Abstract

In the treatment of hepatocellular carcinomas (HCC), interventional techniques such as trans-arterial chemoembolization, trans-arterial radio-embolization, percutaneous ethanol injection, percutaneous thermal ablation and etc. can decrease the size (and overall viability) of the tumors, thus potentially increasing the proportion of patients qualifying for resection and transplantation and improving their quality of lives. This chapter presented almost all the interventional techniques which proved to be clinical efficacy to HCC patients in recent years.

Introduction

Hepatocellular carcinoma (HCC) is the fifth most prevalent cancer worldwide with a poor prognosis [1] and it is the 2nd most frequent cause of cancer-related death in men and the 6th in women [2]. There are about 391,000 patients diagnosed of HCC, 372,500 died from HCC each year in China [3]. Areas of high prevalence include sub-Saharan Africa and Southeast Asia where a large portion of the population is infected with the hepatitis B virus (HBV), the factor most strongly associated with the development of HCC [4], other factors include metabolic syndrome and diet [5,6]. Liver transplantation, surgical resections are ideal treatment options for HCC. Long-term overall survival rates in early HCC has been demonstrated approximately 75% at 5 years after liver transplantation [7,8,9]. Surgical resection can significantly improve clinical outcomes, increasing 5-year survival rates to 75% [10,11,12]. However, only a small proportion of patients...
are suitable for these two options due to multifocal cancer, proximity to the vital vascular or biliary structures and the insufficient functional hepatic reserve in cirrhosis [13,14,15]. The applications of interventional techniques to treat HCC hereby have developed rapidly due to the limitations of those two treatment methods.

In this chapter, we will introduce several interventional techniques which were currently been performed worldwide, including: Hepatic Transcatheter Arterial Chemo-embolization (TACE), Arterial Infusion (HAI) with Port Catheter System (PCS), Percutaneous Ethanol Injection (PEI), Percutaneous Thermal Ablation, Cryoablation, Brachytherapy and High Intensity Focused Ultrasound (HIFU). Each technique has its own distinct benefits and differing roles in the treatment of HCC.

**Interventional Techniques**

**Transcatheter Arterial Chemo-Embolization**

Transarterial chemoembolization (TACE) is the current standard of care for patients with large or multinodular hepatocellular carcinoma (HCC), preserved liver function, absence of cancer-related symptoms and no evidence of vascular invasion or extrahepatic spread [16,17]. Transcatheter arterial embolization, as known as TACE, was first performed by Doyon et al. in 1974 [18] and then was introduced into Asia by Yamada et al. in the late 1970s [19,20]. This technique involves the selective occlusion of blood vessels by purposely introducing emboli, in other words deliberately blocking a target blood vessel. With advances in the embolic material and the biological technology, traditional TACE has developed rapidly into chemo-embolization and radio-embolization. Preliminary embolic materials like Gelfoam, lipiodol and the newly merged like drug-eluting beads (DEB) have demonstrated their effectiveness in chemo-embolization. Yttrium-90 and Licartin have shown a promising future in radio-embolization to HCC.

**Chemo-Embolization**

Chemo-embolization is to block the arterial blood supply for nutrients and oxygen in HCC, with the intra-arterial administration of drugs directly to the tumor. The methods of combinations of cytotoxic drugs and physical embolic materials have been quite different due to the natures of the latter.

**Conventional TACE**

Conventional TACE is to use Lipiodol in the process of embolization and injecting cytotoxic drugs. Lipiodol, which is iodinated poppy seed oil, was the first effective embolic material. Experiments have shown that lipiodol adheres to the tumor cell wall and is actively transported into these cells, causing lysis [21]. As an ideal agent for intra-arterial hepatic embolization, lipiodolis viscous and water insoluble, causing temporary occlusion of the capillaries downstream when injected into the artery [22]. And HCC tends to selectively up take lipiodol when infused into a feeding artery, since it is hypervascular [23]. Due to lipiodol is visualized under the fluoroscopy, it is perfect and safe during catheter injections, which can avoid
the nontarget embolization of adjacent arteries (Figure 1). When the emulsified liquid of chemotherapeutics and lipiodol is injected intra-arterially, the combinations are insoluble and separate minutes after embolization [22]. The lipiodol carry the cytotoxic drugs into the tumor due to blood flow characteristics of HCC, and block the feeding arteries.

