

# Percutaneous Radiofrequency Ablation of Hepatocellular Carcinoma Compared to Percutaneous Ethanol Injection in Treatment of Cirrhotic Patients: An Italian Randomized Controlled Trial

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**Abstract.** *Aim: To compare 5-year survival of patients with a single hepatocellular carcinoma  $\leq 3$  cm randomly assigned to receive percutaneous ethanol injection or radiofrequency ablation. Patients and Methods: A total of 285 patients (192 males, mean age 70 years), with a single hepatocellular carcinoma (mean diameter 2.2 cm) were randomly assigned to receive percutaneous ethanol injection (n=143) or radiofrequency ablation (n=142). The primary endpoint of the study was 5-year survival. Results: Overall 143 patients underwent percutaneous ethanol injection and 128 radiofrequency ablation. In consideration of segmental location, in fact, 14 patients with 14 hepatocellular carcinomas could not be treated with established radiofrequency and were treated with percutaneous ethanol injection; these patients were not included in the survival evaluation. In the percutaneous ethanol injection and in the radiofrequency ablation groups, 3- and 5-year survival rates of 74% and 68%, and 79% and 70% respectively, were observed (p=n.s.). In the percutaneous ethanol injection group, 3- and 5-year local recurrence rates were 9.4% and 12.8% respectively; in the radiofrequency group, the 3 and 5 years local recurrence rates were 7.8% and 11.7%, respectively (p=n.s.). The overall costs of percutaneous ethanol injection and radiofrequency ablation were 1359 Euros and 171.000 Euros, respectively (p<0.0001) Conclusion: Percutaneous ethanol injection and radiofrequency ablation conferred similar 5-year survival. Feasibility is not the same for both procedures. Percutaneous ethanol injection is much cheaper than radiofrequency ablation and should be considered whether in poor and rich countries.*

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Percutaneous ethanol injection (PEI) and radiofrequency ablation (RFA) have gained great popularity in the treatment of hepatocellular carcinoma (HCC) with cirrhosis (1). In the 2001 European Association for the Study of Liver Diseases (EASL) guidelines, PEI was considered the treatment of choice whereas other more invasive and expensive procedures, such as RFA or use of laser or microwaves, needed still to be compared with PEI in trials (2). RFA is replacing PEI in percutaneous treatment of HCC with cirrhosis (1) and in the last five years more data have been added to the literature, with four meta-analyses being recently published (3-6). In these latter meta-analyses, RFA improved both overall 3-year survival and local control of disease in HCC patients with nodules up to 3 cm in diameter compared to PEI (3-6). The results of three Asian random clinical trials (RCTs) comparing PEI and RFA (7-9) support these findings, while in the only Western study available, both PEI and RFA resulted the same 4-year survival (10). Moreover, in the meta-analyses by Cho and colleagues (4) and Germani *et al.* (6) there was no evidence that RFA compared with PEI improves survival of patients with HCC nodules up to 2 cm, and the meta-analyses by Bouza *et al.* (5) concluded that the cost-effectiveness of PEI and RFA needed further evaluation (5).

To our knowledge, no study has investigated the feasibility of the technical performance of PEI or RFA according to the location of the HCC nodules in the different segments of the liver in a RCT.

Therefore, the aim of the present study was to report the data of an Italian RCT comparing the cumulative 5-year survival of cirrhotic patients with a single HCC nodule 3 cm or less treated with PEI or RFA, and also to evaluate local recurrences in the treated patients. In addition, the 5-year survival of patients with HCC  $\leq 2$  cm treated with PEI or RFA, the feasibility in the performance of PEI or RFA according to segmental location of HCC nodules and the cost-effectiveness of both procedures were evaluated.

## Patients and Methods

**Patients.** From January 2005 to January 2010 among 2487 consecutively registered patients with HCC seen at our Institution, 285 patients had a single HCC nodule 3 cm or less in diameter and were randomized to receive PEI (n=143) or RFA (n=142). One hundred and ninety-two were males and the patients groups had a mean age of 70 years. One hundred and forty-five patients had Child-Pugh A liver cirrhosis and 140 had Child-Pugh B cirrhosis and all had a single HCC nodule (range 1.1-3 cm, mean 2.2 cm). The HCC nodules ranged in diameter between 1.1 and 2 cm in 40 patients of the PEI group (28%) and in 31 of the RFA group (22%). Cirrhosis was due to HCV in 168 patients and HBV in 117 patients. Patients with nodules near to the gallbladder or main large blood vessels, or under the liver surface or the diaphragm were not excluded from randomization and assignment of percutaneous procedure. None of the patients had ever been treated before and in all of the patients the presence of the nodule was seen for the first time during US surveillance of their known liver cirrhosis. In no case was there ascites or presence on imaging of thrombosis of the main portal vein and/or its branches or even of segmental portal vein thrombosis in regards of these data.

