Percutaneous Ethanol Injection Therapy in the Treatment of Hepatocarcinoma – Results Obtained from a Series of 88 Cases

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Abstract

Aim: To assess the efficacy of Percutaneous Ethanol Injection Therapy (PEIT) for the treatment of hepatocarcinoma in a series of Romanian patients, and to compare it with previous studies. Material and method: We retrospectively evaluated 88 patients with liver cirrhosis (LC) and hepatocellular carcinoma (HCC) treated by PEIT. Multiple sessions of PEIT were performed to treat a single nodule of 2-10 cm in diameter. The Child-Pugh classification was used for evaluating the severity of LC and the Okuda and Barcelona scores for HCC. The efficacy of PEIT was assessed by CT or MRI one month after the therapy. The patients' survival after PEIT was calculated starting from the first PEIT procedure until the moment of death or the end of study (2000-2005). We analyzed the main factors which influenced the survival of the treated patients. Results: The global survival was 38.07±3.97 months, longer in patients with Child-Pugh A class, than in Child-Pugh B class (Log Rank 0.04). Patients with HCC less than 3 cm in diameter survived significantly longer than patients with tumors more than 5 cm (Log Rank 0.007). Also, survival was better in the Barcelona A stage than in the Barcelona B and C stages (Log Rank 0.002) and in patients with alpha-fetoprotein less than 200 ng/l (Log Rank 0.002). Conclusion: The main factors which influenced the survival of patients treated by PEIT were: the size of the HCC, the Child-Pugh class, the Barcelona stage and the level of alpha-fetoprotein at the time of initiation of therapy.

Key words

Liver cirrhosis – hepatocellular carcinoma – Percutaneous Ethanol Injection Therapy

Introduction

Percutaneous Ethanol Injection Therapy (PEIT) and Radiofrequency Ablation (RFA) are the two most studied percutaneous ablative therapies for the treatment of hepatocellular carcinoma (HCC). The two methods have been proven to be safe and efficient when applied to HCCs smaller than 3 cm, having similar results regarding efficacy and survival [1-3]. The two methods ensure a complete response in 80% of the tumors less than 3 cm in diameter and only in 50% of HCCs 3-5 cm in diameter, with a 5 year survival of 40-70% [4, 5].

Unfortunately, the percutaneous therapy is efficient only in the case of small tumors, less than 3 cm, which can be completely destroyed. In these cases, percutaneous therapy is used with curative intent, with a good post-therapeutic survival. Percutaneous therapy, PEIT as well as RFA, can also be used in larger tumors (even 10-12 cm in diameter), but not with curative intent, just as a palliative therapy, in order to increase the survival rate of this category of patients [6-8].

The aim of this paper was to assess the efficacy of PEIT for the treatment of hepatocarcinoma in a series of Romanian patients, and to compare it to previously reported series.

Material and method

Our retrospective study included 88 consecutive patients admitted to the Department of Gastroenterology and Hepatology Timisoara with liver cirrhosis (LC) and HCC who were treated by means of PEIT, and were followed-up for 5 years (2000-2005).

The patients included in our study fulfilled the following criteria: unique nodule 2-10 cm in diameter found by ultrasound examination and confirmed by CT or MRI, no additional nodules detected by CT or MRI, no ascites, thrombocyte counts > 50,000/mm³, prothrombin index > 50%.

The diagnosis of HCC was established by imaging methods: contrast CT or MRI (arterial enhancement of the nodule and rapid “wash-out”) and, in uncertain cases, by means of ultrasound-guided biopsy of the nodule. HCCs
were rated according to the Okuda and Barcelona scoring systems and the severity of LC was assessed according to the Child-Pugh criteria.

The diameter of the treated HCCs ranged between 2 and 10 cm. In tumors < 3 cm and in tumors 3-5 cm in diameter, PEIT was performed with curative intent. For tumors larger than 5 cm, PEIT was used with palliative intent: the destruction of a large volume of the tumor in order to obtain an increase in the survival rate in these patients. In all these cases, multiple sessions were used.

