

Transcatheter Arterial Chemoembolization and Percutaneous Ethanol Injection for Hepatocellular Carcinoma: A Retrospective Review of the Veterans Affairs Caribbean Healthcare System

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Background: Hepatocellular carcinoma (HCC) is a common malignancy worldwide and has a poor prognosis. Although surgery and liver transplantation provide better outcomes, most patients are not candidates due to advanced disease, lack of donor availability, or presence of comorbidities. Several percutaneous approaches such as transcatheter arterial chemoembolization (TACE) and percutaneous ethanol injection therapy (PEIT) have been developed for local control and can potentially increase survival in these patients.

Methods: We retrospectively reviewed 33 patients with HCC who were treated with TACE, PEIT, or both from 2000 to 2005 at the VA Caribbean Healthcare System in Puerto Rico to evaluate tolerability, response, and survival. Patients were evaluated with cross-sectional computed tomography imaging to determine response using response evaluation criteria in solid tumors (RECIST).

Results: Thirty-three men with a mean age of 66 years were treated. Mean tumor size was 5.6 cm, ranging from 2 cm to 16 cm. All patients had cirrhosis, with alcohol abuse and hepatitis C as the most common etiologies. Objective radiographic partial response was observed in 28% of patients and 48% had disease stabilization. Most of the patients had a therapeutic response demonstrated by necrosis of the tumor and decreased contrast enhancement. Patients who underwent both TACE and PEIT had a higher response rate and disease stabilization but no difference in survival compared with those who received TACE or PEIT alone. Median survival for the whole group was 2 years. Causes of death included tumor progression, hepatic failure, gastrointestinal bleeding, and infections. The initial tumor size and Child-Pugh class did not confer a significant difference in survival rate.

Conclusions: In Puerto Rico, where liver transplantation is not performed at present, percutaneous treatments are effective local therapies for patients who are not candidates for surgery and who have disease limited to the liver.

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide, with approximately 626,000 cases and 598,000 deaths occurring annually.¹ Primary cancers of the liver are therapeutically frustrating; most

patients die within 6 months of onset if untreated.^{2,3} Surgical resection has been the major treatment to offer potential cure in HCC, with survival rates that range from 25% to 50% at 5 years. However, only 30% of patients with HCC are candidates for surgery, and operative mortality in cirrhotic patients can be as high as 15% to 30%.⁴ Liver transplantation is also potentially curative, but donor availability and patient selection limit the procedure.⁵

Due to these limitations, several percutaneous approaches have been developed for the treatment of HCC including transcatheter arterial chemoembolization (TACE) and local ablation with percutaneous ethanol injection therapy (PEIT). It is well established that both primary and secondary liver tumors derive their blood supply from the hepatic artery, while about 50% of the oxygen supply to the normal liver is from the portal system.⁶ Arterially directed treatment is attractive not only because of its delivery and safety, but

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Abbreviations used in this paper: HCC = hepatocellular carcinoma, TACE = transcatheter arterial chemoembolization, PEIT = percutaneous ethanol injection therapy.

also because the tumor can be made ischemic while uninvolved liver is spared. Cumulative survival rates following TACE range from 54% to 88% at 1 year, 33% to 64% at 2 years and 18% to 31% at 3 years.⁷⁻¹¹ However, TACE has not been a curative technique when used alone. Local tumor ablation with PEIT has a 4-year survival rate ranging from 45% to 71% in single HCCs less than 3 cm in size.¹²

HCC is more prevalent in Puerto Rico than in the mainland. This has been attributed to a higher prevalence of hepatitis C infection (6.3% vs 1.8% in the mainland) and also to the high number of cases of cirrhosis induced by alcohol abuse.¹³ Liver transplantation is not currently performed in Puerto Rico, and the use of radiofrequency ablation is limited. This led our group to investigate the use of TACE, PEIT, or both in patients with HCC who were not considered surgical candidates and who had predominantly liver-limited disease with a dominant lesion.

