

ORIGINAL RESEARCH

Role of percutaneous ethanol ablation in malignant liver tumours

Satnam Singh¹, Jagjeet Singh², Pankaj Dugg^{*2}, Sanjiv Sharma¹, Vijay Thakur¹, Kamaljeet Kaur², Shikha Sood¹, Mouluk Vora¹, Prabhjyot Singh³, Jitender Parmar¹

¹IGMC, Shimla, India

²All India Institute of Medical Sciences (AIIMS), India

³Govt. Medical College Patiala, India

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ABSTRACT

Purpose: To study the effectiveness of image-guided percutaneous ethanol injection (PEI) to ablate malignant hepatic lesions.

Methods: It was a hospital based prospective study. Study included 15 patients (8 men, 7 women); aged 40-75 years (mean age 58.3 years); involving 4 hepatocellular carcinoma (HCC) (ranging from 2.8 cm-8.0 cm in diameter) and 18 liver metastases (ranging from 0.78 cm-4.5 cm in diameter). Forty eight sessions (18 sessions for 3 HCCs and 30 for 11 liver metastases) using 99.9% ethanol injection were done under image guidance to treat 21 tumours in 14 patients. Under local anaesthesia, absolute ethanol (99.9%) was instilled into the tumour via 22 gauge spinal needle. Triple phased Contrast enhanced computed tomography (CECT) was used in all the cases to assess the treatment response.

Results: The 3 patients having solitary HCC tumours measuring 2.8 cm, 6.5 cm and 8 cm were assigned into complete response, partial response and progressive disease categories respectively after PEI. Treatment response was not assessed in 1 patient. Among 11 liver metastases patients; complete response, partial response, stable disease and progressive disease was assigned in 5 (45.5%), 1 (6.6%), 2 (18.1%) and 3 (27.2%) patients respectively.

Conclusions: PEI is a safe and effective technique for treating smaller liver neoplasms and less than 3 lesions for each patient as per BCLC criteria.

Key Words: Ablation, Ethanol, Liver, Hepatocellular carcinoma, Metastasis

1. INTRODUCTION

Liver tumours including hepatocellular carcinoma (HCC) and metastases are among some of the most common tumours worldwide. Hepatic resection is considered the curative treatment of choice but very few patients are suitable for surgery. Moreover chemotherapy and radiation therapy are ineffective treatment methods especially for HCC.^[1] Various percutaneous treatment modalities used for treating liver neoplasms include percutaneous ethanol or acetic acid in-

jection, radiofrequency ablation (RFA), microwave ablation, laser photocoagulation, cryotherapy, trans-arterial chemoembolization (TACE), and direct chemotherapeutic agent injection.^[2] In percutaneous ethanol injection (PEI) technique, absolute ethanol is directly injected into the lesion through a needle placed into the lesion under image guidance. Ethanol causes dehydration and necrosis of tumour cells, accompanied by small vessel thrombosis, leading to tumour ischemia and destruction.^[3,4] It has shown promising results particu-

*Correspondence: Pankaj Dugg; Email: pankajdugg84@gmail.com; Address: All India Institute of Medical Sciences (AIIMS), India.

larly in HCC lesions less than 3 cm in diameter.^[5] PEI had been less successfully used in treatment of liver secondaries and cholangiocarcinomas.^[6-8] Currently, RFA is a first-line treatment of the major local ablative techniques but PEI is preferred in technically difficult masses located in the hepatic dome, in the subcapsular area, and exophytic in position, or are surrounded by large blood vessels.^[9]

2. MATERIALS AND METHODS

A hospital based prospective interventional study was conducted. Informed consent was taken from each patient or their attendants before the study commenced. The study was approved by the institutional review board.

From May 2011 to October 2012, 15 patients (8 men, 7 women; aged 40-75 years; mean age 58.3 years) with 22 liver tumours were recruited for the study. The tumours included 4 HCCs ranging from 2.8 cm-8.0 cm in diameter and 18 liver metastases ranging from 0.78 cm-4.5 cm in diameter and were treated with image guided percutaneous ethanol ablation.

Inclusion criteria - Patients with HCC having single lesion of 3 cm-8 cm in diameter or ≤ 3 lesions per patient measuring less than 3 cm in diameter, liver metastasis not suitable for systemic chemotherapy or residual tumour/failure after systemic chemotherapy was having ≤ 3 lesions of less than 5 cm in diameter.

