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.

Keywords: hepatocellular carcinoma (HCC), percutaneous liver ablation (PLA), radiofrequency ablation (RFA)

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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

out depending on the size of the tumor. There is a chance of incomplete ablation with tumors close to main branches of the portal or hepatic veins as continuous blood flow leads to dissipation of thermal energy—the ‘heat sink effect’. There are reports of occasional occurrence of cholecystitis following lesions close to gall bladder. (Figure 1 shows the CT scan of patient with small HCC before and after RFA.)

RFA has established itself in the treatment of small HCCs (<3.0 cm). In tumors of up to 3.0 cm, complete response is in the range of 90%–100%. In addition to ablating the entire tumor RFA also ablates a safety margin around the tumor, similar to the principle of surgical resection. As the tumor size increases, the complete response rate declines. The methods to augment the efficacy of RFA include 1) balloon occluded RFA in which the arterial supply to the tumor tissue is occluded and thereby achieving a larger ablation zone,¹⁸ 2) temporary hepatic

vein or portal branch occlusion during RFA which can safely facilitate ablation of large tumors or tumors in contact with large vessels,¹⁹ 3) creating artificial ascites, for tumors close to major organs or bowel, RFA is done after introducing 5% dextrose solution intraperitoneally to separate the bowel from the tumor and prevent thermal injury and the heat-sink effect in the ablation zone.²⁰ Though the best results are achieved with lesions <2–3 cm, some guidelines recommend that it can be used in tumors where the numbers of lesions do not exceed three or have a maximum diameter of 5 cm. When the lesion diameter is between 3 and 5 cm, sequential treatment should be considered. If the lesion measures more than 5 cm, ablation is not recommended because it is difficult to achieve 100% necrosis of the lesion.²¹ EASL (European Association for the Study of the Liver)-EORTC (European Organization for Research and Treatment of Cancer) recommends that RFA may also be considered an acceptable alternative to resection in

Figure 1 Small HCC treated by RFA. **A & B:** Pre-RFA CT scan, **C:** Schematic diagram of RFA. **D & E:** Post-RFA CT scan.

resectable BCLC 0 lesions.²² There are reports of RFA being used as a bridge to liver transplant.²³

RFA is a safe procedure with a minimal rate of major complications. A mortality rate of 0.3% and major complication rate of 2.2% has been observed in a large study assessing the complications of RFA.²⁴ The minor complication rate ranges upto 5% and most of these complications are transient and self-limiting. Tumor seeding was uncommon (0.5%) as the procedure involves ablation of the track at the time of withdrawal of the needle. Haemorrhage, bile duct injury, hepatic abscess and intestinal perforation are some of the rarely encountered adverse outcomes.²⁴ RFA also has some limitations. It is relatively expensive and is difficult to reach in many resource-poor countries.

Comparison of RFA with PEI shows that RFA has an advantage over PEI in terms of better tumor control and survival particularly for lesions >2.0 cm in size. Most of the recommendations state that the number and diameter of lesions treated by RFA should not exceed five and 5 cm respectively.^{3,11} Relatively fewer treatment sessions are required for achieving complete tumor response with RFA.^{25,26} Bouza et al, in a meta-analysis (six studies, total 396 patients of unresectable HCC treated by RFA and 391 treated by PEI, mean size 2.5 cm) comparing the two modalities²⁷ showed a better outcome with the use of RFA in the treatment of small HCCs. The 1-, 2-, 3- and 4-year survival rates are 96%, 86%, 73% and 62% for RFA and 91%, 75%, 58% and 51% for PEI, respectively. Disease-free survival at 1, 2 and 3 years is 80%, 61% and 40% with RFA and 70%, 42% and 19% with PEI, respectively. Complete tumor response is achieved in 93.5% and 84.5% cases following RFA and PEI, respectively. However, RFA was associated with greater morbidity though no significant difference was found in terms of major complications (RR 1.85; 95% CI 0.68–5.01).