**Figure 1 (A-D):** CT performed in a 28-year-old HCC patient with rapidly rising alpha-fetoprotein level (>3,000). (A) CT demonstrated a hyperheightened mass on arterial phase (arrows). Biopsy confirmed well-differentiated HCC. (B) Left hepatic artery angiogram demonstrating a well-defined 2.5-cm hypervascular mass correlating to the CT lesion (arrows). Embolization was performed with lipiodol mixed with epirubicin. (C) Left hepatic artery angiogram after embolization demonstrating supply arteries of the tumor were blocked. (D) Non-contrast CT performed 4 weeks postembolization demonstrating preferential lipiodol uptake in the tumor (arrows).

**Figure 2:** Principle of conventional transarterial chemoembolization. Reproduced with the permission from reference [28].

Basically, Lipiodol combines four characteristics that determine its wide use in TACE procedures (Figure 2): (I) it is opaque to X-rays; (II) it can be used for drug delivery purposes, with substantial versatility regarding the therapy that can be delivered (including immune or gene therapies); (III) it has tumor-seeking properties; (IV) it induces a transient and plastic embolization of tumor microvessels [24-27]. This technique could remarkably
increase the local concentration of the chemotherapeutics after chemo-embolization compared with systemic intravenous therapy [23].

**DEB-TACE**

DEB is a relatively novel drug delivery embolization system, comprising biocompatible, nonresorbable PVA polymeric microspheres doped with sulfonyl groups resulting in astatic charge leading to reversible ionic binding with polar molecules such as doxorubicin (Figure 8). Compared with conventional chemoembolization, DEBs presented significant reductions of peak plasma concentration according to previous studies [29,30]. Two particles are currently available in the universal market, DC/LCBeads* (Biocompatibles, UK) and HepaSphere* (BioSphere Medical, Inc., USA), and one in Chinese market, Callispheres* (Suzhou Hengrui Callisyn Biomedical Co., China), that can all be loaded with doxorubicin for the treatment of HCC. DC/LCBeads* and HepaSphere* ionically bind to negatively charged chemotherapeutics, and are most commonly attached to doxorubicin (Figure 3). These beads range from 100 to 1,200μm and have been proven effectively both in vitro and in vivo to slowly elute the doxorubicin up to 7 days after embolization [32]. Callispheres* comprises a range of hydrogel microspheres that are biocompatible, hydrophilic, nonresorbable, precisely calibrated and available in the following size ranges: 70-150μM, 100-300μM, 300-500 μM, 500-700 μM, 700-900 μM, 900-1200 μM.

In comparison to conventional TACE with iodized oil as a drug carrier, numerous studies have examined the clinical efficacy of TACE with drug-loaded microspheres. But the results seemed to be controversial. Several studies showed DEB resulted in a prolonged 5-year survival rate and a higher rate of tumor necrosis and no obvious increased complication rate [33-37]. While other studies have found that DEB have no obvious advantages
compared to iodized oil [38-41]. Surely with the emboli materials technologies progressed, TACE with these microspheres can partially replace conventional TACE with iodized oil as a drug carrier.

Radio-Embolization

External beam irradiation has historically played a limited role in the treatment of HCC due to the radiosensitive nature of normal hepatic tissue. More than 70 Gy radiation exposures in non-cirrhotic liver and 50 Gy in cirrhotic liver may result in a clinico-pathological syndromes like ascites, anicteric hepatomegaly and elevated liver enzymes, developing weeks to months through the following therapy. With the emergence of minimally invasive transarterial radioembolization (TARE), this situation has changed with inspiring result. In 1962, Kim, Lafave and MacLean successfully treated a tumor by local and transarterial injection of colloidal Yttrium 90 (Y-90). And in 2000, metuximab combined with Iodine-131 (Licartin), which was bio-engineered in China, have proved to be effective in HCC treatment. These technology progresses began a new era of local irradiation to treat tumors [42,43].