Table I reports the main clinical and imaging data of the patients studied. No statistically significant difference was present between the PEI and RFA groups.

**Exclusion criteria.** Patients with surgical indication (*i.e.* patients suitable for liver transplantation or hepatic resection) and patients with Child C class of cirrhosis were excluded from the study. Patients with more than one nodule on both US and enhanced (CT) and/or (MRI) and patients with nodules >3 cm were also excluded. Patients with extra-hepatic disease were also excluded from the study.

**Diagnosis of HCC.** In accordance with the 2005 American Association of the Study of Liver Disease (AASLD) practice guidelines (11), diagnosis of HCC nodules >2 cm was made in 214 patients (75%) with contrast-enhanced ultrasound (CEUS) alone or enhanced CT or MRI that were used for staging of the tumoral disease; diagnosis of HCC nodules >1 and <2 cm in 71 patients (24.9%) was made with CEUS and concomitant findings of a hypervascular pattern in the arterial phase and washout in the portal phase both on CEUS and concomitant enhanced CT or enhanced MRI; in 21 out of 285 patients (7.4%), diagnosis was made with percutaneous US-guided biopsy using a cutting needle (18-G needle, Surecut, HS, Japan).

The primary end point of the study was 5-year survival of patients with single HCC ≤3 cm.

Secondary end points were the evaluation of local recurrences in patients with HCC nodules ≤3 cm, 5-year survival of patients with HCC nodules ≤2 cm, feasibility in the technical performance of both procedures according to nodule's segmental location and, finally, the evaluation of the costs of PEI and RFA.

Randomization to PEI or RFA was carried out prospectively with the use of a coded list compiled from a random number generator; the code was fully blinded to the field staff and trial participants were blinded to the code. The sample size was calculated considering 50% 5-year survival rate in the control group (PEI group) (12) and assuming that the experimental group (RFA group) would obtain more than a 20% increase in survival. An alpha error of 0.05 and a study power of about 80% (beta=0.20) were considered. The number of patients per arm was calculated to be more than 106.

Table I. Baseline clinical characteristics by treatment group.

	PEI	RFA
No. of patients	143	142
Age (years)		
Range	68-79	68-74
Mean (±SD)	72±6	70±2
Gender		
Male	102	105
Female	41	37
Child-Pugh class		
A	75	70
B	68	72
Hepatitis B virus infection	56	61
Hepatitis C virus infection	87	81
Tumor diameter (cm)		
Range	1.3-2.9	1.1-3
Mean (±SD)	2.27±0.48	2.34±0.45
Follow-up (months)	22	22
Baseline clinical variables		
Albumin (g/dl) mean (± SD)	3.41±0.92	3.37±0.81
Bilirubin (mg/dl) mean (± SD)	0.87±0.29	0.85±0.47
INR: mean (± SD)	1.02±0.3	1.05±0.14
Platelets (x10 <sup>3</sup> /mm <sup>3</sup> ) mean (±SD)	114.06±8.32	116.50±10.29
Alfa-fetoprotein (mg/ml) mean (±SD)	59.21±141.12	56.24±127.32

**Percutaneous procedures.** Both procedures were performed under unconscious sedation by the same physician (A.G.) with more than 25 years' experience in interventional US and were performed within 18 days of diagnosis.

PEI was performed under US guidance, according to standardized criteria (12, 13) injecting of 4-20 ml of 95% sterile ethanol according to the volume of nodules though a 22-21 gauge needle (Ecojet HS; Tokyo, Japan) so as to obtain a homogeneous perfusion of the nodule that appeared homogeneously hyperechoic at the end of the treatment.

RF was performed under US guidance, using a perfused electrode needle (HiTT, Integra; Nottingham, Germany), connected to an RF generator at a power of 45-55 W for 10-15 minutes: when the nodule appeared completely hyperechoic, the RFA application was considered sufficient and the electrode needle was withdrawn with the RF generator still on, so as to avoid seeding (14). In our experience, this needle gave excellent results in inducing complete necrosis of HCC nodules up to 96% ≤3 cm. Patients with HCC nodules up to 2 cm were treated with a 1.7 mm calibre perfused electrode needle with a 2 cm active tip. In patients with HCC nodules >2 cm, a 2 mm calibre perfused electrode needle with 3 cm active tip was employed.