CHEMICAL ABLATION

Percutaneous Ethanol Injection (PEI)

The most common method of chemical ablation is percutaneous ethanol injection (PEI).²⁸ Even with the availability of advanced methods such as RFA, cryoablation and

laser ablation, PEI retains its relevance because it is inexpensive, simple in terms of technique and can be performed without special equipments. Alcohol is cytotoxic, it penetrates tumor cells and causes coagulative necrosis due to dehydration of cytoplasmic proteins. It also causes local ischaemia due to thrombosis of the microcirculation of the tumor. The toxic action of ethanol is facilitated by the hypervascularity and softer consistency of HCCs in comparison with the surrounding cirrhotic liver. Alcohol therefore selectively diffuses within the nodule.²⁹

PEI is done using a 23G spinal/Chiba needle under USG or CT guidance, using local anaesthesia (Figure 2) The volume of ethanol injected is calculated using the following formula:

$$V = 4/3\pi(r + 0.5)^3$$

where V is the target volume of ethanol, *r* the maximum radius of the lesion and 0.5 the correction for the additional margin. This dose is injected slowly in 0.1–0.2 ml aliquots through a needle (fine, noncutting with a single end hole or multiple side holes) in multiple sittings, using continuous USG monitoring. The tumor site becomes hyperechoic following PEI. The procedure need to be repeated and multiple sessions can be carried out, once or twice weekly, depending on the size of the lesion, the distribution of intralesional ethanol within the tumor and the condition of the patient. PEI produces complete tumor response in lesions up to 3 cm in 80% of patients. It is well tolerated and has few minor complications.³⁰ In larger tumors (3–5 cm) or in multinodular HCCs, the efficacy is complete in 50% of patients. Local recurrence is influenced by the size of the tumor.³¹ For HCCs >3 cm, despite multiple treatment sessions, local tumor progression of >30% is encountered.³² The 1- and 5-year survival rates with PEI are reported to be 64%–100% and 32%–59%, respectively.³³ However in the presence of intratumoral septa and extracapsular spread, PEI does not produce complete tumor necrosis. There is also a risk of tumor recurrence which is seen in upto one third of cases in lesions <3 cm and in about 40% cases where the tumor is > 3.0 cm.³⁴ Different methods have been tried to enhance the efficacy of PEI, one such is to combine PEI with trans-arterial chemoembolization (TACE) that has yielded a high complete

Figure 2 HCC treated by percutaneous ethanol ablation. **A:** Pre-ablation CT scan, **B:** Ablation being done with a needle, **C:** Post-ablation CT scan.

response rate and 3- and 5-year survival rates of 75%–100% and 59%–75%, respectively.^{35,36}

Consensus Statement 1

Local ablation with RFA or PEI is considered the standard of care for patients with BCLC 0-A tumors not suitable for surgery (Level of evidence 1a, Grade of recommendation A).

Consensus Statement 2

The number and diameter of lesions treated by RFA should not exceed five and 5 cm respectively (Level of evidence 2b, Grade of recommendation B).

Consensus Statement 3

RFA and PEI are having similar efficacy in lesions <2.0 cm and RFA provides better local control and overall survival in HCCs ≥ 2 cm (Level of evidence 1a, Grade of recommendation A).

Percutaneous Acetic Acid Injection (PAI)

Another agent for chemical ablation is percutaneous acetic acid injection (PAI). Acetic acid has a higher diffusion capacity; it is easily available and cheap. A smaller volume of acetic acid and fewer treatment sessions achieve the same degree of tumor ablation as ethanol.³⁷ In addition PAI unlike PEI helps in infiltrating the tumor septae and capsule. There is not much of literature about the efficacy of PAI for ablating HCC.^{37–40}

The procedure of PAI is similar to PEI. This amount is injected in multiple sessions (1–2 ml of acetic acid per tumor per session per week) using a 23G spinal/Chiba needle. The response to the treatment is assessed by a CECT of the liver after 4 weeks. CECT characterizes the liver lesion better, and the residual or recurrent disease can be seen well. Ideal lesion for PEI is small HCC, <3 cm in size. The local tumor recurrence rate is 51% at 1 year and 74% at 3 years. The survival rate at 1 and 3 years is 84% and 51%, respectively.³⁹

PAI is a safe technique, with no major complications. The rare side effects include transient hemoglobinuria (but without any renal impairment), fever, right upper abdominal pain and with larger doses segmental infarction and metabolic acidosis can occur.^{39–42} Transient haemoglobinuria can occur immediately after tumor ablation, even after using small volumes (5–10 ml) of 50% acetic acid and it usually clears with a few urinary voids. Precautionary alkalization of urine by administering intravenous fluids containing bicarbonates can be helpful. Like with PEI, combination of PAI with TACE has been tried for large HCCs.

