

Percutaneous ethanol injection for ablation of hepatocellular carcinoma

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Summary

Percutaneous ethanol injection (PEI) has been most widely performed as one of the effective ablative techniques for small Hepatocellular carcinoma (HCC). The ideal patient for alcohol injection should have fewer than three HCC tumors, each of which is well defined, less than 3cm in diameter, surrounded by a fibrous shell and not near the surface of the liver. It is contraindicated in patients with gross ascites, uncorrectable coagulopathy, obstructive jaundice and main portal vein thrombosis. This procedure is performed under ultrasound guidance in an outpatient basis with a 21-22 G needle & 95-100 % alcohol. Ethanol causes dehydration and subsequent necrosis of the HCC. Depending upon the tumor size, 2 - 12 ml ethanol per lesion is given, the numbers of session, generally, are once or twice per week for four to six sessions. Adverse effects are pain, fever, a feeling of alcohol intoxication and elevated transaminase. A major problem of PEI is tumor recurrence. Follow-up is done by imaging, tumor marker assay and selective use of fine-needle aspiration and biology. Several studies have shown similar or even better results with PEI than with surgical resection. PEI should be considered as first line treatment option for small HCC for its ease of execution, safety, low cost, repeatability & therapeutic efficacy.

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Introduction

Hepatocellular carcinoma (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 were found in Asia and Africa, respectively.^{1,2} With the widespread use of alpha fetoprotein (AFP), ultrasound, and other diagnostic modalities as screening tools, many small HCC tumors are detected before symptoms develop and are treated effectively.^{3,4} The prognosis of HCC is generally poor. Partial hepatectomy remains the best hope for a cure but is suitable for only 9% to 27% of patients.^{5,6} The presence of significant background cirrhosis often precludes liver resection in patients with HCC. Further resection is often not possible for recurrent tumor because of limited liver reserve. Several studies have shown similar or even better results with PEI than with surgical resection.^{7,8} If the tumor is relatively small (<5 cm), few in number (three or fewer), and confined to the liver, local ablation of the tumor 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.⁹

Percutaneous ethanol injection (PEI) was one of the first effective ablative techniques to be widely adopted for the treatment of small HCCs. PEI therapy was first performed in 1983 in Japan. Ultrasound guidance is used to place up to absolute alcohol into the lesion. Now this modality has been widely used and is accepted as an attractive alternative to surgery in

patients with small hepatocellular carcinoma. 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, percutaneous ethanol injection has been most widely performed^{10,11} and is now well established as an alternative to surgery in patients with small HCC; the prognosis of PEI for small HCC has been reported to be equivalent to that of surgical resection.^{12,13}

Principle

Ethanol causes dehydration and subsequent necrosis. The alcohol induces tumor destruction by drawing water out of the tumor cells (dehydrating them) and denaturing the structure of the cellular proteins, resulting in complete ablation of the tumor. Pure alcohol also blocks blood flow to the tumor bed resulting small blood vessels thrombosis that leads to tumor necrosis.¹⁴

Intratumoral injection of ethanol causes dehydration and necrosis of cells. Sometimes a larger volume is required as some of the ethanol may enter the circulation. PEI is usually repeated twice a week for up to four to six sessions. Follow-up serum alpha fetoprotein, ultrasound, and computed tomography are commonly used to monitor the therapeutic response. Additional ethanol injections are repeated for patients with large tumors, incomplete tumor necrosis, or new lesions that are still amenable to local ablation.

Patient selection

The ideal patient for alcohol injection has three or fewer than three HCC tumors, each of which is well

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defined (distinct margins), less than 3 cm in diameter, surrounded by a shell consisting of scar tissue (fibrous encapsulation) and not near the surface of the liver. Additionally, patients with HCC undergoing alcohol injection should have no signs of chronic liver failure, such as ascites or jaundice. (Patients with liver failure would not be able to tolerate the alcohol injections). Alcohol injection may be appropriate for patients with any of the following- a single HCC lesion smaller than 5 cm in diameter, up to three lesions smaller than 3 cm in diameter.