Yttrium 90

In 1992, Y-90 was first reported to be applied to treat liver cancer [44]. And Yan et al. reported details on the experimental and clinical use of Y-90 glass microspheres to treat HCC [45], creating a new field involving radioactive microspheres.

Y-90 is a pure beta emitter that decays to stable zirconium, which characterized by short half-life (64.2 h) and limited tissue penetration (mean 2.5 mm, maximum 11 mm). This limited tissue penetration allows for local high dose radiation with less risk of radiation induced hepatic necrosis than may be seen with external beam therapy. Two types of microspheres are commercially available, i.e., SIR-Spheres® (Sirtex Medical Limited, Australia), made of glass and TheraSphere® (Biocompatibles, UK), made of resin. SIR-Sphere® consists of biodegradable resin-based microspheres containing 90Y. The average size of a sphere is 35 μm (range, 20-60 μm) in diameter. Each vial contains 3 GBq of 90Y in a 5 mL vial. Each vial contains 40-80 million spheres. TheraSphere® is composed of non-biodegradable glass microspheres ranging from 20 to 30 μm in diameter, in which 90Y is an integral constituent of the glass. One GBq (27 mCi) of 90Y per kilogram of tissue provides a dose of 50 Gy.

The results from consistent, large cohort series involving patients with more advanced HCC, not suitable for other locoregional therapies or who have failed to TACE have proved the clinical efficacy of TARE to HCC patients. Salem et al. [46] performed radioembolization in 123 patients, compared with 122 subjects who had received TACE: overall, median time to progression was longer after radioembolization and TARE had showed similar adverse events with TACE. Other results have been reported [47-50] presenting consistent and similar results, lower incidence of adverse events and need for hospitalization when compared with conventional TACE.
Licartin

Metuximab combined with Iodine-131 was a recombinant humanized monoclonal antibody targeting specific to HCC tumor cells with radionuclide [51]. In-vivo research have demonstrated after 12h injection, Licartin mainly accumulated in tumor lesion, normal liver tissue, bladder, and showed no visualization of distribution in other important organs like heart, spleen and kidneys [52]. In combination of TACE, Licartin had proved to be high clinical efficacy in tumor size shrinkage, serum AFP levels, quality of life and overall survival rate with rare damages to liver and kidney functions [53-56].

HAI with PCS

Implanted port catheter systems (PCS) for hepatic arterial infusion of chemotherapy was first reported in patients with colorectal liver metastases [57]. When all the interventional techniques introduced above are not suitable for end-stage liver cancers patients due to their progressing liver failure, hepatic arterial infusion (HAI) with PCS seems to be an alternative. Yata Y et al. reported [58]: hepatic arterial infusion (HAI) with PCS, low-dose 5-FU and CDDP was performed for a patient with rapidly progressing HCC, treated with 3 courses of low-dose FP, and the diffuse-type HCC was completely diminished. No recurrence was seen 22 months after chemotherapy.

Hepatic arterial infusion (HAI) is a medical procedure to deliver chemotherapy to the liver through arteries. Port catheter system (PCS) consists of a reservoir compartment (the portal) that has a silicone bubble for needle insertion (the septum), with an attached plastic tube (the catheter). The device is surgically inserted under the skin in the upper chest or in the arm and appears as a bump under the skin. Catheters are usually put into subclavian artery or groin, and placed in the proper hepatic artery, drugs are given through the catheters directly to the liver. Since 2012, we have performed 12 cases with progressing HCC, which are contradicted to TACE, 8 cases showed promising results (CR:3, PR:3, SD:2) (Figure 4).