Both PEI and PAI can be used to treat HCC <3 cm successfully, but the number of sessions of treatment required for PAI are fewer.^{39,42} Some studies have shown that the local recurrence rate is lower with PAI than PEI (8% and 37%, $P < 0.001$). The 1- and 2-year survival rates are upto

100% and 90% with PAI and 85% and 65% with PEI.^{39–42} Another randomized controlled trial of 60 patients with one to four HCCs <3 cm (31 and 29 patients respectively were treated by PAI or PEI) had shown that 1- and 2-year survival rates were 100% and 92% in PAI and 83% and 63% in PEI group ($P = 0.0017$).⁴³

Consensus Statement 4

Percutaneous acetic acid injection could be a cost effective substitute for percutaneous ethanol injection. (Level of evidence 5, Grade of recommendation D).

Other Methods of Ablation

Microwave Coagulation Therapy

Percutaneous microwave coagulation therapy (MCT) is another form of thermal ablation for HCC, involves the use of microwave energy that causes molecular vibration of dipoles, especially water molecules in tissue, and produces dielectric heat and thermal coagulation around the electrode.⁴⁴ No grounding pads are needed. It was used previously during liver surgery for the control of bleeding from ruptured HCC and for liver resection.⁴⁴ It can also ablate unresectable HCCs during laparotomy and laparoscopy.^{45,46} Even though the agent of ablation in both RFA and microwave ablation is heat, the mechanism of delivery differs. The amount of heat in the latter does not depend on the passage of electricity through tissues. Hence, simultaneous activation can be achieved with multiple antennae without electrical disturbance (a problem with RF probes).

MCT has the advantages of having a higher thermal efficiency. It has high efficacy in coagulating blood vessels and is relatively a fast procedure.⁴⁷ The time required for ablation is short and the shape of necrosis is elliptical. There is no heat-sink effect and it can be used to ablate tumors adjacent to major vessels. These factors yield a large ablation volume, and result in good local control and fewer complications. MCT can achieve complete ablation of 89%–94% of tumors. The local progression rate is 6%–8%. It is associated with a 5-year survival rate of 51%–57% and a major complication rate of 0%–8%.^{48–50} The 1-, 2-, 3-, 4- and 5-year cumulative survival rates are 93%, 82%, 72%, 63% and 51%, respectively.⁴⁹ Comparison with RFA reveals that the complete ablation rates are quite similar (89% for MCT and 96% for RFA).⁵¹ The survival outcome studies show that, there was no difference in the survival rate⁵² or even RFA having a better 3-year survival rate and higher complication and recurrence rates with MCT.⁵³

Percutaneous Laser Ablation

Percutaneous laser ablation (PLA) PLA produces thermal coagulation from the heat produced by light energy. This form of ablation has been found to be successful in complete tumor ablation in upto 90% cases.⁵⁴ The heat is

absorbed either directly or after the light is scattered by tissue. The extent of necrosis depends on the power (in watts), exposure time, wavelength of light and absorption characteristics of the tissue, including proximity to major blood vessels. Complete tumor ablation of up to 90% has been reported. Failures occur in tumors >3 cm in size and those located at sites not allowing optimal fibre placement. Tumors located near vessels require more illumination for ablation. Complications are rare, and are mostly associated with excess energy and tumors at high-risk locations.⁵⁵

Cryoablation

Cryoablation is the oldest local ablation technique for primary and secondary malignant hepatic tumors.^{56–59} The procedure requires general anesthesia and laparotomy for probe placement. Tissue freezing produces the largest ablations. Sub-freezing temperatures are delivered through penetrating or surface cryoprobes that carry cryogen. Irreversible tissue damage occurs between temperatures of -20°C and -30°C results in denaturation of cellular proteins, cell dehydration and ischaemic hypoxia.⁶⁰ The long-term results with cryoablation are variable. The survival rates reported for 1 year are 82%–90%, for 3 years 32%–40%, and for 5 years 13.4%–20%.^{59,60} For more advanced tumors, the survival rates drop significantly (59% and 22% at 1 and 3 years, respectively).⁵⁹ Better survival is noticed in the case of primary HCC compared to metastases.⁶¹ The complication rate following cryoablation is higher than that following RFA.⁶²