Exclusion criteria - Patients with irreversible coagulopathy, prothrombin time ratio $< 50\%$ and platelet count $< 50 \times 10^3/\text{mm}^3$, patients with brain metastasis, portal venous thrombosis, massive ascites, and Child-Turcotte-Pugh (CTP) class C liver cirrhosis.

Laboratory tests including Serum Alpha feto protein (AFP) levels, Serum Albumin, Serum bilirubin, Serum glutamic oxaloacetic transaminase (SGOT), Serum glutamic pyruvic transaminase (SGPT), Prothrombin Time (PT), Prothrombin Time ratio (PTR), International normalized ratio (INR), Platelet count, Renal function test (RFT), Hepatitis B or C antigen were obtained.

All the HCC patients were diagnosed according to European Association for the Study of the Liver (EASL) criteria and all the liver metastases were confirmed with fine needle aspiration cytology (FNAC). In two cases of HCC with cirrhosis diagnosis was made by arterial hypervascularisation on triple phase Contrast enhanced computed tomography (CECT) with washout in Portal venous (PV)/equilibrium phases and elevated Serum AFP levels ($> 400 \text{ ng/ml}$). Arterial enhancement on both triple phase CECT and triple phase Contrast enhanced magnetic resonance imaging (CEMRI)

was used in one case of HCC with liver cirrhosis. FNAC was used to confirm one case of HCC with cirrhotic liver.

Twenty-two gauge (G), 7 cm long spinal needle was used to inject ethanol in all the patients except for 1 HCC patient in which 22 G 15 cm long spinal needle was used for 11 sessions. In all the 15 patients, ethanol was instilled under Ultrasonography (USG) guidance. Computed tomography (CT) was additionally used for one treatment session in one patient with HCC. "Toshiba Xario XG" ultrasonography equipment was used for image guidance, assessment of treatment response and follow-up. CT equipment used was a "GE Light Speed VCT Xte" - 64 slice Multidetector computed tomography (MDCT) scanner. Triple phase liver scans were obtained after injecting 80-100 ml of non-ionic iodinated contrast material at a rate of 3.5 cc/sec through the antecubital vein by using a power injector (Stellant D; Medrad). MDCT protocol with .625 mm collimation, 5 mm slice thickness, pitch of 1.375, table speed/gantry rotation of 55 mm, tube current of 100-700 mA with automatic adaptation, 140 kV of tube voltage were used. The arterial phase, Portal venous phase (PVP), equilibrium phase images were obtained at 30-35 sec, 60-70 sec and 180 sec after the initiation of contrast injection. MRI equipment used was a "Seimens Magnatom Avanto 1.5 T". Plain axial T1 and T2 weighted images and contrast enhanced triple phase images were obtained after injection of 0.1 mmol/kg of gadolinium chelate with scan delays similar to as described for multiphase MDCT.

Percutaneous ethanol ablation was performed on admitted patients who were kept fasted for at least 4-6 hours prior to the procedure. Multi-session conventional technique was used for all subjects comprising of 2-3 sessions per week until the entire tumour was treated. The total volume of ethanol for a given tumour was estimated as $4/3\pi(r + 0.5)^3$, whereby r being the tumour radius.

After cleaning and draping the abdomen, 5 ml-10 ml of 2% Lignocaine hydrochloride was infiltrated subcutaneously at region of interest in all patients. Butorphenol 1 mg-2 mg intravenously was used in 5 patients for 9 treatment sessions, as they were apprehensive or complained of pain despite adequate local anaesthesia. Under ultrasound guidance, a 22 gauge spinal needle was inserted into the lesion. Absolute ethanol was then administered slowly as 0.2 ml-0.4 ml boluses every 10 sec. Care was taken to inject the deepest portions of the lesion first, then the central and finally the superficial portions. The hyperechoic ethanol diffusion was observed and reposition of needle was done as required. Needle was withdrawn slowly, 30 seconds after injection completion.

Triple phased CECT was used in all the cases to see the

treatment response. Tumour load was longest diameter of enhancing tumour. Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 criteria was used for tumour response assessment.