Figure 4 (A-B): PCS was performed in a 59 year-old HCC patient. (A) Catheter was implanted through subclavian artery into properhepatic artery. (B) Catheter angiogram after implantation demonstrating the visualization of left and right hepatic arteries.

Percutaneous Ethanol Injection

In the early 1990s, percutaneous ethanol injection (PEI) under image guidance was considered the primary percutaneous treatment for HCC with cirrhosis, before RFA was introduced. The theory as to its efficacy is based on the fact that the tumors tend to be soft and the sur-
rounding liver tissue is cirrhotic and hard, which restricts the alcohol from diffusing out into the liver. In addition, there is often a capsule around small, well-differentiated HCC tumors [69]. Since the materials used for PEI are inexpensive, and the procedures are straightforward and mini-invasive, this procedure was quite popular in the world. The volume of ethanol to be injected is determined by calculating the volume of the tumor. But the complication rates and the need of operators’ plentiful experience restricted its widely accepted. Another reason of its limited use is that it often requires more than four treatments to treat each mass, even with tumors < 3 cm [59].

**Percutaneous Thermal Ablation**

**RFA**

Eighty years ago, William T. Bovie, who invented the Bovie electro-surgical device, first introduced radiofrequency ablation technology into clinical application. In 1996, Rossi et al first reported that RFA as a new treatment of liver cancer. In recent years, image-guided radiofrequency ablation is now accepted as a curative treatment for early-stage HCC [60-64]. Imaging-guidance tools, which incorporate MRI, CT-scan or ultrasonography are used for probe guidance.

Coagulative necrosis of the tumor using electrical heating around a probe generating electromagnetic radiation occurs after RFA (Figure 5) [65-67]. The necrosis area is dependent on the maximum temperature and the ablation time. Immediate cell death can be caused by a temperature of 50° or higher, however, less temperatures will also cause lysis after a longer periods of time application [68,69]. Around the ablation area, heat-induced cell necrosis releases many immunogenic intracellular substrates. Heat shock protein (HSP) was the most important RFA-induction, and HSP70 palys a key role in stimulating the anti-tumor immune response. Furthermore, an elevated serum level of HSP70 in patients after RFA correlates with improved survival [70,71].

![Figure 5 (A-B): RFA was performed for a HCC patient with massive tumor. (A) tumor enhancement was observed in dynamic CT scan. (B)CT scan after 4 weeks of RFA, a hypovascular area and complete vanishing of the enhancement were showed after 10 min RFA.](image-url)

Contraindications of RFA for HCC are a platelet count less than 50000, refractory ascites, hemostasis disturbances, jaundice and pacemaker installed. Relative contraindications are tumors near the hollow organs, such as...
gastrointestinal tract and biliary system [72]. For tumors near the hilum there is a risk of biliary tract or vascular injury and for lesions which are located within 1 cm of the hepatic portal tract, RFA should be avoided. The major complications of RFA are liver failure, abscess, hemorrhage, pneumothorax, intercostal nerve injury, infection, tumor lysis syndrome and adjacent organ injury [54,73].

According to the recent Barcelona Clinic Liver Cancer treatment strategy, RFA is highly recommended as a first-line therapy alternative to resection when patient with a small HCC measuring less than 2 cm in diameter [60]. Meantime, complete response rates of HCC (< 3.5 cm) after RFA have approached 70%, which had been confirmed by subsequent surgical resection or explantation of the treated liver [74-77]. In a randomized trial of RFA vs. surgical resection in patients with a solitary HCC measuring less than 5 cm in diameter, no differences in the overall survival rates and cumulative recurrence-free survival rates were observed [77]. Therefore, the studies above demonstrate that RFA could be an efficient management for local ablation in small HCCs when surgery or transplantation is not an option. Nowadays, combined approaches including TACE and RFA have been used to increase the efficacy of RFA in the treatment of HCC tumors of intermediate or large size [78].