Generally PEI is used in small liver cancer not suitable for resection, either because they are multiple, because of their position in the liver, or because of severe hepatic dysfunction. Patients with tumor recurrence or residual tumor after successful chemoembolization are also good candidates for PEI.¹⁵

Contra indication

The technique is difficult for patients with multiple tumors (more than three) because of the need for repeated puncture. It is contraindicated in patients with gross ascites, coagulopathy that cannot be corrected, obstructive jaundice due to the potential risk of bleeding and bile peritonitis and main portal vein thrombosis. Increased risks of bleeding and peritoneal tumor seeding must be considered when the tumors are situated at or protruding from the liver surface. Tumors hiding under the diaphragm or too close to vital structures (bile ducts, major blood vessels, stomach and gut) would also pose a problem for PEI.

It does not appear that PEI will be as effective in the patient with metastatic cancer to the liver, since most metastases are relatively hard and avascular in a normally soft liver. This allows spillage of the alcohol into the surrounding liver substance, hurting the liver next to the tumor while not killing the tumor because the alcohol doesn't stay in place long enough to have the desired effect. On the other hand, in the hard, cirrhotic liver with a highly vascular and soft HCC, PEI is worth consideration as a method of liver cancer treatment.

Procedure

The 95-100% (absolute) alcohol is injected through the skin (percutaneously) and into the tumor using a very thin (21-22 G) gauge needle with the help of ultrasound or CT guidance. PEI is usually carried out under ultrasound guidance. This needle has two side holes at its tip, which allows better dispersion of the alcohol into the tumor tissue. The needle tip is placed close to the peripheral margin of the tumor. Absolute alcohol is slowly injected under real-time ultrasound control and given until the ethanol is distributed throughout the whole lesion (Fig 1).

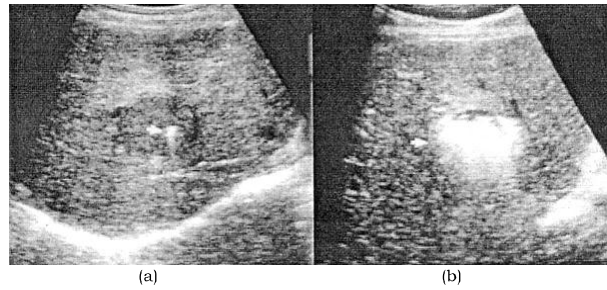


Figure 1. US guidance of ethanol ablation (a) Pretreatment sonogram shows a 3.2-cm hepatocellular carcinoma with the tip of the treatment needle (arrow) visible in the tumor. (b) Sonogram obtained after injection of ethanol shows diffuse increase in echogenicity of the tumor (arrow).

If the alcohol ran off quickly into the blood stream rather than staining the tumor tissue, as observed by real-time ultrasound, then this indicates that the needle tip is not in the substance of the tumor, or ethanol spreads unevenly and the needle needs to be repositioned accordingly. To achieve complete ablation the ethanol must reach all parts of the tumour. A maximum of 10 ml alcohol is injected per site, with maximum of 20 ml per session. At the end the procedure, 1% Lidocaine is injected along the needle track as the needle is slowly being withdrawn. The injection appears to lessen the amount of discomfort the patient experiences following the session. The session is terminated prematurely, that is by using less than 10 ml of alcohol, if the patient experiences significant discomfort or if the tumor tissue appears to be completely ablated. The numbers of sessions per patient, generally, are once or twice per week for four to six sessions, depending upon the tumor size and the amount of residual tumor identified on CT (Fig 2) or ultrasonography. For lesions smaller than 3 cm usually 6 sessions are performed to completely destroy the cancer. Intratumoural injection of 2 - 12 ml ethanol, depending on the size of the lesions results in extensive coagulative necrosis of tumour cells without damage to the normal liver parenchyma.^{15,16}

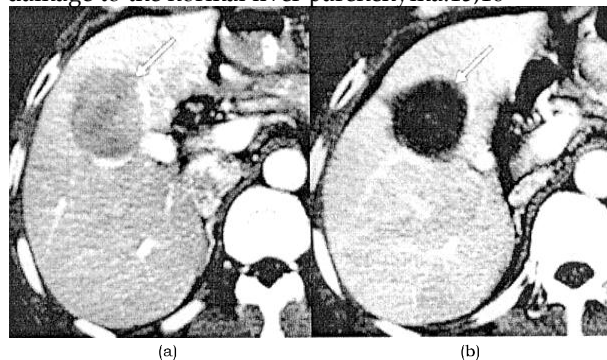


Figure 2 : a) Preablation scan (portal phase) shows 4.0 X 4.2-cm tumor (arrow) located close to porta hepatis. (b) Scan obtained 1 month after ethanol ablation (one session, 35 mL of ethanol injected) shows hypoattenuating ablation zone completely enveloping target tumor site (arrow, portal phase).

