Comparison of Percutaneous Ablation Technologies in the Treatment of Malignant Liver Tumors

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Abstract

Tumor ablation is a minimally invasive technique used to deliver chemical, thermal, electrical, or ultrasonic damage to a specific focal tumor in an attempt to achieve substantial tumor destruction or complete eradication. As the technology continues to advance, several image-guided tumor ablations have emerged to effectively manage primary and secondary malignancies in the liver. Percutaneous chemical ablation is one of the oldest and most established techniques for treating small hepatocellular carcinomas. However, this technique has been largely replaced by newer modalities including radiofrequency ablation, microwave ablation, laser-induced interstitial thermotherapy, cryoablation, high-intensity–focused ultrasound ablation, and irreversible electroporation. Because there exist significant differences in underlying technological bases, understanding each mechanism of action is essential for achieving desirable outcomes. In this article, the authors review the current state of each ablation method including technological and clinical considerations.

Keywords
- percutaneous chemical ablation
- radiofrequency ablation
- irreversible electroporation
- cryoablation
- microwave ablation
- high-intensity–focused ultrasound ablation
- interventional radiology

Objectives: Upon completion of this article, the reader will be able to describe the underlying mechanism of various ablation techniques, including percutaneous chemical ablation, irreversible electroporation, high-intensity–focused ultrasound ablation, laser ablation, microwave ablation, radiofrequency ablation, and cryoablation, as well as the clinical outcomes in the management of patients with primary and secondary liver tumors.

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Percutaneous Chemical Ablation

Percutaneous chemical ablation is a relatively safe and effective procedure used in the treatment of small hepatocellular carcinoma (HCC). It is well tolerated by patients and has very low reported major and minor complication rates ($\sim$2%).[1,2] Although the technique requires adequate expertise in placing the needle with imaging guidance, the procedure is simple and does not require any specialized equipment,

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except multi–side-hole needle if one chooses. Chemical agents for percutaneous ablation include ethanol, acetic acid, and sodium hydroxide.[2] Percutaneous ethanol injection (PEI) is well established and the most commonly used chemical ablation technique. It was shown that PEI can safely achieve complete necrosis of small HCCs, and achieve 5-year survival rates of 32 to 38% in nonrandomized trials in the 1990s.[3–5] However, due to multiple session numbers, high local tumor progression rate, and variable ablation zone in PEI compared with radiofrequency (RF) ablation, the use of PEI is now limited to situations when RF ablation should not be performed, such as when the tumor is in close proximity to large vessels or critical organs.[1,6–8] In one study evaluating the treatment of small HCC, RF ablation demonstrated an approximately 20% higher survival rate at 3 to 4 years and fewer treatment sessions than PEI in three randomized controlled trials.[9–11] It has been confirmed again in recent meta-analyses evaluating these randomized controlled trials that RF ablation is better than PEI in the treatment of small HCC.[12,13]

The basic mechanism of action of ethanol is through cytoplasmic dehydration, denaturation of cellular proteins, and microvascular thrombosis. These changes eventually result in coagulation necrosis of tumor tissue.[2,14] For a chemical agent to exert its cytotoxic effect, it must be transported from the point of injection through the interstitial space into the cytoplasmic compartment of the tumor. This is primarily accomplished through two mechanisms: diffusion and convection. Chemical agents with a relatively low molecular weight, such as ethanol and acetic acid, are transported mainly by diffusion and rely on the concentration gradient between two compartments.[15] Direct injection of a high-concentration agent using a multi–side-hole needle placed into a tumor at multiple sites will not only increase the interstitial pressure but also establish a much higher local concentration gradient, resulting in high convective and diffusive flux of the agent into the cytoplasm. Factors associated with homogeneous diffusion of ethanol include soft and small (< 3 cm) hepatic tumors with fewer septations or daughter nodules.[2] While ethanol is incapable of penetrating the septae, acetic acid has an advantage of dissolving lipids and infiltrating the septae and tumor capsules.[16] As a result, the total injected volume and the number of treatment sessions with acetic acid are less than those with ethanol to achieve the same cytotoxic effect. The typical volume of acetic acid needed for each treatment session is approximately one-third the volume used for ethanol ablation based on earlier observations of animal study and clinical experiences.[17,18]