Patients and Methods

Patients

We retrospectively evaluated the medical records of all patients with HCC who underwent TACE and/or PEIT between January 2000 and May 2005 through their participation in a local protocol. Approvals for retrospective chart review were obtained from the Institutional Review Board. All patients had histological confirmation of HCC and had an ECOG performance status of 0 to 2. For protocol eligibility, patients needed adequate hematologic parameters (white blood cell count more than 2,000/mm³, platelets greater than 75,000/mm³, and hematocrit over 30%). Patients with uncontrolled encephalopathy, portal vein occlusion, or high risk of hepatic failure secondary to the procedure were not considered eligible for this treatment. The underlying hepatic function was assessed using the Child-Pugh classification. All treated patients signed an informed

consent and our Institutional Review Board reviewed and approved the study.

TACE and PEIT Procedures

PEIT was performed in patients with a single HCC measuring less than 5.0 cm in longest diameter. In patients with larger tumors, a combination of TACE and PEIT was used. Since 2003, all tumors could be treated with TACE as the initial procedure. TACE and PEIT could be repeated as clinically indicated according to response and tolerance to treatment.

For PEIT, sterile 95% absolute ethanol was used, and the total volume was estimated by using the following formula: volume (vol) = $\frac{4}{3} \pi (\text{radius} + 0.5)$.³ Single-session treatments were attempted whenever possible. The number of sessions varied depending on the size of the lesion and were scheduled at least 1 week apart. The alcohol was injected using computed tomography (CT) guidance with a 22s gauge needle with a maximum volume of 40 mL per session. The PEIT endpoint was determined when the CT scan showed a diffuse hypodense lesion in the site of injection.

For TACE, prophylactic antibiotics (1 g of cefazolin, 500 mg of metronidazole) and antiemetics (16 mg of ondansetron, 10 mg of dexamethasone and 50 mg of diphenhydramine [Benadryl]) were administered intravenously 30 minutes preceding the procedure. A diagnostic visceral arteriography was performed, and a chemoembolic mixture of 100 mg of cisplatin, 50 mg of doxorubicin, and 10 mg of mitomycin C dissolved in radiographic contrast emulsified with 10 mL of ethiodized oil was administered superselectively to the involved artery. Following delivery of the chemoemulsion, 300 to 500 μm of polyvinyl alcohol particles were injected until complete stasis was achieved (Fig 1A-B). After the procedure, hydration and antiemetic therapy were continued as needed. Patients were observed in the hospital for 24 hours and oral antibiotics (875 mg

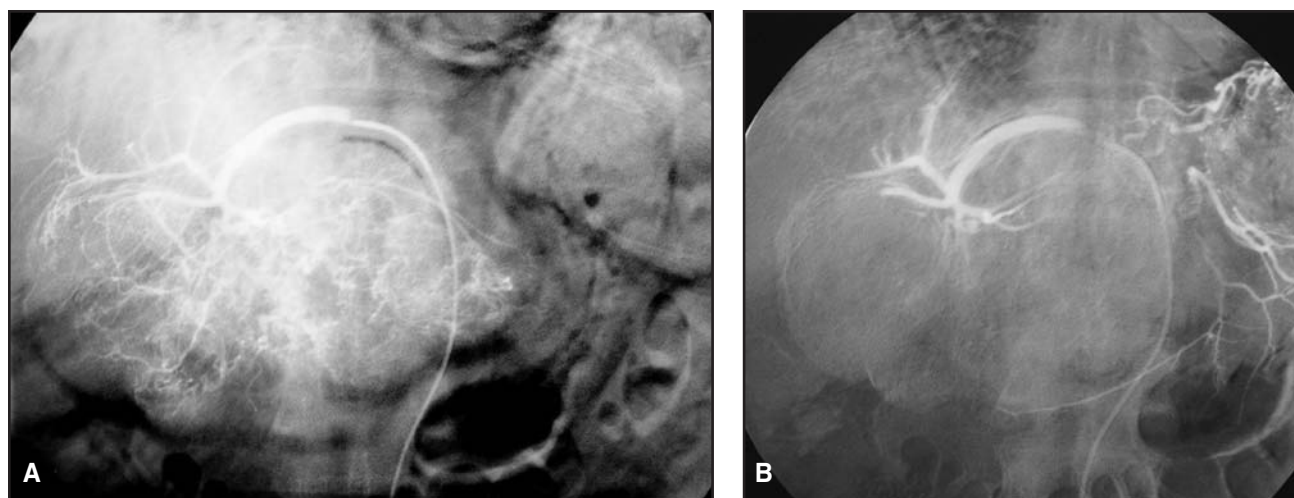


Fig 1A-B. — (A) Selective catheterization of left hepatic artery in a 10-cm tumor. (B) Arteriogram following chemoembolization showing complete stasis of flow in selected vessel.