The minimum platelet count was 50,000 and the minimum INR was 1.4 in all patients for both percutaneous procedures. The day after percutaneous PEI/RFA procedures all patients underwent clinical and laboratory tests and abdominal US.

The efficacy of both PEI and RFA was evaluated in all cases with enhanced CT one month after the procedure and necrosis was defined as complete when none of nodule appeared enhanced in the arterial phase. In cases of incomplete necrosis, the patients were re-treated with the same original percutaneous procedure. After establishing complete necrosis, all patients were followed up with (αFP) and US every 2 months. In cases of recurrence in the treated area (local

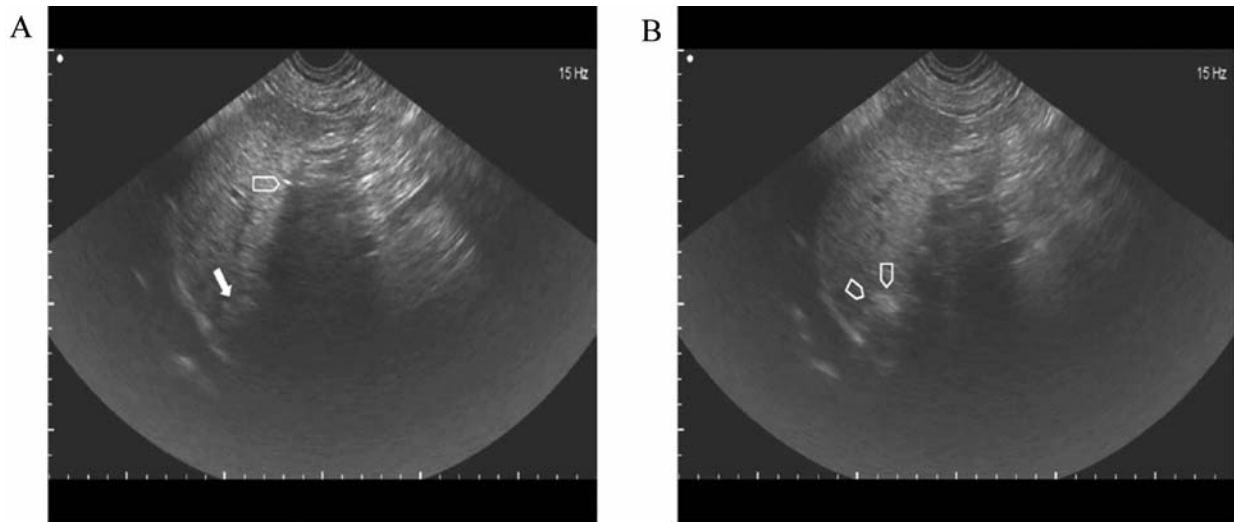


Figure 1. Imaging of tumor in a 69-year-old man with HCC in cirrhosis. A: Ultrasound image shows HCC nodule in a patient who was randomized to receive RFA and then shifted to PEI needle, which can be safely inserted within the HCC nodule avoiding the gastric wall. Using the larger RF electrode needle, the risk of perforation of the gastric wall was higher. B: Ultrasound image showing the HCC nodule (open arrows) perfused by the ethanol.

recurrence) or in distant areas (new HCC nodule, all patients were treated with PEI or RFA according to the same original procedure.

**Cost-effectiveness analysis.** As in Italy the medical costs of both procedures were the same, the cost of PEI and RFA was calculated only on the basis of the cost of the technical material for PEI or RFA used in the overall period of the study *i.e.* the cost of the needles and the ethanol used for PEI and the costs of the generator and the perfused electrode needles for RFA. The costs are reported in Euros.

**Statistical analysis.** Quantitative and qualitative variables were calculated according to Student's test and chi-square test, respectively. Survival was calculated using the Kaplan-Meier method and the differences between the two curves calculated with the log-rank test. Univariate and multivariate analyses were carried out using the Cox proportional hazards models. Results are presented as hazard ratios (HRs) with corresponding 95% confidence intervals (CI) and *p*-values. A *p*-value less than 0.05 was considered as being statistically significant.

The study was approved by our Institutional Review Board and an Informed written consent was obtained from all patients.

## Results

The volume of ethanol injected ranged from 4 to 20 ml (mean 8.7 ml) and the RF application time ranged from 10 to 15 minutes (mean 11.5 minutes). The follow-up ranged from 8 to 68 months (mean 37 months). The number of procedures needed to achieve complete necrosis after the first treatment was 8 for PEI and 5 for RFA with no statistically significant difference.