High Intensity Focused Ultrasound

A recently introduced method is high-intensity focused ultrasound (HIFU). In HIFU, the external source of high-energy ultrasound waves is projected into a target area within the liver. The increased local sound pressure results in the production of heat and the destruction of tissue.⁶³ There is no needle puncture into tumor tissue in this technique and general anesthesia is used. Rib resection may be required if the lesion is obscured by the overlying ribs. The survival rates that have been reported with HIFU are 100%, 83.3%, 69.4% and 55.6% at 1, 2, 3 and 5 years, respectively.⁶⁴ It is still at an early stage of development and has not gained wide acceptance.

Recently multimodality strategies to ensure better treatment for large tumors are described. A combination of RFA and TACE⁶⁵ or PEI⁶⁶ has been shown to cause more effective tumor necrosis in larger lesions than is possible with RFA alone. Ablation is increasingly used to treat primary and secondary liver cancer. Ablation near portal pedicles and hepatic veins has always been challenging. Irreversible electroporation (IRE) is a novel, nonthermal form of tissue ablation using high-voltage electrical current to induce pores in the lipid bilayer of cells resulting in cell death.⁶⁷ IRE does not rely on heat and, in animals, appears to be

safe and effective when applied near hepatic veins and portal pedicles. Kingham et al, in a recent study with IRE on 28 patients with perivascular malignant liver tumors found the method to be safe.⁶⁸

Lee et al in a prospective study of 30 patients with single medium-sized HCCs (mean, 3.5 cm; range, 3.1–4.4 cm, with a mean follow up of 11.5 months) had shown that switching monopolar RFA to multiple electrodes achieved sufficient ablation volume and was safe and efficient.⁶⁹ Switching from single to multiple needle and placement of these under CT guided stereotaxy has been applied recently.⁷⁰ Widmann et al in a series of 90 patients (72 HCC and 105 metastases with a mean size of 2.9 cm, range 0.5 cm–11 cm) showed that stereotactic RFA (SRFA) allowed for efficient, reliable, and safe ablation of large-volume liver disease.⁷¹ Stereotactic multi-needle techniques with 3 dimensional planning and guided needle placement significantly widen the spectrum of treatable lesions including large sized lesions. Treatment success is due to large intentional ablation margins of tumor free tissue (A0 ablation similar to R0 resection).⁷² Fusion of post with pre-ablation images during post ablation follow up can confirm success of ablation.

Cyberknife is a new stereotactic body radiation therapy (SBRT) or stereotactic ablative radiotherapy (SABR) technique.^{73–76} This technique delivers high dose radiation accurately sparing adjacent normal tissue in a small number of fractions. A number of studies of SBRT in HCC not suitable for standard locoregional treatment or resection have reported promising results. It also has utility as local salvage treatment after TACE achieving local control in 95%.⁷³ To this date no serious SBRT related toxicities being reported^{74–76} but it is not clear whether it can be applied to patients with more severe liver diseases as its threshold for tolerance is not defined.

To summarize, PLA techniques are safe, minimally invasive, efficacious and cost-effective. These ablative methods have an established role for the treatment of small HCCs. RFA is considered as first line treatment in some centers, though mostly it is used as ablative therapy for the treatment of small HCCs where surgery is not possible. In developing countries PEI and PAI may be used instead of RFA. For large HCCs, advances in electrode designs and newer techniques of ablation, including microwave ablation, are increasingly proving successful. Combination treatment modalities have shown promising results as compared to single-therapy treatment for large tumors. The decision to select the most appropriate method for ablation depends on the size and number of lesions. Also the choice depends on the liver function status, patient's financial resources and availability of a particular technique and the expertise of radiologist or hepatologist.

CONFLICTS OF INTEREST

All authors have none to declare.

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