of amoxicillin/clavulanate p.o. b.i.d. and 500 mg of ciprofloxacin p.o. b.i.d.) were continued for 5 days after discharge. Patients undergoing TACE returned in 2 to 4 weeks to start their PEIT sessions according to tumor volume.

Cross-sectional CT imaging was done 3, 6, and 12 months following the procedures. Clinical data including liver profiles and tumor markers (α -fetoprotein levels) were measured at baseline, then monthly for the first 6 months, and then every 3 months. Patients were followed for overall survival. The best overall response for the target lesion was determined using response evaluation criteria in solid tumors (RECIST) based on the contrast abdominal CT scan performed 3 months after the procedure.

Statistical Analysis

The main endpoint evaluated was the survival from the date of first treatment. The survival curve was estimated according to the Kaplan-Meier method. The patients were stratified according to the tumor size (smaller than 5 cm in longest diameter or greater or equal to 5 cm) and Child-Pugh class. Comparisons were made using a student's *t* test.

Table 1. — Patient Characteristics of 33 Men With HCC Treated With TACE, PEIT, or Both

Characteristic	Mean	No. of Patients	%
Age (yrs)	66 (47–82)		
HBsAg positive		1	3
Anti-HCV positive		15	45
HBsAg positive and HCV positive		1	3
Child-Pugh grade			
A		20	60.6
B		11	33.3
C		2	6.1
Bilirubin (mg/dL)	2.15		
Albumin (g/dL)	3.5		
International normalized ratio (INR) to test coagulation	1.2		
Platelet count ($\times 10/\text{mm}^3$)	158 491		
α -fetoprotein level (ng/mL)	(1–4,167)		
No. of tumors			
unicentric		21	63.6
multicentric		12	36.4
Tumor size (cm)	5.99	4.33	5.78
Tumor pathology			
well		28	84.9
moderately		1	3
poorly		1	3
no tissue disease		3	9.1
HBsAg = hepatitis B surface antigen HVC = hepatitis C virus			

Results

Patient Characteristics

Patient characteristics of the whole group are summarized in Table 1. The mean age was 66 years (range: 47 to 82 years). Among the 33 men in the group, 42% were positive for hepatitis C infection and alcohol abuse was the cause of cirrhosis in 37%. Three patients had concomitant human immunodeficiency virus (HIV) disease. Mean tumor size was 5.6 cm in longest diameter (range: 2.0 to 16.0 cm), and 84.9% of tumors were well differentiated. A single hepatic lesion was present in 63.6% of patients. The α -fetoprotein level was less than 20 ng/mL in 54.5% (normal values 0 to 8.6 ng/mL), between 20 and 400 ng/mL in 15.2%, and more than 400 ng/mL in 30.3%. Mean α -fetoprotein level for the whole group was 491 ng/mL (median 16.2 ng/mL). Three patients had a history of localized prostate cancer. The patients had adequate baseline liver function (mean total bilirubin was 2.15 mg/dL and albumin was 3.5 g/dL) and adequate platelet counts (mean 158,000/ mm^3). Child-Pugh classification was 60.6% as class A, 33.3% as class B, and 6.1% as class C.