Ethanol can reflux along the needle tract and cause pain; this limits the amount that can be injected at any one time in the conscious patient PEI is therefore either performed as a multi-stage, outpatient technique under conscious sedation or as a single stage procedure under general anaesthesia.

Tumor response

Tumor response rates to alcohol injection have been reported to be 90-100% in liver cancer smaller than 2 cm in diameter, 70% in liver cancer of 3 cm in diameter, and 50% in 5 cm in diameter. Tumors larger than 5 cm have a lower percentage of complete necrosis and a higher rate of recurrence. Independent risk factors for recurrence after ablation are hepatitis C infection, multifocal tumor, and a high pretreatment alfa fetoprotein level.¹⁷

Advantages

PEI has the advantages of being safe, inexpensive, easy to perform, and repeatable. Side effects are usually minimal, including pain, pyrexia, and a transient rise in transaminase. Like all other methods of local ablative therapy, it does not cause significant damage to the surrounding uninvolved hepatic parenchyma. There are also advantages for treating HCC rather than liver metastasis with ethanol. HCC typically occurs against a background of cirrhosis, so that the tumors are soft while the surrounding hepatic parenchyma is hard. This promotes the distribution of ethanol within the tumor, particularly when the HCC is encapsulated. Patients with liver metastases typically have normal (soft) underlying hepatic parenchyma, whereas the metastasis is hard, a situation that promotes the egress of ethanol from the lesion into the normal liver.¹⁸ In addition, HCC is more hypervascular compared to liver metastasis, so that small vessel thrombosis after ethanol injection would induce more ischemia and necrosis.^{18,19} PEI is usually performed with ultrasound guidance under conscious sedation often on an outpatient basis.

Follow up

Follow-up typically includes a combination of imaging, tumor marker assay, and selective use of fine-needle aspiration and biopsy (FNAB). Following serial levels of AFP in the cases of HCC is useful only in cases in which the serum levels of this marker is elevated prior to the initiation of therapy. Random FNAB is subject to sampling error, such that it is only definitive if positive for malignancy. This fact, together with the reliability of CT in differentiating tumor necrosis from residual tumor, has led to FNAB being reserved for equivocal cases.^{15,16}

Recurrence

A major problem of local ablation is tumor recurrence in the liver remnant. The 3 year recurrence-free

survival rate after either PEI or thermal ablation is about 50%. Recurrence is commonly intrahepatic,²⁰ and adjuvant therapy after local ablation may theoretically reduce the recurrence rate. Posttreatment adjuvant therapy is the next step to reduce the rate of recurrence in the liver remnant that should be tested in an attempt to improve treatment outcome.²¹

Complications

Most common adverse effects of PEI are pain, fever, a feeling of alcohol intoxication and elevated transaminase. Pain most often is localized to the injection site. Occasionally pain is experienced elsewhere in the abdomen or the shoulder, probably related to leakage around the hepatic capsule. Pain and fever have been shown to be dose-related. With dose under 10 ml per session, pain sufficiently severe to require analgesia has been reported to occur in 11% to 13% of sessions versus 29% with injection doses greater than 10 ml in a given session.

Similarly, fever over 38 degrees celsius occurred in 6% of sessions in which the administered dose was less than 10 ml versus 29% of sessions in which more than 10 ml of ethanol were injected. Although the mechanism of the phenomenon has not been elucidated fully, it is likely to be in part related to the volume of tumor necrosis. Transient pain has also been shown to be more intense following injection of lesions on the surface of the liver than following injection of deeper lesions.^{15,16}

Segmental chemical portal vein thrombosis has been known to occur in a few patients. Spontaneous resolution has been reported within 1-6 months in most cases.²²