**WMA**

Microwave ablation is a heat-based thermal ablation therapy, it can generate very high temperatures in a short time and produce a coagulation area that provides reliable ablation for HCC. Currently available MWA systems function at 915 MHz or 2.45 GHz frequencies [79]. The MWA antennae are needle-like, it can transmit microwave from the magnetron into the tumor tissue. Compared with RFA, MWA can lead to larger ablation zones and improved treatment efficiency because of its less heat-sink effects [80]. Because of its convenient and real-time imaging, Ultrasound is the most commonly applied. Meantime, CT and MR guidance can be useful for the treatment of HCC which is invisible on ultrasound (Figure 6).

![Figure 6 (A-B): (A)tumor was observed in Ultronosography; (B) a MWA antennae was inserted into the tumor by the Ultrasonography guided. (C)a complete ablation area was confirmed by the contrast-enhanced ultrasound after 15 min.](image-url)
receive its due attention in Western countries. RFA currents are the most used in worldwide, while MWA are becoming increasingly popular, especially in China. Nowadays, this technology has been more popular because of its potential benefits. MWA is aimed to treat patients with tumors or unresectable HCC. Firstly, MWA was limited for the management for small HCC measuring less than 2 cm in diameter. However, with the improvement of antenna and ablation strategy, large HCC which measuring more than 5 cm in diameter can also be ablated effectively [81-85].

Dong et al [83] reported the long-term results of 339 HCC nodules with a mean size of 4.1 ± 1.9 cm treated with MWA. After a mean follow-up period of 27.9 month, the 1-, 3- and 5-year cumulative survival rates were 92.70%, 72.85%, and 56.70%, respectively. Liang et al [86] reported 288 patients with 477 tumors that received MWA treatment, the 1-, 2-, 3-, 4- and 5-year cumulative survival rates were 93, 82, 72, 63 and 51%, respectively. Local tumor regression was observed in 8% of the patients. Compared to RFA, the result showed similar effectiveness and survival in the treatment of small HCC nodules. But for the ‘curative’ treatment of HCC, the following criteria need to be met: single HCC lesion of 6 cm or smaller: three or fewer multiple HCC lesions with a maximum diameter of 4 cm or less, and absence of portal vein thrombosis or extrahepatic metastases [87].

The major complications of MWA, similar to RFA, include bile duct stenosis, uncontrollable bleeding, intercostal nerve injury, infection, liver abscess, colon perforation and skin burn, etc. [83,88]. Currently, as the time goes on and the technology evolves, MWA is emerging as a valuable alternative to RFA in the treatment of hepatic carcinoma [89,90].

**Cryoablation**

Cryoablation technology uses physical properties of argon gas to reach temperatures far below freezing and create tumor tissue injury. The temperature drops to −160 °C and an iceball forms at the tip of the cryoprobe after high-pressure argon gas is circulated through the lumen of the probe (Figure 7,8). The ice ball is thawed when helium gas is circulated through the probe lumen. This freezing and thawing process induces direct and indirect cell damage, causing tumor cell death. When the temperature drops during the freezing process, ice crystals form inside and outside the cell, osmotic pressure increases inside the cell, cell dehydration occurs, and the cell membrane is damaged [91]. Cell death has been confirmed that at the temperatures of −20°C or after rapid freeze and slow thaw cycles at higher temperatures by vitro and vivo studies over the past 50 years [92]. Cryoablation probes are needle-shaped, large kill zones are not possible with a single probe. Therefore, more probes are required when the large tumor need to be treated by cryoablation. Each additional probe increases procedure time and the risk of organ injury and bleeding [93].
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Figure 7 (A-B): (A) enhanced MRI demonstrates hypointense mass (arrow); (B) ablation zone was demonstrated by CT immediately after cryoablation.

Figure 8 (A-B): (A) enhanced CT demonstrates hypointense mass (arrow); (B) ablation zone was demonstrated by CT 2 month after cryoablation.