3. RESULTS

A total of 48 treatment sessions were done to treat 21 tumours in 14 patients. Eighteen sessions of ethanol ablation were performed in 3 HCC tumours and thirty in 11 liver metastases. In one HCC patient, procedure was abandoned. Number of sessions ranged from 1 to 11 per tumour. Maximum of 11 ethanol ablation sessions were done in a case of HCC measuring 6.5 cm × 5.5 cm. The smallest primary liver tumour *i.e.* HCC lesion measuring 2.6 cm required 2 sessions of ethanol ablation. Maximum of 5 ethanol ablation sessions were done in liver metastasis patient having 3 tumours. The

smallest liver metastatic lesion measuring 0.78 cm required only a single PEI session for treatment.

Average volume of ethanol used per tumour was 22.9 cc (range 2.5-110 cc). For HCC it was 65 cc (range 20-110 cc) and 15.9 cc for liver metastasis tumour (range 2.5-45 cc).

Treatment response was assessed in 3 out of 4 HCC patients (see Table 1). The 3 patients having solitary HCC tumours measuring 2.8 cm, 6.5 cm and 8 cm were assigned into partial response (see Figure 1), complete response (see Figure 2) and progressive disease categories respectively after PEI (see Table 2). Treatment response was not assessed in 1 patient. Among 11 liver metastasis patients, complete response, partial response, stable disease and progressive disease (see Figure 3) was assigned in 5 (45.5%), 1 (6.6%), 2 (18.1%) and 3 (27.2%) patients respectively (see Table 3).

Table 1. Characteristics of patients with HCC and treatment response

Size of tumour (cm)	S. AFP level (ng/dl)	Associated liver disease	CTP class	% reduction in tumour load	Treatment response
6.5	1,069	Hep.B induced Cirrhosis	A	57%	PR
8.0	1,000	Hep.B induced Cirrhosis	A	Increased	PD
2.6	5.5	Alcohol induced Cirrhosis	B	100%	CR

Table 2. Tumour characteristics and treatment response in HCC

No. of patients	4
Tumour number	
Solitary	4
Multiple	0
Tumour size	
< 3 cm	1
3 cm-5 cm	0
> 5 cm	3
Location of tumours	
Favourable	1
unfavourable	3
Av. Ethanol (ml)/per patient	65
Treatment response	
Complete response	1
Partial response	1
Stable disease	0
Progressive disease	1
Not assessed	1

All 4 HCC patients had cirrhosis. Of the 4 HCC cases, two had hepatitis B and 1 had hepatitis C. The fourth HCC patient was a chronic alcoholic. Mild ascites was present in 2 patients with HCC. None had encephalopathy. CTP class A was assigned in three and class B in 1 patient. All (100%) HCC patients had solitary tumour. Among liver metastasis patients, 6 (54.5%) had solitary and 5 (45.4%) had multiple tumours. Five (45.4%) patients had liver metastasis from

Gastrointestinal (GIT) primary, 1 (0.9%) from gallbladder, 2 (18.1%) each from carcinoma cervix and carcinoma lung and 1 (0.9%) from carcinoma ovary (see Table 3). Among liver metastasis tumours of GIT origin, 3 patients had metastatic adenocarcinoma from anorectum, 1 from stomach and 1 from oesophagus. Tumours located close (≤ 5 mm) to the liver capsule, the gallbladder, the gastrointestinal tract, the inferior vena cava, the hilum, the heart, or the diaphragm were considered as unfavourable sites. Twelve (54.5%) out of 22 tumours were located at favourable sites and 10 (45.4%) were located at unfavourable sites.

Pain at injection site was the chief complaint in most of the patients. Other complications or side effects were low-grade fever, vomiting, and pneumothorax (see Table 4). There were no major systemic complications.