Procedure-related mortality is rare. It was shown that this modality does carry the risk of disseminating the tumor by facilitating the passage of malignant cells into the blood stream, but that was opposed by other authors, who consider that because ethanol diffuse along the needle tract, its cytotoxic effect and small vessel thrombosis minimize the risk seeding.²³

The most common side effect of alcohol injection is leakage of alcohol onto the surface of the liver and into the abdominal cavity, thereby causing pain and fever. It is important that the location of the tumor relative to the adjacent blood vessels and bile ducts is clearly identified. The reason for needing to locate these structures is to avoid injuring them during the procedure and causing bleeding, bile duct inflammation, or bile leakage.²⁴

Single session PEI

A new version of the procedure known as "single session" PEI, designed for treatment of large HCC under general anesthesia, was proposed in 1993. Single session PEI is as effective in inducing liver tumor necrosis as traditional PEI. Its advantage are shorter

treatment time and the capability of treating larger and multiple HCC. The One-shot technique proved a more aggressive therapeutic modality than traditional PEI.²⁵

Multipronged ethanol ablation

To improve the conventional ethanol ablation technique (small aliquots 2-10ml multiple sessions), a retractable multipronged injection needle was developed. By using this multipronged needle delivery system ethanol eradicates HCC up to 5.0 cm in diameter even in high risk location with a single-session high-dose (average 31 ml per lesion) strategy.²⁶

Other percutaneous & interventional procedures for HCC

Intralesional injection of agents that have the ability to kill tumor cells (chemicals particularly acetic acid, radioactive isotopes or chemotherapeutic drugs) or application of an energy source that can produce thermal ablation such as radiofrequency ablation (RFA), laser and microwave), and cryotherapy (liquid nitrogen), High intensity focused ultrasound (HIFU) also used. Transarterial chemoembolization (TACE) is an interventional procedure which selectively delivered embolic materials to hepatic arterial feeders of the tumors.²⁷

Surgical treatment for HCC

Surgical modalities are Wedge resection, partial hepatectomy, lobectomy and liver transplantation.²⁸

Comparison of PEI to other treatment

Nonrandomized studies have shown PEI to give a 3-year survival rate of 47% to 77%.²³ The endpoint of local ablation is complete tumor necrosis with a margin of tissue. Of the methods of ablation, PEI and RFA are commonly performed and are effective as well. For tumors less than 5 cm, the percentages of complete necrosis for treated lesions are over 90% with thermal ablation (RFA).^{29,17} However, the percentage of complete necrosis is lower for PEI.²⁹ A prospective randomized study has shown that RFA is superior to PEI in terms of local recurrence rate.²² The number of sessions required for thermal ablation is also less than that of PEI.³⁰ Therefore, thermal ablation has become popular and is the standard treatment in many centers. However, for lesions that are close to the main portal vein or intestine, thermal ablation may not be feasible, and PEI is preferred.

The long-term treatment results of PEI with respect to recurrence rate, progression-free survival, and overall survival are similar to those for surgical resection.³¹

PEI is most effective in encapsulated HCC and of little benefit in infiltrating HCC or in metastases. Thermal techniques are preferred for the treatment of

metastases. In HCC, thermal techniques provide more necrosis in less time and in fewer sessions.³² PEI still has a role in the treatment of HCC not amenable to RF, e.g. exophytic lesions which can rupture, with disastrous consequences, during heating. Some centres prefer PEI for small lesions (<2 cm) because of the relative ease of implementation and lower cost.³³

Researchers in randomized clinical trials revealed that a higher rate of complete response with fewer treatment sessions, compared with ethanol ablation, can be achieved with thermal ablative techniques, such as radiofrequency ablation.³⁴

On the contrary, ethanol ablation is a low-risk procedure with a major complication rate of 1.3%-3.2% and a mortality rate of 0.09%,³⁵. PEI carries a lower complication rate than RFA, therefore, percutaneous ethanol injection will continue to play a role in the treatment of HCC.³⁶

Conclusion

During the past 20 years, Percutaneous ethanol injection (PEI) has become one of the most widely used procedures for treating hepatocellular carcinoma (HCC). In HCC with the background of cirrhosis PEI deserve ideal treatment option. Although RFA has recently emerged as a real competitor, PEI should be considered first line treatment option for small hepatocellular carcinoma for its ease of execution, safety, low cost, repeatability, therapeutic efficacy and survival rates.

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