Heat sink, need considered in all the thermal ablation, can allow tumors that are adjacent to large vessels to remain outside the kill temperature. Compared with RFA, cryoablation has a lesser heat-sink effect, and permits precise evaluation of the ablation zone by the “ice ball” which allows for real-time visualization [94,95]. Cryoablation also causes less pain and often allows to be performed without anesthesia [96].

In 2003, Xu et al. [97] reported that 65 patients with HCC received percutaneous cryoablation. After one year follow-up, 32 (78%) were alive despite tumor recurrence, seven patients (10.8%) died because of disease recurrence, and three patients (5%) died of non-cancer–related diseases. Wang et al. [98] reported three hundred HCC patients, all the patients were treated with percutaneous argon-helium cryoablation under ultrasound guidance, and the mean survival of early-, intermediate-, and advanced-stage patients was 38.7 ± 3.8, 26.5 ± 4.2, and 16.9 ± 1.4, respectively. A meta-analysis of cryoablation versus RFA for hepatic malignancies shows that there were no statistically significant difference in mortality of at least six months and local tumor progression between the two group of patients. However, we need to pay attention that the risk of complications was significantly higher in the cryoablation group than that in the RFA group [99].

The major complication of cryoablation include hypothermia, bile fistula and collections, hemorrhage, cryo-shock, liver capsular cracking, asymptomatic right-side pleural effusion, liver abscess and transient thrombocytopenia [100]. Among the above complication, cryoshock is a rare syndrome of multiorgan failure, coagulopathy, and disseminated intravascular coagulation (DIC). It is specif-
ic to cryotherapy in the liver with large-volume ablations [101,102].

**Brachytherapy**

The I-125 seeds were the most widely used in clinical application. The most common seeds (diameter: 0.8 mm, length: 4.5 mm) were enclosed in a 0.05 mm thick titanium alloy. The activity of the I-125 seeds used for implantation was in the range of 0.5-0.8 millicuries (mCi) per seed, and the half-life was 59.4-60.2 days. The mean energy of each seed was 27.4–35.5 keV, with a tissue penetration of 17 mm [103-105]. Brachytherapy is the implantation of radioactive seeds into tumors to impart high-dose irradiation to the tumors, and the treatment is a precise method of radiotherapy that has been extensively used for treating prostate cancer [106]. Studies were reported that the treatment of malignant hepatic tumors using brachytherapy lead to good efficacy [107,108].

CT-scan, ultrasonography or MRI can be used as imaging guiding device. I-125 implantation in the treatment of liver cancer, which is brachytherapy, it has many advantages compared with external radiation therapy. Firstly, the whole liver tolerated dose is 30 Gy [109], which limit the dose of external radiation therapy. However, the cumulative dose can reach up to 140 Gy in gross tumor volume (GTV). Secondly, compared with short fractionated irradiation of external radiation therapy, tumor cells can be continuous acted on by I-125 seed and arrested in G2/M phase. Therefore, tumor cells lost the reproductive ability. Lastly, radioactive seeds can make less damage to surrounding tissues and organs.

Usually, I-125 seeds implantation combined with TACE were used to treat hepatic tumors, which contain primary tumor and liver metastases. Song et al [110] reported the survival rate of 12 months was 72.0% (18/25), 43.3% (13/30) in group of I-125 seeds implantation combined with TACE and control group, respectively (X² = 4.556, P=0.033). Nag et al [108] recruited 64 patients with unresectable or residual disease after surgical resection for intrahepatic malignancies under I-125 seeds implantation between 1989-2002. The overall 1-year, 3-year, and 5-year actuarial intrahepatic local control rates were 44%, 22%, and 22%, respectively, with a median time to liver recurrence of 9months (95% CI, 6–12 months). Portal vein thrombosis (PVT) is the main factor leading to liver metastasis and relapse after treatment, it is also an important prognostic factor. However, the effects of traditional surgery, external radiation therapy and chemotherapy for PVT are poor. Brachytherapy has been used in PVT treatment (Figure 9). In a randomized controlled trial for PVT treatment, the group of I-125 seeds combined with TACE was 88.5% and the median survival time was up to 210.0 ± 17.5 d. The overall 3-month, 6-month, and 12-month cumulative survival rate was 97.6%, 58.9% and 12.3%, respectively. The study showed that the efficacy of I-125 seeds combined with TACE was better than the group of received RFA only [112].
Figure 9: PVT was confirmed by enhanced-CT when the patient received TACE one month later, I-125 seeds implantation were conducted in the CT-guided.