4. DISCUSSION

HCC accounts 4.1% of all human cancer cases in the world. It is prevalent in Southeast Asia and sub-Saharan Africa, about 70% and 12% of all cases was found in Asia and Africa, respectively. Metastatic lesions are most common malignant liver tumours. With the widespread use of AFP, ultrasound, and other diagnostic modalities as screening tools, many small malignant liver tumours are detected before symptoms develop and are treated effectively.^[10-12] Partial hepatectomy

remains the best hope for a cure but is suitable for only 9% to 27% of patients. Further resection is often not possible for recurrent tumour because of limited liver reserve. If the tumour is relatively small (< 5 cm), few in number (three or fewer), and confined to the liver, local ablation of the tumour using minimally invasive techniques is a recognized form of treatment. Local ablative therapy has the advantages of preserving the uninvolved liver parenchyma, has no systemic side effects compared to systemic or intra-arterial chemotherapy, and also avoids the morbidity and mortality of major hepatic surgery. Several local ablation therapies, most of which are performed percutaneously under imaging guidance, have been performed as minimally invasive therapy for hepatocellular carcinoma. Among them, PEI has been one of the most widely performed because of its low cost and wide availability.

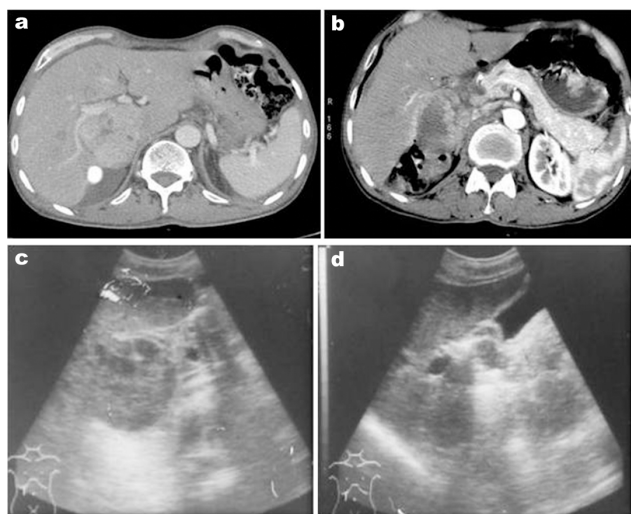


Figure 1. A 48 years old male patient with cirrhosis (CTP class-A) and positive for hepatitis B serology. Pre-ablation late arterial phase image (a) shows heterogeneously enhancing mass of size 6.5 cm × 5.5 cm in segment I of liver. S. AFP was raised (1,069 ng/dl). Post-ablation arterial phase axial image (b) shows non-enhancement of the necrotic or ablated tumour. In this case necrosis of 57% was achieved and response was categorised as Partial Response (PR). The medial most part of the tumour could not be injected as it was encased by PV and its right branch. (c) and (d) Ultrasound images taken during ablation showing needle tip and hyperechoic diffusion of ethanol in the tumour.

PEI has shown good results in HCC tumours particularly in < 3 cm size. Shina *et al.*^[6] has mentioned other indications including liver metastasis, cholangiocarcinoma, peritoneal lymph-node metastasis, adenomatous hyperplastic nodules in the cirrhotic liver, and malignant PV tumour thrombosis

in HCC. It is contraindicated in patients with massive ascites, a marked bleeding tendency, or extrahepatic metastasis. Two HCC and four patients with metastasis had mild ascites in our study. Patients with moderate to severe ascites were not included in the study. Large HCC tumours up to 8.2 cm and liver metastatic tumours up to 5.8 cm have been ablated in single session by Ada *et al.*^[11] Giorgio *et al.*^[8] ablated 62 large (> 3.5 cm) liver metastasis with one-shot PEI under general anaesthesia.

Table 3. Tumour characteristics and treatment response in metastasis

No. of patients	11
Tumour number	
Solitary	6
Multiple	5
Tumour size	
< 3 cm	13
3-5 cm	5
> 5 cm	0
Location of tumours	
Favourable	11
unfavourable	7
primary tumour	
Ca rectum	3
Ca oesophagus	1
Ca stomach	1
Ca ovary	1
Ca lung	2
Ca cervix	2
Ca GB	1
Treatment response	
Complete response	5
Partial response	1
Stable disease	2
Progressive disease	3
Not assessed	0

Table 4. Post-ablative complications

Complication	Episodes	Percentage
Pain	24	80%
Fever	3	10%
Vomiting	2	6.7%
Pneumothorax	1	3.3%
Total Episodes	30	100%

We performed forty eight sessions of ethanol ablation using 22 G, 7 cm-9 cm spinal needle or long spinal needles measuring 15 cm. The main disadvantage with 22 G long spinal needle was that it got clogged repeatedly. So we believe that 18-20 gauge long spinal needle should be used instead of 22 G long spinal needle. Shinna *et al.*^[6] in 1991 introduced a new technique of inserting 2-3 needles into the lesion before start injecting the ethanol to reduce no. of treatment sessions which is the main drawback of conventional technique.