**Feasibility.** At the end of the study, 143 patients had undergone PEI and 128 RFA. Considering segmental location, 14 patients with 14 HCC nodules (caudate lobe=4 nodules; II segment=3

nodules; VII segment=2 nodules; VIII segment=5 nodules) could not be treated with scheduled RFA on the basis of randomization and they were shifted to PEI treatment (Figure 1 A, B). These 14 patients were not included in the PEI survival evaluation.

**Survival. Patients with HCC 3 cm or less:** In the PEI group, the cumulative 1-, 2-, 3-, 4- and 5-year survival rates were 95%, 83%, 78%, 70% and 68%, respectively, and in the RFA group were 95%, 90%, 83%, 73% and 70%, respectively, with no statistically significant differences between the two groups (HR=0.81, 95% CI=0.46-1.39; *p*=0.451) (Figure 2).

**Patients with HCC up to 2 cm:** In the PEI group, the cumulative 1-, 2-, 3-, 4- and 5-year survival rates were 94%, 88%, 79%, 70% and 68%, respectively; and in the RFA group were 96%, 88%, 79%, 72% and 70%, respectively, again with no statistically significant difference (HR=0.81, 95% CI=0.46-1.39; *p*=0.451) (Figure 3).

**Local recurrences in patients with HCC 3 cm or less.** In the PEI group, the 1-, 2-, 3-, 4- and 5-year local recurrence rates were 5.2%, 6.7%, 9.4%, 11.5% and 12.8 %, respectively, and in the RFA group were 4.1%, 5.7%, 7.8%, 8.9% and 11.7% respectively (*p*=0.0429).

Univariate analyses, the Child-Pugh Class B (HR=2.38; 95% CI=1.29-4.03, *p*<0.002) and serum  $\alpha$ FP levels >200 ng/ml (HR=1.69, 95% CI=0.61-4.93, *p*=0.02) were the variables with a positive significant association with the risk of death. On multivariate analyses, Child-Pugh Class B was the only variable associated with the poor prognosis (HR=2.97, 95% CI=1.58-5.47, *p*<0.001).

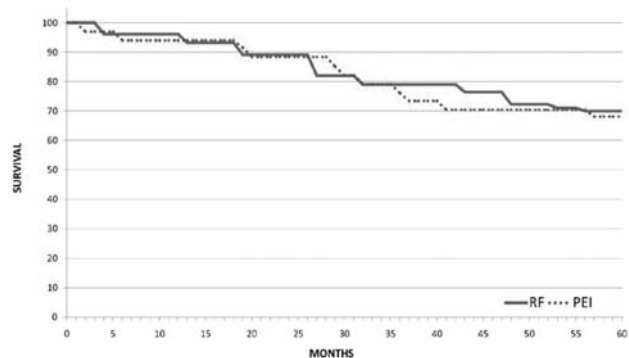


Figure 2. Graph showing cumulative 5-year survival curves of patients with HCC nodule up to 2 cm treated with RF (solid line) and PEI (dashed line).

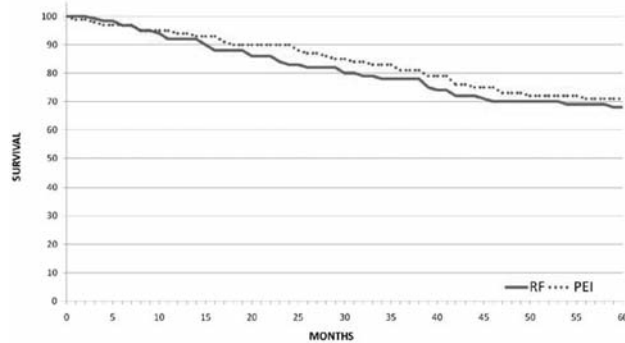


Figure 3. Graph showing cumulative 5-year survival curves of patients with HCC nodule up to 3 cm treated with RF (solid line) and PEI (dashed line).

**Complications.** No death related to either procedure was observed during the entire study.

The rate of major complications was 1.9% in the PEI group and 0.9% in the RFA group ( $p=n.s$ ).

No case of seeding, neither in clinical nor imaging settings, was observed during the follow-up.

**Costs.** The overall cost for PEI needles plus ethanol was 1359 Euros plus VAT, instead the cost of the generator plus that of the RFA electrode needles was 171.000 Euros plus VAT, with a statistically significant difference of ( $p<0.001$ ).