Table 2 includes the patient characteristics divided by treatment group. Nineteen patients (58%) were treated with TACE only. Patients in this group had an

Table 2. — Patient Characteristics in 33 Men With HCC According to Treatment (TACE, PEIT, or TACE Plus PEIT)

Characteristic	TACE	PEIT	TACE Plus PEIT
No. of men	19	6	8
Mean age (yrs)	66	70	62
HBsAg positive	0	0	1
Anti-HCV positive	11	1	3
HBsAg positive and HCV positive	1	0	0
Child-Pugh grade			
A	12	4	4
B	5	2	4
C	2	0	0
Bilirubin (mg/dL)	2.7	0.9	1.6
Albumin (g/dL)	3.5	3.4	3.4
International normalized ratio (INR) to test coagulation	1.2	1.2	1.2
Platelet count ($\times 10/\text{mm}^3$)	168	145	144
α -fetoprotein level (ng/mL)	582	215	482
No. of tumors			
unicentric	11	5	5
multicentric	8	1	3
Tumor size (cm)	5.99	4.33	5.78
Tumor pathology			
well	16	5	7
moderately	0	1	0
poorly	0	0	1
no tissue disease	3	0	0
HBsAg = hepatitis B surface antigen HVC = hepatitis C virus			

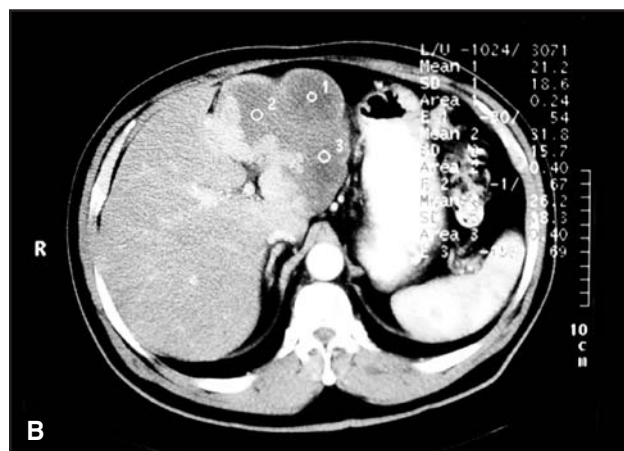
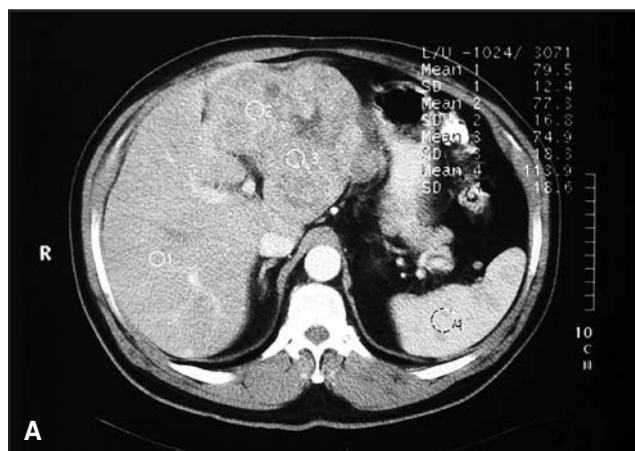


Fig 2A-B. — (A) 10-cm tumor in left hepatic lobe prior to TACE. (B) Contrast CT scan 3 months after TACE showing marked necrosis of tumor.

increased total bilirubin and α -fetoprotein compared with other those treated with PEIT or TACE/PEIT and tumors were on average slightly larger in size, but this did not reach statistical difference. In the patients receiving TACE alone, 63% had an adequate liver function as per Child-Pugh grade (Child A). Six patients received PEIT alone and 8 patients a combination of TACE and PEIT. As previously noted, patients with single tumors less than 5 cm in diameter were initially treated with PEIT, until 2003 when all patients could be treated initially by TACE according to the assessment of the interventional radiologist. The patients in the three groups fulfilled the laboratory criteria and characteristics (ie, no uncontrolled encephalopathy or portal vein occlusion) established for protocol eligibility.

Treatment and Response

Among the 33 patients, 19 (58%) underwent TACE only, 6 (18%) PEIT only, and 8 (24%) a combination of PEIT and TACE. Treatment was well tolerated, with 1 death within 30 days of TACE due to hepatorenal syndrome. The patient had concomitant HIV infection and a Child-Pugh class C.