One other chemical agent that has been used is sodium hydroxide. Sodium hydroxide has been studied in an animal model that demonstrated that sodium hydroxide has a concentration-dependent necrotizing effect with less systemic toxicity.[19] When acetic acid and sodium hydroxide are mixed together, an exothermic neutralization reaction occurs. Exothermic neutralization is a chemical reaction between an acid and a base in which heat, salt, and water are produced. In a recent study, Farnam et al injected acetic acid and sodium hydroxide simultaneously into an ex vivo porcine liver to investigate the exothermic neutralization reaction for potential use in tissue ablation.[20] The authors confirmed that the reaction between the two reagents released a significant amount of heat energy at the site of injection and created histologic changes consistent with coagulation necrosis. A high concentration and volume of acetic acid and sodium hydroxide correlated with higher temperatures and larger areas of gross pathologic changes.

Irreversible Electroporation

Percutaneous irreversible electroporation (IRE) is a nonthermal ablative technique in which short (microsecond to millisecond) pulses of high voltage electrical energy are applied to a targeted tissue through electrodes.[21] Ninety pulses of 1,000 to 3,000 V/cm direct current energy are delivered to generate destabilizing electrical potential across the cell membrane, resulting in the formation of permanent nanopores in the lipid bilayer. This irreversible disruption and increased permeability of the cell membrane is the key mechanism for cell death.[22–24]

Electroporation is a dynamic phenomenon that can cause either reversible or irreversible damage, depending on the transmembrane electric voltage to the cell membrane. If the cells are located within areas where the electric field magnitude is greater than the threshold, reversible electroporation occurs in the cell membranes. If the voltage surpasses a second threshold, it creates irreversible and persistent pores in the cell membrane that induce cell death.[25]

IRE has been investigated by Edd et al in an animal model to analyze the efficacy as an independent tissue ablation method.[24] In perfusion-fixed animal livers, the authors observed microvascular occlusion, endothelial cell necrosis, and diapedeses, resulting in ischemic damage to the parenchyma and massive accumulation of erythrocytes in sinusoids approximately 3 hours after electroporation. However, the integrity of vascular structures around the treated site was preserved in this study.

The finding of preserved blood vessels at the margin of ablated tissue was again observed in a study with porcine liver by Rubinsky et al[21] in 2007. These authors hypothesized that the vessel-preserving effect of IRE is likely caused by a higher proportion of collagenous connective tissue and elastic fiber, as well as the lack of a normal cellular membrane in the vessel wall. This is supported by the finding of mild inflammatory change in the vessels located in the ablated zone.

In a recent study using Yorkshire pig livers, Lee et al demonstrated that IRE is a safe and effective ablative method, inducing complete tissue death via apoptosis while fully preserving the periablative zone structures including blood vessels, bile ducts, and surrounding normal tissues.[26] This finding is explained by the presence of gap junctions of the smooth muscle cells, in addition to higher contents of collagenous and elastic fibrous tissue in both bile ducts and blood vessels. Gap junctions are the distinctive cellular structure of the smooth muscle cells that may act as a barrier preventing the electrical current from traveling through the junction between cells, thereby the integrity of the smooth muscle cell membrane is not disrupted or changed. Hence, the bile ducts and vessels around the ablated zone are preserved.

This advantage of IRE with lack of a heat-sink effect enables better tumor ablation with less risk of damage to the adjacent vessels, ducts, or critical organs compared with other thermal ablation techniques including RF ablation, microwave (MW) ablation, and cryoablation. For this reason, interest in IRE application is increasing, especially for use in the pancreas or liver where vital structures and ducts can easily be damaged by thermal ablation methods.

The safety of IRE for tumor ablation in humans was first reported by Thomson et al[27] in a single-center nonrandomized cohort study in 2011. In the 38 patients with advanced malignant tumors in the liver, kidney, or lung, a total of 69 IRE ablations were performed with no mortalities at 30 days. Complete ablation was achieved in 66% of tumors; most treatment failures occurred in renal and lung tumors. Adverse events directly related to electroporation included cardiac dysrhythmias and obstruction of the upper ureter. Though there was one unintentional ablation of the adrenal gland, there was no other evidence of adjacent organ damage related to the IRE. Owing to transient ventricular arrhythmia occurring in four patients, ECG-synchronized delivery was used subsequently in the remaining patients. The authors concluded that IRE is safe for human clinical application when adequate ECG synchronization is used.