PEIT was performed using Dikinson needles (22 Gauge spinal needle – Shandong Weigao Group Medical Polymer Co). Under ultrasound guidance, the needle was inserted into the tumor and 95% sterile ethanol was injected. We tried to inject the optimal volume of ethanol into all the neoplastic tissue. The efficacy of PEIT was assessed by contrast CT or MRI one month after treatment, the aim being the complete absence of enhancement of the treated tumor following contrast. If complete necrosis was not achieved, another session of PEIT was performed. The adverse effects of PEIT were assessed in all the treated patients.

Every 6 months after PEIT, the patients were evaluated by means of contrast CT or MRI, as well as by serum alpha-fetoprotein (AFP) measurement. Abdominal ultrasound was performed every three months to follow-up the dimensions of the treated tumors and in order to discover new nodules, but CT was performed only every 6 months in order to minimize the radiation exposure (MRI was not available to us at the beginning of the study). The cut-off level of AFP for the diagnosis of HCC was considered to be 200 ng/l (according to the 2006 AASLD guidelines) [9].

Also, in all the patients treated by PEIT the total number of sessions and the total volume of injected ethanol were evaluated (in patients who needed more than one session, PEIT was repeated after 3-4 days, maximum two sessions per week).

The Kaplan-Meyer curves were used for cumulative survival assessment and differences between survival curves were evaluated with the log-rank test.

**Results**

The mean age of the treated patients was 64.9±8.5 years in women, and 64.4±8.2 years in men. The M/F ratio was 2/1: 59 men - 67.0% men and 29 women - 33.0 % (Table 1). Most patients (38.6%) were 60-69 years old, and many patients (30.7%) were older than 70 years.

The main etiology of LC was hepatitis C virus (HCV) infection in 67% cases, followed by hepatitis B virus (HBV) infection in 18.2% cases. The treated HCCs were mainly in Okuda I stage and Barcelona A and B stages (Table 1).

The volume of ethanol injected in one PEIT session varied between 5 and 20 ml, depending on the tumor size, and the number of PEIT sessions in one patient varied between 1 and 19, the average being 3.7 sessions/patient. The number of PEIT sessions performed in all the patients was 333, the total volume of injected ethanol was 4,547 ml and the mean volume of injected alcohol during one session was 13.6 ml.

### A. Evaluation of PEIT efficacy

Complete tumor necrosis, defined as lack of enhancement with contrast by CT or MRI, was obtained in 33 cases (37.5%) from the total of 88 treated patients.

Considering the initial diameter of the tumor before PEIT, complete tumor necrosis after treatment was obtained in 82% of unique tumors < 3 cm and in 33.3% of the tumors 3-5 cm in diameter.

### B. Survival of percutaneously treated patients

The global mean survival rate was 38.07±3.97 months with 77.6% survival at one year, 53.7% at 2 years, 35.3% at 3 years, 32.6% at 4 years and 25% at 5 years (Fig. 1).

The mean survival rate, considering the Okuda stage at the moment of diagnosis, was 43.09±5.60 months for Okuda stage I and 29.51±4.41 months for Okuda stage II. The survival rate was not statistically significant different in patients Okuda I vs. Okuda II stage (Log Rank 0.240) (Fig. 2).

According to the Barcelona classification, the mean survival rates were: 42.56±4.54 months in Barcelona stage A; 33.92±5.70 months for stage B; and 13.20±3.42 months for stage C. As expected, the survival was significantly longer for patients with Barcelona class A HCCs (Log Rank 0.002) (Fig. 3).

Considering the HCCs dimensions at the initiation of PEIT, the mean survival rates were: 46.96±5.80 months for
tumors smaller than 3 cm in diameter; 31.58±3.79 months for tumors 3-5 cm in diameter; and 27.91±5.58 months for tumors larger than 5 cm in diameter (Fig.4). Patients with HCC < 3 cm survived significantly longer than patients with tumors larger than 5 cm (Log Rank 0.007).