Objective radiographic partial response was observed in 28% of patients and 48% had disease stabilization, while 24% had disease progression according to RECIST. Although most patients had no significant decrease in tumor size as per RECIST, a therapeutic response was demonstrated by necrosis of the tumor and decreased contrast enhancement (Fig 2A-B). Table 3 presents response by treatment groups, in which

Table 3. — Response by Treatment Group

Response	TACE (n = 19)	PEIT (n = 6)	TACE Plus PEIT (n = 8)
Stable disease	6 (32%)	1 (17%)	5 (62%)
Partial response	3 (16%)	2 (33%)	3 (38%)
Progressive disease	5 (26%)	1 (17%)	0 (0%)

patients who underwent both TACE and PEIT had a higher response rate and disease stabilization but not a statistical difference in survival.

Survival Analysis

Median survival was 24 months, with 67%, 58%, 24%, 12%, and 6% alive at 1, 2, 3, 4 and 5 years, respectively (Fig 3). There was no difference in survival between patients who underwent TACE only (24 months), PEIT only (21 months), or TACE plus PEIT (26 months) (Fig 4). At the end of follow-up, 57% of patients in the TACE group were alive compared with 17% in the PEIT group and 37% in the TACE plus PEIT group. Causes of death included tumor progression in 22%, hepatic failure in 33%, gastrointestinal bleeding in 11%, and infections in 33%, most commonly urosepsis and pneumonia (Table 4). As already noted, there was 1 treatment-related death following TACE. The 2 patients with Child-Pugh class C received TACE as treatment and had an inferior survival of only 2 months. However, the initial

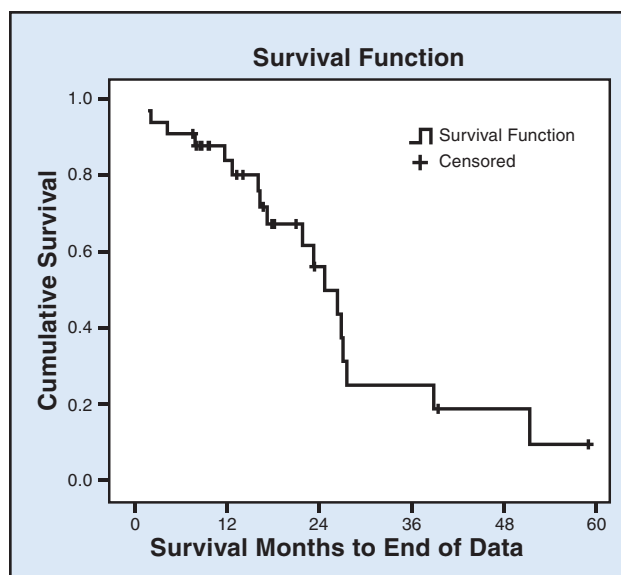


Fig 3. — Overall survival.

tumor size and Child-Pugh class did not confer a significant difference in survival rate ($P=.537$ and $P=.55$, respectively) among all the patients.

At the time of this article, the patient with longer survival has controlled disease 60 months after the initial procedure and has undergone three chemoembolizations and two ethanol ablation sessions. Another patient with more than 4 years of survival after two chemoembolizations is been evaluated in the mainland for a liver transplantation.

Discussion

TACE and PEIT are effective local therapies for nonsurgical HCC by improving long-term survival compared with survival of untreated patients as reported in the literature.³ TACE and PEIT appear to be safe and effective palliative alternative treatments for nonsurgical HCC. Failure to find a statistically significant difference between survival and Child-Pugh class or tumor size might be due to the small sample size. Chemoembolization may be an effective method of controlling hepatic disease in patients with HCC. All of our patients have clinically diagnosed liver cirrhosis and had a mean tumor size of 5.6 cm, thus limiting eligibility for other modalities such as liver transplantation or radiofrequency ablation. Surgical resection has been proposed only in patients with extremely well-preserved liver function. Even in patients with a Child-Pugh class A, more than 50% suffer hepatic decompensation after surgery.¹⁴ Also, the recurrence rate has been reported as exceeding 70% after 5 years.¹⁵ In our series, TACE was applied as the primary treatment, with the addition of PEIT for tumors less than 5 cm in longest diameter or as an adjunct to TACE. Some patients were able to tolerate more than one chemoembolization, but the small size of the sample does not

Table 4. — Cause of Death According to Treatment Group

Cause of Death	TACE (n = 19)	PEIT (n = 6)	TACE Plus PEIT (n = 8)
Hepatic failure	2 (11%)	2 (33%)	2 (25%)
Gastrointestinal bleeding	2 (11%)	0	0
Infections	1 (5%)	3 (50%)	2 (25%)
Tumor progression	3 (16%)	0	1 (13%)

permit statistical analysis of those cases in regard to response or overall survival. However, our patient with the longest survival (5 years) has been treated with three TACE and two PEIT sessions.