Narayanan et al reported on the feasibility and clinical safety of computed tomography–guided percutaneous IRE in 14 patients with unresectable locally advanced pancreatic cancer.[28] The percutaneous pancreatic IRE procedure was well tolerated with a low complication rate. Complications included spontaneous pneumothorax and pancreatitis that were self-limited and completely reversible; there were no deaths related to the procedure.

The safety and efficacy of percutaneous IRE ablation for hepatic tumors located centrally or close to the major bile ducts, portal pedicles, or hepatic veins has been evaluated in several studies.[29–31] Kingham et al tested the safety of IRE for treating hepatic tumors located within 1 cm from major hepatic veins or major portal pedicles.[29] In this study, they reported complications including cardiac arrhythmia and portal vein thrombosis. However, the overall morbidity was only 3% with no treatment-associated mortalities. Cannon et al also examined the safety and early efficacy of IRE for hepatic malignancies in proximity to vital structures.[31] A total of 48 procedures were performed in 44 patients with centrally located tumors in proximity to major vascular/biliary structures or adjacent organs. Technical success was achieved in 100%, and five patients had nine transient adverse events with complete resolution within 30 days. In a retrospective study, Silk et al suggested that IRE may be an option for centrally located peribiliary hepatic tumors.[30] Although these studies demonstrated the safety of IRE, larger studies and longer follow-up are necessary to determine long-term efficacy.

High-Intensity–Focused Ultrasound Ablation

High-intensity–focused ultrasound ablation (HIFU) is one of the thermal ablation therapies using high temperature to treat a targeted lesion. It is a noninvasive therapeutic modality, in which focused acoustic energy is precisely delivered from an extracorporeal source to the focal zone. This high-intensity–focused energy is then converted to heat, which destroys diseased tissues without damaging overlying and surrounding normal structures.

A high-frequency ultrasound beam (0.5–10 MHz) is generated by a therapeutic ultrasound transducer and arranged into a spherical form by an acoustic lens to create a small and discrete focal point. As the beam approaches the focal point, the power density of the converging ultrasound increases and the energy is accumulated at the focal zone. This phenomenon subsequently induces coagulation necrosis of the targeted lesion by creating acoustic cavitation and elevating tissue temperature to above 60°C.[32,33] Temperatures can rise from 65 to 85°C; however, higher temperatures are avoided to prevent boiling of liquids inside the tissue.

HIFU technology was first described by Lynn et al[34] in 1942. These authors designed an efficient generator of focused ultrasound that was successfully operated to produce focal heating in the center of the liver tissue with minimal effects at the surface and no effects on the intervening tissue. In animals, high-intensity focal ultrasound produced local cerebral changes through intervening scalp, skull, and meninges. Since its first introduction in 1942, the technology of HIFU has continuously evolved, and recent developments have allowed its application to treat tumors of various solid organs, including the pancreas, liver, prostate, breast, uterus, bone, and soft tissue.[35–38]

Recently, the addition of magnetic resonance (MR) guidance for HIFU has generated a renewed interest in this technology for tumor ablation. MR imaging–guided HIFU or focused ultrasound is mainly used in the treatment of uterine fibroids for which it has been approved for use by the U.S. Food and Drug Administration (FDA). It is, however, being tested to determine its clinical application for other benign and malignant tumors of the breast, prostate, liver, and uterus.[39,40]

In the liver, the utility of HIFU has been examined in the treatment of unresectable HCC or metastases. Despite the challenges of targeting within the liver due to respiratory motion, HIFU has been shown to be safe and effective. Xu et al reported their experience in treating 145 patients in whom symptoms were relieved in 84.4% and tumor size was decreased by various degrees.[41] The 2-year overall survival rate was dependent on tumor stages. HIFU has also been shown to be safe in treating liver tumors located in close proximity to major vessels. In a study by Zhang et al,[42] 39 patients with HCC were treated with HIFU and there was no evidence of any major blood vessel injury when treating tumors located less than 1 cm from the inferior vena cava (IVC), main hepatic vein, or portal vein.