Considering the Child-Pugh class of LC at the moment of HCC diagnosis, the mean survival rate was 43.06±5.38 months for patients in Child-Pugh A class, significantly longer than for patients in Child-Pugh B class (24.80±4.31 months) (Log Rank 0.04) (Fig.5).

The mean survival rate was higher in patients with a low AFP level at the beginning of the treatment: 42.08±4.04 months for patients with AFP < 200 ng/l versus 17.10±2.90 months for patients with AFP > 200 ng/l (Log Rank 0.002).

The survival rates at 1, 2, 3, 4 and 5 years are presented in Table II.

C. Complications

The following complications occurred after PEIT:

a) Major complications occurred in 9% of the patients treated by PEIT (8 of 88): death in 1 patient (1.1%) due to extensive necrosis of gastric and duodenal wall; upper digestive hemorrhage (due to variceal bleeding or from gastric or duodenal ulcers) in 6 patients (6.8% cases); thrombosis of the inferior vena cava in 1 case (1.1%) (a 74 year old patient, in whom a 6.5/5.8 cm HCC was treated...
with 5 sessions of PEIT in 3 months); tumor seeding in one case (1.1%).

b) Minor complications: local pain or pain irritating in the right shoulder in 21.6% of the cases; fever in 14.8% cases; vascular decompensation of the LC [a small quantity of ascites observed by ultrasound in 4 patients (4.5%)].

The complication rates considering the total number of PEIT sessions (333 sessions) were: vascular decompensation in 1.5% cases, upper digestive hemorrhage in 1.8% of the cases; seeding in 0.3% of the cases; inferior vena cava thrombosis in 0.3% and death in 0.3% cases.

**Discussion**

In the last years, 4 randomized trials have compared PEIT or percutaneous acetic acid injection (PAAI) results to RFA [1-3, 10]. Significant percentages of necrosis after RFA were reported by Livraghi et al in 1999 [11] and higher survival rates by Japanese authors [1, 2, 10]. In European studies [3], the reported survival rates after 2 years were 98% for RFA and 88% for PEIT (difference not statistically significant), but recently Brunello et al [12] reported a similar 4 year survival rate for both PEI and RFA. In our center, RFA was not available at the time of the study.

The major limitation of PEIT is the high local recurrence rate, which may reach 33-43%. Recent studies have shown that RFA can achieve more effective local tumor control than PEIT with fewer treatment sessions [13]. In three recent review studies, RFA was superior to PEIT in the treatment of small HCCs with respect to overall survival, 1, 2, and 3 years survival rates, 1, 2, and 3 cancer-free survival rates, and tumor response [14-16]. RFA showed a significantly lower risk of local recurrence [14].

In a randomized study performed by Lin et al [10], which compared the results of PEIT, RFA and PAAI in patients with HCCs smaller than 4 cm in diameter, the complete tumor necrosis was obtained in 88.1% of the tumors treated by PEIT, the survival rates at 1, 2 and 3 years being 88%, 66% and 51% (in our group: 84.8%, 78.8%, 57.8% respectively), and tumor recurrence 35 months after the treatment was 34.5%.

In our study, complete tumor necrosis after PEIT was obtained in 82% of the HCCs smaller than 3 cm in diameter, but only in 33% of larger tumors, 3-5 cm in diameter, less than in the reported studies.

Although PEIT is indicated as a method of treatment for tumors < 3 cm in which it was proved to have very good results, it was used also for the treatment of large tumors. In a study performed by Livraghi et al [7], PEIT was used to treat large HCCs (5-10 cm in diameter): ethanol was injected into the tumor in a single therapy session (“one shot therapy”). The survival rates at 1, 2, 3 and 4 years were 72, 65, 57 and 44% in HCC smaller than 8.5 cm and 46%, 25%, 0% and 0% in HCCs up to 10 cm. PEIT was echo-guided, under general anesthesia and the mean dose of ethanol was 62 ml/session. Major complications were reported in 0.6% of the cases (intraperitoneal and variceal bleeding, hepatic and kidney failure, intestinal necrosis).

Other studies [7, 8, 17] showed better results in the treatment of larger tumors using one shot therapy of PEIT and concluded that PEIT of large and multiple HCCs showed survivals similar to conventional PEIT for patients with smaller tumors.

