective than PEI.

Consistent with other studies (14,31) RF required fewer treatment sessions and shorter hospitalization than ethanol injection: although we could not evaluate the quality of life in these patients, the decrease in hospitalization certainly has a good impact on the life of patients in terms of less distress.

The efficacy of the treatment with regard to the tumor size was reported across the five studies considering different cutoffs and it was not possible to perform a pooled evaluation.

As regards the occurrence of new lesions, no differences were found between the two groups. This finding is reasonable because the occurrence of new tumors is correlated with the underlying disease and the treatment does not affect this outcome.

A small number of adverse events were reported in the two treatments indicating that both treatments are safe.

The results of this meta-analysis are subject to some limitations. Differences in the baseline characteristics of the population's illness (size and number of lesions) and in the different technical procedures may limit accuracy in RCTs. Pooled results describe variations only among the studies and not among the patients, because they reflect group averages rather than individual data. More detailed treatment comparisons could be achieved only with a meta-analysis of data regarding individual patients. Owing to the need to maintain each study as a distinct analytic unit, it was not possible for the analysis to directly compare the benefit of different technical procedures and to simultaneously maintain comparability of treatment groups.

The available data is sufficient to conclude that RF significantly improves survival, cancer-free survival and, in addition, reduces the percentage of local recurrence compared to PEI.

The results of RCTs in terms of life gain, when pooled together, support the use of RF as a first-line treatment in patients with small HCC according to the Milano criteria and with well-preserved hepatic function. PEI should be reserved only when RF is not technically executable (pericholecystic and subcapsular lesions and lesions near the hilum). The cost and quality of life should be assessed in future RF vs. PEI trials.

CONFLICT OF INTEREST

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Specific author contributions: Study concept, study design, literature search, data acquisition and interpretation, article preparation, article definition of intellectual content, article editing, article revision, and final version approval: Ambrogio Orlando; statistical analysis, article definition of intellectual content, article revision, and final version approval: Gioacchino Leandro; literature search, data acquisition and interpretation, article preparation, article definition of intellectual content, article editing, article revision, and final version approval: Mirko Olivo; article definition of intellectual content, article revision, and final version approval: Angelo Andriulli; article preparation, article

definition of intellectual content, article editing, article revision, and final version approval: Mario Cottone.

Financial support: None.

Potential competing interests: The authors declared no potential competing interests.

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