Role of Local Ablative Therapy for Hepatocellular Carcinoma

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Percutaneous local ablation (PLA) techniques are currently considered as the best treatment option for patients with early-stage hepatocellular carcinoma (HCC) who are not candidates for surgical resection. They are safe, minimally invasive, efficacious and cost-effective. Radiofrequency ablation (RFA) is considered as the first line treatment in some centers, though most of the guidelines recommend it for small HCCs, where surgical resection is not feasible. In developing countries percutaneous ethanol injection (PEI) and percutaneous acetic acid injection (PAI) may be used instead of RFA. For large HCCs, advances in electrode designs and newer techniques of ablation, including microwave ablation, are increasingly been used. Combination treatment modalities have shown promising results as compared to single modality for large tumors. The selection of the most appropriate modality depends on the size, number of lesions, the liver function status, patient's financial resources, availability of a particular technique and the expertise available. (J Clin Exp Hepatol 2014;4:S104–S111)

Percutaneous local ablation (PLA) is being increasingly used in treatment of hepatocellular carcinoma (HCC). It is currently considered the best therapeutic modality for patients with early-stage HCC who are not candidates for surgical intervention.[1] Several techniques of PLA have been developed for the treatment of small HCCs. It includes application of chemical agents, radiofrequency ablation (RFA), microwave ablation (MWA), cryoablation and laser ablation(Table 1). PLA is a relatively simple procedure which is minimally invasive. It selectively targets the tumour and an additional intentional margin of healthy tissue from 0.5 to 1.0 cm. This additional margin helps to achieve complete ablation (A0) similar to R0 resection after surgery. Due to selective ablation of liver tissue, PLA does not have the morbidity and mortality associated other major surgical procedures. Local application of chemical agents, radiofrequency waves and other agents does not usually cause systemic side-effects. PLA is usually done under real-time ultrasonography (USG) guidance, using local anesthesia and intravenous conscious sedation. Rarely, Computed tomography (CT) guidance is required if either the tumor is not localized on USG or a proper acoustic window is not available to visualize the tumor. These procedures require a short hospital stay and are cost-effective compared with surgery. In patients with significant liver disease, PLA has been tried as a temporizing treatment prior to liver transplant, but requires further studies to clarify its role.[2]

The indications for PLA includes HCC in BCLC A and B stages with Child–Pugh class A/B cirrhosis, an ECOG performance status of 0–1, tumor <5 cm (ideal <3 cm), focal nodular lesion, solitary or multiple lesions. Contraindications include the presence of vascular invasion, extrahepatic metastatic disease, sepsis, severe debilitation, Child–Pugh class C cirrhosis and uncorrectable coagulopathy.[3] Lesions close to gall bladder, liver capsule and diaphragm are associated with a higher risk of complications. Ablations of such lesions require extreme care and should be performed by experienced radiologists. There are no data to indicate superiority of one modality over the other. Also, there are limited data supporting the use of PLA as an adjuvant or neo-adjuvant treatment modality.[3] In patients with elevated serum alpha feto protein (AFP) level prior to treatment, and in whom AFP returned to normal after therapy, a subsequent rise in AFP may signal the possibility of HCC recurrence. However, this is not reliable, and the monitoring of AFP levels after therapy does not replace imaging (preferably with a triphasic computed tomography scan). The ideal imaging interval is unknown, but initially a 3–4 month interval is commonly used to monitor HCC lesions after initial treatment. After about 2 years of recurrence- free survival, the interval of follow-up imaging examinations can be at less frequent intervals.

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Abbreviations: AFP: alpha feto protein; CT: computed tomography; HCC: hepatocellular carcinoma; HR: hepatic resection; PEI: percutaneous ethanol injection; PLA: percutaneous local ablation; RFA: radiofrequency ablation; USG: ultrasonography
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Table 1 Percutaneous Methods for Local Ablation of Hepatocellular Carcinomas.