In a single-center study, Ng et al reported that HIFU, when used as the primary therapy, achieved an overall effectiveness rate of 79.5% in 49 patients with unresectable HCC.[32] When the total number of ablated tumors is considered, a complete ablation rate reaches 91% for small HCC ($\leq$3 cm). The 1- and 3-year overall survival rates were 87.7 and 62.4%, respectively. Child-Pugh liver function grading was the most significant prognostic factor influencing the overall survival rate. The authors concluded that HIFU is an effective modality in the treatment of unresectable HCC, with a high technique effectiveness rate and favorable survival outcomes.

Because the ultimate goal for liver ablation is to improve the overall survival of the patient, it is critical when assessing new technologies that survival data be examined. In a recent study, Cheung et al compared survival rates between patients with small HCC ($\leq$3 cm) treated with HIFU and RFA.[43] In this study, the 1- and 3-year overall survival rates of HIFU and RF ablation groups were 97.4 versus 94.6% and 81.2 versus 79.8%, respectively ($p = 0.530$). The corresponding 1- and 3-year disease-free survival rates were 63.6 versus 62.4% and 25.9 versus 34.1%, respectively ($p = 0.683$). The authors concluded that in the treatment of small HCC, HIFU provides outcomes comparable to that of RF ablation.

Transarterial chemoembolization (TACE) has been combined with thermal ablation therapies in an attempt to achieve more complete necrosis of HCC. Because TACE may reduce blood flow of a tumor, heat loss caused by adjacent vessels may be reduced.[44] Likewise, HIFU has been used in conjunction with TACE and a randomized clinical trial has shown a significant survival benefit in the group with TACE and HIFU compared with the TACE-only group.[45] Jin et al reported a similar experience of HIFU and TACE in patients with unresectable HCC.[46] This study demonstrated that 45.2% of patients achieved complete tumor ablation when TACE was combined with HIFU. Ablation response and tumor size were major prognostic factors.

Other indications for HIFU have been investigated in animal studies by Vaezy et al and Noble et al.[47,48] Namely, HIFU has been tested in the treatment of a variety of benign splenic conditions. Specifically, HIFU has been found to be effective in achieving hemostasis in hemorrhagic spleen models with no apparent harmful effects to the spleen. Another recent experimental study demonstrated HIFU to be feasible and effective for treating splenomegaly and hypersplenism.[49] Zhu et al also reported the efficacy and safety of HIFU in patients with HCC and hypersplenism.[38] After HIFU treatment, mean splenic ablation of approximately 28% was achieved and the white blood cell count, platelet count, and liver function were improved.

Laser Ablation

Percutaneous laser ablation is a hyperthermia-based technique that destroys targeted tissues by using heat energy converted from absorbed light. Laser light is transmitted to the lesion via bare-tip quartz fibers with diameter of 300 to 600 µm inserted through multiple small-caliber needles (21 gauges). Inside the tissue, laser light travels for a short distance (12–15 mm) as a result of scattering, reflection, and absorption.[50] The absorbed light energy is then evenly distributed (mainly by scattering) and is converted to heat that is further spread by conduction, creating a large area of coagulation necrosis.[51–53] Using 21-gauge needles for placing multiple fibers is considered less traumatic compared with 7F or 9F single cannulation needles in patients with liver cirrhosis who have higher risk of bleeding.[54]

Because of its optimal penetration depth into surrounding tissues, since the first introduction of phototherapy in tumors in 1983, Nd:YAG (neodymium:yttrium aluminum garnet) lasers (wavelength, 1,064 nm) have been widely used in the treatment of various liver malignancies.[55,56] The optimal penetration of laser light is directly associated with a lower temperature gradient throughout the ablation zone, less risk of carbonization and vaporization of tissue, and better treatment results for tumors.[57] The penetration depth of laser light is greater in metastatic tumors than in normal liver tissue, and coagulation necrosis results in reduced penetration by approximately 20% in both tissues.[57,58] A single bare-tip fiber can create a spherical ablation zone with a diameter of 12 to 16 mm.[59] When multiple fibers are arranged in the tumor, the area of ablation can be significantly increased.