We also used PEIT to treat HCCs larger than 5 cm in diameter, but repeated sessions were performed and the maximal quantity of ethanol injected in one session was 30 ml. In tumors 5-10 cm in diameter, survival rates at 1, 2 and 3 years were 64%, 29% and 21%, respectively. The results are inferior to the ones reported in “one shot therapy” studies.

PEIT of HCCs is a low risk method regarding major complications, with 0.9-1% mortality and a seeding risk lower than 1% [18, 19]. The most frequently reported complications are local pain and fever, rarely hepatic abscesses, intraperitoneal bleeding, jaundice, encephalopathy and upper digestive hemorrhage. In our patients, major complications were rare, and the mortality was 0.3%.

A major complication of percutaneous treatment techniques is needle dissemination (“seeding”). Llovet et al [20] reported seeding in 12.5% cases, but Livraghi et al [21] in only 0.5% of cases. The risk factors for seeding are the subcapsular placement of the tumor, the low grade malignancy and the high level of AFP. The high incidence of seeding in Llovet’s study can be explained by the small number of tumors treated and also by the high number of biopsies performed before RFA (50% of seeding occurred in patients in whom biopsy was performed before RFA), suggesting the important role of biopsy in tumor dissemination. Seeding (confirmed by pathological exam)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Okuda</th>
<th>Barcelona</th>
<th>Diameter of the nodule (cm)</th>
<th>AFP (ng/l)</th>
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<tr>
<td></td>
<td>I</td>
<td>II</td>
<td>A</td>
<td>B</td>
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<tr>
<td>1 year</td>
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<td>75.9</td>
<td>68</td>
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<tr>
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<td>53.7</td>
<td>53.4</td>
<td>46.5</td>
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<td>22.3</td>
<td>50</td>
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<td>42.2</td>
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<td>30</td>
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<tr>
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<td>38.07±</td>
<td>29.51±</td>
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<td>0.007</td>
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occurred only in 1 of our patients (1.1%), or 0.3% if reported to the total number of PEIT procedures. An explanation for the low rate of seeding in our group could be the small number of diagnostic core biopsies performed before PEIT. More recent studies report lower seeding rates as a complication of percutaneous therapy: 0.13% in a study performed by Tung et al [22].

A rare complication, observed in 3 patients, was the occurrence of gastric and duodenal ulcers post PEIT. Two cases had a favorable outcome under conservative treatment. One case had an unfavorable evolution, with extension of the gastric and duodenal lesions: the patient died 21 days after PEIT.

Gastric injury after PEIT is very rare, only a few cases being reported in literature. The mechanism of injury is probably vascular, due to a particular vascular pattern of the liver, when the left hepatic artery arises from the left gastric artery (10% of cases) or when the left hepatic artery arises from the celiac trunk but there is another left accessory hepatic artery, having its origin in the left gastric artery (8% of cases) [23-26]. The volume of injected ethanol, as well as the speed of injection, could contribute to the severity of gastric lesions. Tseng et al recommend that a smaller quantity of alcohol should be injected slowly (1cc in 5-10 seconds) [25].

The multivariate analysis performed in our patients showed that the main factors influencing survival of PEIT patients were: the Child-Pugh class, the initial size of the HCC, the Barcelona stage and the AFP level at the beginning of PEIT. The global survival rate at 5 years of the treated patients was 25% in our group, with a mean survival of 38 months.

The main limit of our study is that it was retrospective and uncontrolled, but it did assess the results on a series of Romanian patients treated by PEIT by the same operator in one or multiple sessions.

Conclusions

In patients with HCC treated by PEIT, we obtained complete tumor necrosis in 82% of the tumors smaller than 3 cm and only in 33.3% of the larger tumors, 3-5 cm diameter. The survival rate of the treated patients was related to the Child-Pugh class of liver cirrhosis, to the tumor size, the Barcelona stage and the AFP level at the beginning of the therapy.

Conflicts of interest
None to declare.

References