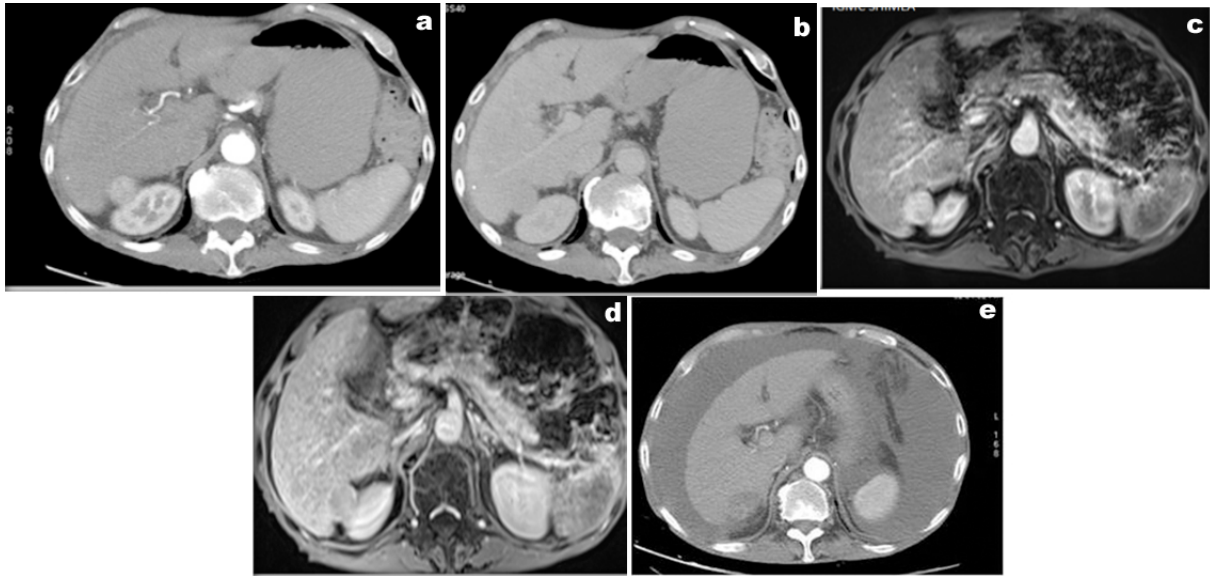


Figure 2. A 72 years old male patient having alcohol induced liver cirrhosis (CTP class B) and oesophageal varices. S. AFP levels were normal (5.5 ngm/dl)

Axial CECT images (a) arterial phase and (b) equilibrium phase images and axial CEMRI image (c) arterial phase and (d) equilibrium phase images show well defined, rounded-oval, partially exophytic tumour measuring 2.6 cm × 2.4 cm in segment VI of liver. It show arterial hypervascularisation and wash-out on PVP (not shown) and equilibrium phase images. Capsular enhancement is seen in equilibrium phase MR image (d). Diagnosis of HCC was made on the basis of arterial hypervascularisation and washout in PV or equilibrium phases on two imaging modalities i.e. CECT and CEMRI in the cirrhotic liver. (e) Post ablation follow-up CECT at 4 weeks show complete necrosis of tumour. There is marked ascites which was part of disease process.