In a single-center study, Pacella et al first reported that laser ablation is a highly effective therapeutic modality in patients with HCC smaller than 4 cm.[60] The study, involving 82 patients with 99 lesions, demonstrated a complete tumor ablation rate of 90.9%. The safety of the procedure was investigated by Arienti et al in a larger multicenter study involving nine centers in Italy with 520 patients who underwent 1,004 treatment sessions for 647 HCC nodules.[61] There were four (0.8%) deaths and 15 (1.5%) major complications without any tumor seeding. Major complications were associated with excess energy deposition and high-risk locations. Sixty-two (6.2%) sessions resulted in minor complications associated with excess energy, high bilirubin level, and low prothrombin time. Complete necrosis was achieved in 60% of all HCCs, and in 81.1% of small nodules ($\leq$ 3 cm). The authors concluded that the procedure is safe in the treatment of small HCCs. In a separate retrospective study evaluating 87 patients with 180 liver metastases from colorectal carcinoma, Puls et al reported a technical success rate of 99%, an effectiveness rate of 85.6% on follow-up after 24 to 48 hours, and a local tumor progression rate of 10% after 6 months.[62] Median survival time was 54 months and survival rates were 95.7% at 1 year, 86.2% at 2 years, 72.4% at 3 years, 50.1% at 4 years, and 33.4% at 5 years.

As laser ablation is increasingly being used in the treatment of liver malignancies including HCC and metastases, the technology is being compared with RF ablation in an attempt to validate its technical reliability and efficacy.[59] Recently, Orlacchio et al compared the two ablation technologies in the treatment of HCC smaller than 4 cm in patients with liver cirrhosis.[63] Thirty patients with single HCC $\leq$ 4 cm in diameter were randomly assigned to one of two treatments and followed up for up to 12 months. Complete response rates with laser and RF ablations were 87 and 93%, respectively; this finding was not statistically significant. There were also no differences in the overall local recurrence-free survival rates between the two groups; however, patients treated with laser ablation did show a higher recurrence rate for HCC larger than 2 cm ($p = 0.0081$), and tumor necrosis factor-α with postablation syndrome was found to be significantly higher in the RF ablation group ($p < 0.05$). Overall, in this study, RF ablation appears more effective compared with laser ablation for treating larger HCCs. However, laser ablation can be considered an alternative treatment option for tumors smaller than 2 cm for its lower complications rates.

Laser ablation may also be combined with other modalities to achieve an increased volume of tumor necrosis. In an animal study, Zou et al investigated the effects of laser ablation combined with PEI on rabbit VX2 liver tumors.[64] VX2 tumors in the liver of 80 rabbits were randomly separated into four groups; each group was treated with laser ablation alone, PEI alone, laser ablation immediately followed by PEI, or PEI immediately followed by laser ablation. The study demonstrated that combined therapy with PEI immediately followed by laser ablation resulted in a significantly larger volume of coagulation necrosis with reduced residual tumor volume. It was hypothesized that tissue destruction by ethanol may have resulted in increased thermal conduction. In addition, PEI is associated with a sclerosing effect on blood vessels, thus reducing the heat-sink effect and enhancing the effect of the laser ablation.

Microwave Ablation

In MW ablation, the mechanism of heat generation is based on rapid frictional movement of water molecules in the high-frequency (900–2,500 MHz) electromagnetic field. An oscillating electromagnetic field around the antenna forces water molecules to continuously realign, resulting in high kinetic energy that is converted to heat in the tissue.[11,65,66]

MW ablation has several advantages, including greater penetration of energy into tissue (resulting in a larger area of ablation), less susceptibility to convective heat-sink effect from surrounding vessels, higher intratumoral temperatures, faster ablation times, and simultaneous activation of multiple antennae.[66–69] In addition, MW ablation does not require grounding pads or other ancillary devices. Even in tissues with high impedance, such as lung or charred and desiccated tissues, MW can be used effectively due to its low sensitivity to local variation in tissue physical properties. The incidence and severity of postablation syndrome (flu-like illness, low-grade fever, nausea, and/or vomiting) is found to be similar to that reported for RF ablation. Postprocedural pain for MW ablation is correlated with total ablation volume.[70]

The safety, effectiveness, and survival rates have been reported in several studies with MW ablation in the treatment of HCC. In a cohort study with 234 patients who underwent MW ablation, Dong et al showed a complete ablation rate of 89%, local recurrence rate of 7%, and cumulative survival rates at 1, 2, 3, 4, and 5 years of 92.7, 81.6, 72.9, 66.4, and 56.7%, respectively.[71] In a retrospective study of 102 patients with HCC, Lu et al reported that MW ablation and RF ablation are both effective in treating HCC. The local tumor control, complications related to treatment, and long-term survivals were equivalent for the two modalities[72]; complete tumor ablation rates with MW ablation and RF ablation were 94.9 and 93.1%, respectively. The local recurrence rate was 11.8% for MW ablation versus 20.9% for RF ablation, and there was no significant difference between the two modalities in treating either large or small tumors. In a well-matched randomized controlled trial involving 72 patients with HCC, Shibata et al compared MW ablation with RF ablation.[73] This study found that complete therapeutic effects with RF ablation and MW ablation were 96 and 89%, respectively. Complication rates and rates of residual foci of untreated disease were also equivalent for both ablation techniques.