Percutaneous chemical ablation
1) Ethanol
2) Acetic acid
Percutaneous application of an energy source
1) Thermal ablation
a) Radiofrequency ablation
b) Microwave ablation
c) Laser photocoagulation
2) Cryoablation
3) High-intensity focused ultrasound
4) Irreversible electroporation

COMPARISON OF ABLATIVE TECHNIQUES WITH SURGICAL RESECTION

A recent meta-analysis comparing RFA with surgical hepatic resection (HR) that included one randomized controlled trial, and 9 nonrandomized controlled trials enrolled a total of 1411 patients: 744 treated with RFA and 667 treated with HR. It showed that HR has a better 3-year (OR: 0.56, 95% CI: 0.44–0.71) and 5-year (OR: 0.60, 95% CI: 0.36–1.01) overall survival rate than RFA.[4] Though local intrahepatic recurrence has been reported following RFA, no significant difference in survival has been seen in the case of tumors of ≤3 cm in size. RFA is now used at many centers as the first choice of treatment for small HCC (<2 cm).[5] There are many studies comparing percutaneous ethanol injection (PEI) with surgical resection.[6–9] In a study of 39 patients treated by PEI and 58 who underwent HR for small HCC (smaller than 3 cm and ≤3 in number), the 1-, 3- and 5-year overall survival rates were comparable in the 2 groups (100%, 82.1% and 59% in the PEI group and 96.6%, 84.4% and 61.5% in the HR group, respectively, $P = 0.96$).[7] PEI is a cost-effective modality and there is no statistically significant difference in the recurrence and survival rates compared to HR in carefully selected patients with tumors <3 cm in size.[8,9] On the contrary, better survival has been observed after surgery in patients with tumors >3 cm in size.[8] Controversial results have been seen with respect to the effect of liver function on the outcome in both groups.[6,8] In a retrospective analysis 1-, 3-, and 5-year disease-free survival rates of patients with single HCC of diameter <5 cm, who had undergone curative HR and microwave coagulation therapy (MCT) were 72.8, 54.0 and 33.0%; 68.5, 60.0, and 25.6%, respectively (P value was non significant).[10] There is no literature available that directly compares laser ablation and cryo-ablation with surgery. Most of the recommendations including ESMO-ESDO guidelines indicate that maximum upto 5 lesions can be successfully ablated using different techniques of PLA.[11]

RADIOFREQUENCY ABLATION

Radiofrequency ablation (RFA) was first used in 1990 and approval by the US Food and Drug Administration in 2001. Since then, the method has been continuously refined, leading to better outcomes.[11–13] It is now the most commonly utilized ablation technique worldwide. RFA induces thermal injury through delivery of electromagnetic energy. Application of rapidly alternating RF current results in marked ionic agitation and frictional heat generation around the electrode, leading to coagulative necrosis of the tissue. The thermal injury is dependent on both the temperature achieved and the duration of heating. Irreversible cellular damage occurs if the tissue is heated at 50–55 °C for 4–6 min. The system includes the RF generator, an electrode needle and a large dispersive electrode (ground pads), which completes a closed-loop circuit through the patient.

There are two types of RFA systems: monopolar and bipolar with cooled/non-cooled tip electrodes. A variety of electrode designs are available for different types of use: single, cluster and multi-tined electrodes, which are different forms of non-expandable and expandable array electrodes. The radiofrequency electrode is electrically insulated in its proximal part, while a short part near the tip, from which the electric current is passed into the tumor, is uninsulated. In cooled tip type electrodes, there is continuous cooling of the needle tip by circulating saline, which allows tissue heating and coagulative necrosis far from the electrode without tissue charring. These are single-use disposable electrodes, which are costly. The latest addition in RFA is bipolar and multipolar technology, which is more effective for ablation of larger tumors and there is no requirement for a grounding pad.[14,15]

The procedure is performed by a skilled radiologist where the patient receives intravenous sedation with continuous monitoring of the vital parameters. Under USG or CT guidance, the electrode is introduced into the tumor through the subcostal or intercostal approach. In most instances RFA is performed through percutaneous route. Tumor tissue can also be approached through open or laparoscopic routes.[16,17] As per the specifications of the equipment, the energy parameters are set on the generator. A pulsed RF energy is applied for 15–30 min, which causes a local rise of the temperature at the target from 80 °C to 110 °C. At the completion of ablation, the mass becomes echogenic due to microbubble formation and subsequently the electrode is withdrawn by applying additional lower energy during the withdrawal to prevent seeding of tumor cells in the needle track. A triple phase contrast enhanced computed tomography (CECT) done at 4 weeks after RFA can provide the information about completion of ablation. Multiple treatment sessions may be required to completely ablate the tumor(s). If residual disease is present on CECT; further sessions are carried