Both TACE and PEIT can be safely implemented as a single treatment or in combination in a community hospital. Its success depends on careful selection of patients and on availability of the technique. In Puerto Rico, our institution is the only center that offers these interventional radiology procedures. Our median survival of 2 years in a patient population with HCC and cirrhosis who are not able to undergo liver transplantation supports continued endeavors to expand the procedure in Puerto Rico. Our results compare with prior studies of TACE and/or PEIT in different populations. Alcohol ablation is generally used for single tumors less than 3 cm with reported survival rates of 79%, 64%, 46%, and 38% at 1, 2, 3, and 4 years, respectively.¹⁶ Some clinicians prefer radiofrequency ablation over alcohol ablation due to the potential to treat larger tumors, but this technique is not widely available at present on the Island. Two randomized, controlled trials have shown a survival advantage for TACE, mainly in a selected subset of patients.^{17,18} In the first trial performed at the University of Hong Kong, chemoembolization with lipiodol and cisplatin resulted in a marked tumor response (survival rates of 57%, 31%, and 26% at 1, 2, and 3 years, respectively), compared with controls (survival rates of 32%, 11%, 3% at 1, 2, and 3 years, respectively; $P=.002$).¹⁷ At the University of Barcelona, 112 patients treated with chemoembolization with gelatin sponge and doxorubicin had survival probabilities of 82% at 1 year and 63% at 2 years vs 63% at 1 year and 27% at 2 years for the control group.¹⁸ Since a high percentage of HCC patients die of their cirrhosis and not of their tumor, a reasonable therapeutic target could be to improve patient survival and quality of life, with or without higher tumor response rates.¹⁹ Response rate and survival after TACE are correlated not only with decreased size but also with changes in tumor vascularity and degree of necrosis.²⁰

PEIT and TACE can serve as a bridge to liver transplantation when eventually it is performed in Puerto Rico or when patients can be transplanted in a timely manner upon referral to other centers. We have demonstrated that in a patient population with cirrhosis who are not candidates for resection, percutaneous

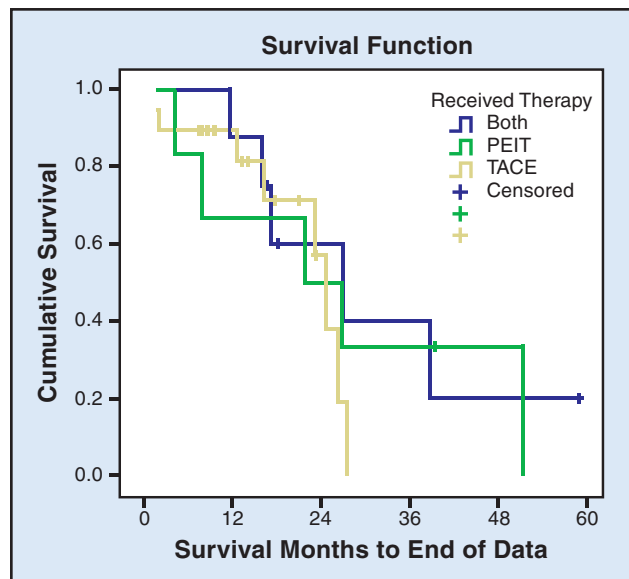


Fig 4. — Survival based on treatment group.

procedures such as TACE and PEIT are both feasible and tolerable. At present, we initially use TACE to treat patients with single tumors until a major response is achieved. We also use TACE combined with ethanol ablation to treat patients with tumor persistence or those with new small lesions. Progress in our results will depend on prospective trials evaluating newer pharmaceutical agents or interventional radiology techniques that can sustain our patients' response.

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Disclosures

No significant relationship exists between the authors and the companies/organizations whose products or services may be referenced in this article.

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