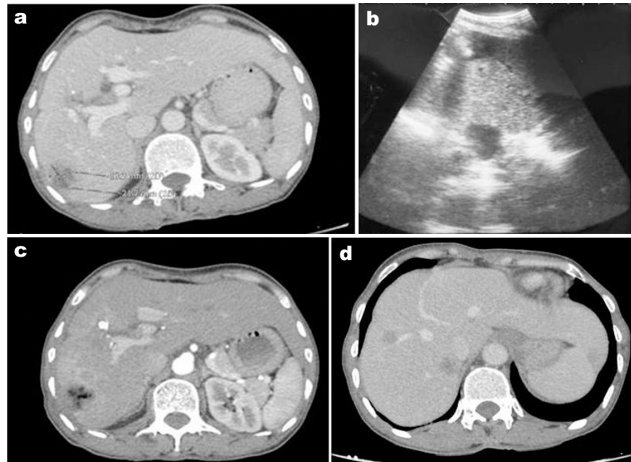


Figure 3. A 48 years old female operated for adenocarcinoma anorectum with single metastatic tumour in segment VII of liver in subcapsular location (unfavourable) Axial CECT image (a) show tumour of size 2.1 cm × 1.8 cm. (b) USG images taken during ethanol ablation. (c) Post-ablation images show complete necrosis of tumour. But the CECT done at an interval of 1 month, (d) shows appearance of multiple new tumours. Patient was assigned into Progressive disease category.

We used ultrasound imaging for guidance during ethanol injection. Fluoroscopy, ultrasound, CT, MRI and CO₂-enhanced sonography can all be employed for image guid-

ance.^[13,15] Ultrasound offered easy manoeuvrability, accurate localisation of tumours and real time monitoring but visibility of tumour and needle was hampered due to echogenicity produced by injected ethanol. So it is advisable to inject the deeper part of the tumour first. CT was additionally used for one treatment session in a patient with HCC without any significant complications.

Triple phased MDCT was used to assess treatment response in all cases. Among the 4 HCC tumours, the smallest tumour measuring 2.8 cm showed complete necrosis after 2 sessions with 20 cc ethanol injection. Another HCC tumour measuring 6.5 cm showed partial necrosis (57%) after PEI. The medial most part of this tumour could not be ablated as it was surrounded by right branch of PV. Another HCC tumour measuring 8 cm showed no change. Necrosis in 1 HCC tumour measuring 6 cm was not assessed as the treatment was abandoned due to continuous dribbling of blood through the injected spinal needle and that patient was removed from the study. Kim *et al.*^[14] in 2009 completely ablated 3 HCCs of < 1.5 cm with PEI instead of using RFA. According to Lencioni *et al.*^[16] complete responses were achieved in 80% of tumours smaller than 3 cm in diameter, but only in 50% of tumours of 3 cm-5 cm in size. The difference in success rate in our study as compared to previous studies could be explained by the fact that our study had larger tumours and

included tumours that we located at unfavourable sites.

PEI is less successful in ablating liver metastasis. Complete necrosis was seen in 9 (50%) tumours of liver metastasis in our study. Of the 55 liver metastatic tumours ablated with ethanol by Giovannini *et al.*,^[7] there was a complete necrosis in 31 cases (56.3%) and partial necrosis in 16 cases (29.1%). The lesions were unchanged in eight cases (14.1%). Giorgio *et al.*^[8] treated 14 tumours (9 HCC, 4 liver metastases and 1 lymph node metastasis) with PEI using Chiba or 22-gauge spinal needle. The success rate for tumours < 3.2 cm (11 cases) was 100%. Tumours > 3.2 cm (3 cases) remained positive for malignant cells. So results of our study is comparable to Giovannini *et al.*^[7] The difference in success rate between Giorgio *et al.* and our study could be explained by the fact that our study had larger tumours (up to 4.5 cm liver metastasis).

Most common side effects or complications are pain at injection site and fever. In this study, pain at injection site was the chief complaint in most of the patients. In a study of 14 tumours ablated with PEI by Giorgio *et al.*,^[8] patients complained of a local burning pain during and immediately

after the injection; this pain was modest in all cases except in one. No systemic complications occurred.

Limitations

There are few limitations to our study. Firstly, sample size was small in our study. Secondly, there were larger liver tumours in our study as compared to previous studies. Thirdly, most patients have multiple lesions resulting in unfavourable results. Fourthly, we used conventional technique of injection alcohol resulting in more number of sessions needed to inject the required amount of alcohol.

5. CONCLUSION

It was thus concluded that image-guided PEI is a time tested, safe, cheap, and easily available technique for treating liver neoplasms. However, we conclude that PEI should be considered first line treatment option reserved for small hepatocellular tumours, measuring less than 3 cm in diameter. Its effectiveness in treatment of metastatic liver lesions is variable and should not be recommended for multiple foci of liver lesions (> 3 lesions), as this can reduce the treatment response.

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