Recent studies using improved MW technology with more powerful generators have demonstrated improved efficacy by creating larger ablation zones. Using a new MW device with a 2.45-MHz generator, Poggi et al were able to achieve an overall complete ablation rate of 94.3% in patients with HCC[74]; for small HCC (diameter ≤ 3 cm), complete necrosis was obtained in 100%. The rates of complete ablation for the intermediate (3–5 cm) and large lesions (≥ 5 cm) were 90 and 69%, respectively.

The evidence supporting MW ablation in the treatment of metastatic liver tumors is limited. In one of the first studies, Shibata el al compared laparoscopic-guided MW ablation and surgical resection in patients with metastatic colorectal carcinoma in the liver.[75] There were no significant differences in mean survival times, complications, and mean disease-free intervals between the two groups. Estimated 1-, 2-, and 3-year survival rates were 71, 57, and 14% for MW ablation and 69, 56, and 23% for surgical resection, respectively. Tanaka et al also reported the efficacy of MW ablation combined with hepatectomy compared with hepatectomy alone for multiple bilobar colorectal metastases to the liver.[76] Although more metastases were found in the group with MW ablation and resection, there were no significant differences in survival rates or in the pattern of progression between the two groups. The study concluded that MW ablation plus hepatic resection expanded the indications for operation to treat multiple bilobar liver metastases, with survival rates similar to those in less-involved hepatic resection patients.

Radiofrequency Ablation

In RF ablation, a complete electrical circuit is formed across the patients' body between a needle electrode and large-surface ground pads. Rapidly alternating RF current (300–500 KHz) is then generated around an electrode and is propagated through the tissue, resulting in resistive heating (the Joule effect). Although initial direct heating occurs within a short distance of the electrode, a larger ablation zone is eventually created by thermal conduction, inducing cell death by coagulation necrosis.[68]

Since RF ablation was first used for HCC[66] in 1990, the technique has been expanding its role in the treatment of primary and secondary hepatic malignancies. In patients with small (≤ 3 cm) to medium (3–5 cm) sized HCC, RF ablation has achieved complete ablation rates of over 80% in a single treatment session and over 90% in two sessions, with 5-year survival rates of 40 to 58%. Local progression rates after complete ablation are 1 to 12%.[8,72–74,77–80] Major complications include peritoneal hemorrhage, bile duct injury, abscess, and intestinal perforation, with acceptable rates of these complications ranging from 0.9 to 5.0%.[75,79] In the treatment of large HCC ($\geq$ 5 cm), conventional RF ablation is limited mainly by incomplete ablation, with reported complete ablation rate of 62% for tumors measuring 5 to 7 cm.[81] However, the efficacy is clearly improved when new devices are used. In a separate study using three bipolar electrodes and internally cooled electrodes, complete ablation rates were 81 and 90%, respectively, in patients with large HCC.[82,83]

RF ablation has been compared with PEI in the treatment of unresectable HCC (2.2–2.9 cm) in several randomized controlled trials.[84] Meta-analysis of these trials showed better 1- and 3-year overall survival in patients treated with RF ablation compared with those treated with PEI. In the RF ablation group, disease-free survival rates were significantly better, and disease recurrence rates at the ablation site were significantly worse than in the PEI group.[9–11,85]

Cryoablation

Cryoablation is based on the rapid cooling of the cryoprobe by the Joule–Thompson effect.[86] As high-pressure argon gas is forced through a narrow opening at the distal portion of the probe and then rapidly expanded to atmospheric pressure, the temperature of the metallic probe is decreased. This cold temperature is transferred to surrounding tissue by convection and conduction. When helium gas passes through the same system, it causes warming of the cryoprobe and thawing of the tissue.[87] Cell death is caused by direct intracellular ice crystal formation, resulting in physical damage to the plasma and cytoplasmic organelle membranes.[88] During thawing, intracellular ice crystals continuously grow, maximizing their biocidal effects.[89] If ice crystal formation occurs in the vascular endothelial cells of blood vessels supplying the targeted lesion, indirect cellular injury is induced by ischemia and inflammation.[89–91]