## Discussion

To our knowledge, only four meta-analysis studies comparing RCTs of PEI vs. RFA in the treatment of HCC with cirrhosis have been conducted (3-6) and all of them agree on the fact that RFA improves 3-year survival compared to PEI in the treatment of HCC nodules sized 3 cm or less. Of the four RCTs available and evaluated in these meta-analyses, only one study by Brunello and co-workers reported the same 4-year survival between patients treated with PEI and RFA, whereas the three Asian studies all favoured RFA over PEI.

According to the 2005 AASLD guidelines (2), identically replicated in the recently published 2010 AASLD recommendations for the management of HCC (15), the volume of necrosis induced by RFA is more predictable than that induced by PEI, as a consequence, the local tumor control and the overall survival also improve with RFA. But both sets of guidelines (15) stated that for HCC <2 cm, the effect of both treatments is similar. This concept is clearly stated by Cho *et al.* (4) and Germani *et al.* (6) in their meta-analyses and Bouza and colleagues (5) pointed out the problem of the therapy costs, especially regarding RFA, which is known to be a much more expensive technique respect to PEI (15). Finally, the 2010 AASLD recommendations, even indicating RFA as the first

choice procedure for percutaneous ablation, state that ethanol injection still has an important role for small tumors and conclude that “robust RCTs, primarily designed to assess survival are still needed” (15) The same conclusions can be found in the last meta-analyses conducted by Germani *et al.* who state that “because of the small size of the trials and few trials further trials are necessary” (6). Moreover, Bruix and Forner asked themselves if “there is a need to have a winning technique” for percutaneous ablation of HCC and, correctly, indicated ethanol injection as a cheap method to destroy HCC, emphasising the role of ethanol especially in the “emerging economies” (16).

Our study seems to reply to all of these questions. In our experience, PEI and RFA lead to the same 5-year survival rate in the treatment of single HCC nodules up to 3 cm in size, with no statistical difference between the two groups of patients. Furthermore, as far as the local control of the treated nodules is concerned, no difference between patients treated with PEI or RFA was found in our series. No death occurred in either of the groups and there was no statistical difference regarding major complications in the groups. Patients with HCC nodules up to 2 cm in size survived equally in both groups, even if the sample size in the two arms was not statistically sufficiently powered. Therefore, our results are in line with those reported by Brunello and co-workers (10). We also agree with the argument made by Brunello *et al.* to explain the difference between the results of the Asian studies and the Western ones; in fact, in the study of Brunello *et al.* and in our own, the number of Child A and B patients treated with PEI is the same as that of the group treated with RFA, while this is not found in the series of Lin *et al.* (8) and Shiina *et al.* (9), where Child A patients treated with RFA were clearly more than those treated with PEI. As a consequence, this discrepancy could explain the different results in terms of survival, favouring one technique (RFA) over the other (PEI).

Finally, not all HCC nodules are candidates for treatment either with PEI or RFA, being dependent on their different segmental location in the liver. In our experience, in 14 cases randomized to receive RFA, it was not possible to perform the procedure and the ablation was shifted to PEI. The technical reasons were mainly due to the accentuated inclination occurring for the insertion of the RF electrode needle into the tumor located in the 7th or 2nd segment of the liver. In such cases, the possibility of cutting the liver parenchyma increases (the calibre of the RF electrode needle is larger than that of the PEI needle) and, as a consequence, the risk of hemorrhage is higher. Another localization not suitable for RFA was that in the caudate lobe; as to avoid vascular structures a thin needle was necessary. Another example is the localization in the 2nd segment as shown in Figure 3 A-B. This occurrence was unexpected, and RFA was not possible, even with considerable expertise.

Our results led finally to another important problem: the problem of costs. Cho and co-workers (4) and Bouza and colleagues (5) clearly pointed out this problem: if the final clinical effect (*i.e.* 5-year survival) of PEI or RFA is the same, it is important to consider the difference between the costs for the two types of treatment. In our case, as the medical costs of PEI and RFA were the same, the difference of costs was only related to the cost of the devices for the two ablation techniques. As far as the price of PEI and RF devices is concerned, the cost was notably different and the choice is clearly in favour of PEI. This is an important consideration given that it is not only in developing or emerging countries that the cost of ablation techniques can be a main limiting factor for therapy, ablation techniques are performed with limited resources even in other countries, for example, in Eastern Europe.

In conclusion, in our experience, RFA and PEI are both useful in the treatment of a single HCC nodule up to 3 cm in size in terms of survival and local control. PEI would appear to be the most suitable technique, as it is suitable for all kinds of tumor localization and all kinds of countries, whether rich or poor.

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