Cryoablation has been used to treat both primary and metastatic liver tumors. A multicenter retrospective study of cryoablation for liver tumors including metastases and HCC for over 7 years reported that cryoablation for noncolorectal metastases had significant long-term survival benefit and is a useful tool for controlling symptoms.[92] Recently, Xu et al evaluated the efficacy of sequential use of TACE and percutaneous cryoablation compared with cryoablation alone for unresectable HCC. A total of 130 patients with intermediate to large HCC (mean size 4.6 cm) were treated with cryoablation alone.[93] During a mean follow-up period of 42 ± 17 months, local recurrence was observed in 23% of patients in cryoablation-alone group, compared with 11% in cryoablation plus TACE group ($n = 290$). The overall 1-, 2-, 3-, 4-, and 5-year survival rates in cryoablation-alone group were 72, 57, 47, 39, and 31%, respectively. Although, the 1- and 2-year survival rates were similar between the two groups, the 4- and 5-year survival rates were 49 and 39% in sequential TACE–cryoablation group, higher than those (29 and 23%) in cryoablation-alone group ($p = 0.001$). The authors concluded that when TACE is combined with cryoablation, the efficacy is increased and adverse effects decreased for patients with unresectable HCC.

In a retrospective study by Adam et al in 2002, a total of 64 patients were treated with either percutaneous cryoablation ($n = 31$) or RF ablation ($n = 33$) for unresectable hepatic malignancies, and the outcomes were compared between the two modalities.[94] Complication rates were 29% in the cryoablation group and 8% in RF ablation group. Although initial treatment success was comparable between the two groups, the local recurrence rate was higher in patients treated with cryoablation than those treated with RF ablation (53 vs. 18%). Another prospective study comparing intraoperative cryoablation and RF ablation also demonstrated a much higher complication rate for cryoablation (41 vs. 3%).[95]

Major disadvantages of cryoablation include a variable ablation zone, cold-sink effect from adjacent vessels, and high complication risk. Local complications are hemorrhage, cold injury to adjacent organs, biliary injury, and hepatic parenchymal damage.[96] Ice ball formation inside the liver may cause cracking or shearing of the liver parenchyma, resulting in major hemorrhage by extension of shearing injury to major vessels. Late hemorrhage and intrahepatic abscess can occur by biliary injury. Cryoablation is also associated with the cytokine-mediated systemic syndrome, which is known as "cryoshock" and includes fever, tachycardia, and tachypnea. Although cryoablation has some potential advantages, its utility in the treatment of liver malignancies is limited mainly due to the higher complication rates, higher local recurrence rates, and the lack of proven efficacy benefit compared with other thermal ablation methods.[8,97]

Conclusion

Although PEI is well established and is the most commonly used chemical ablation technique for small HCC, due to its higher local recurrence rates and lower disease-free survival, RF ablation should be considered the first-line treatment modality in the treatment of primary and secondary liver malignancies. However, conventional RF technology is significantly limited for large HCC ($\geq$ 5 cm) mainly by incomplete tumor necrosis. As the technology in RF devices continues to advance, the efficacy is clearly improved with complete ablation rates for larger tumors now reported in the 81 to 90% range. In addition, newer technologies are being advanced that give hope to expanding the types of lesions that may be treated while potentially reducing the complications. MW ablation has different underlying mechanisms for generating heat and is less affected by a heat sink from adjacent large vessels. Other thermal ablation techniques that also use heat include laser ablation and HIFU. For small HCC, both techniques provide good outcomes comparable to that of RF ablation. IRE is a nonthermal ablation method with lack of a heat-sink effect, thus enabling better tumor ablation with less risk of damage to the adjacent vessels, ducts, or critical organs. For this reason, interest in IRE continues to increase for tumors in the pancreas or liver where vital structures can easily be damaged by heat. Despite some potential advantages, the use of cryoablation for liver tumors is still limited by higher complication rates and the lack of proven efficacy benefit over other techniques.

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