Although the benefits of brachytherapy are apparent, concern about bleeding from needle insertion into a vascular organ has limited the use of radioactive seed implantation in the liver. However, studies show that radiation-related complications were minimal [112,113].

**HIFU**

High-intensity focused ultrasound (HIFU) is a non-invasive treatment that uses an extracorporeal source of focused ultrasound energy. The ultrasound beams are focused by spherical arrangement using an acoustic lens or parabolic reflectors into a small, discrete region that corresponds to the focal point. Thermal and mechanical effects are the main mechanisms of HIFU. By the thermal effect, the temperature of local tissue could be risen to higher than 60°C. The mechanical effects include micro-streaming, radiation force and cavitation. In brief, the mechanisms above lead to cell destruction and coagulation necrosis via a combination of mechanical stress and thermal injury (Figure 10).

Figure 10 (A-B): (A) a tumor enhancement was confirmed in dynamic CT scan. (B) complete necrosis of tumor was demonstrated after HIFU ablation 3 months later.

Use of focused ultrasound was introduced by Lynn et al in 1942 [114]. In the 1970s, therapeutic ultrasound was firstly used to treat cancer [115]. Nowadays, HIFU is used to treat a variety of tumors and palliative care, just like breast, brain, liver, prostate and bone. Vallancien et al. was the first to report the use of therapeutic ultrasound for the
liver [116]. In liver tumor, unresectable, advanced stages of hepatocellular carcinoma or for the treatment of liver metastases can be treated by HIFU.

Clinical HIFU are generally conjunction with magnetic resonance imaging or ultrasound imaging as image guidance and treatment monitoring. Ng KK et al [117] reported a study which involved 49 patients receiving a session of HIFU for unresectable HCC showed that the treatment effectiveness rate was 79.5%. Wu et al. [118] reported 474 patients with primary and metastatic liver tumor by HIFU treatment, the median survival time were 13.4 months. Pathological examination revealed that both tumor cells and tumor vessels presented a typical appearance of coagulative necrosis with severe nuclear damage. Another study include 116 primary liver cancer and 71 metastatic liver cancer cases who were treated with HIFU shows that complete response and partial response were 55 patients (29.4%) and 73 patients (39.0 %), respectively. HIFU is feasible in liver cancer treatment and the efficiency of HIFU ablation may be improved by repeated treatment or increasing treatment times [119].

The complications of HIFU ablation for patients with hepatic tumor include biliary obstruction, pleural effusion, pneumothorax, fistula formation, diaphragmatic rupture and rib fracture [120]. No large blood vessel injury was observed among the tumors [121] and no severe complications occurred during and after HIFU for patients with advanced hepatocellular carcinoma [122].

HIFU has been well demonstrated to be an effective ablation modality which is non-invasive. And it has been concluded that HIFU is a safe ablation therapy. However, there are many challenges for extracorporeal ablation of liver tissue by HIFU, including respiratory movement of the liver, beam propagation through the ribs, and long ablation times due to huge tumors [123,124].

**Conclusion**

Interventional technologies have been effective alternatives for the patients which were not qualified for liver resection or transplantation. Each method introduced above has its own features and limits, and plays its own distinct role in the treatment to HCC.

TACE is currently the most popular neo-adjuvant treatment option for patients with HCCs [126-128]. Several randomized studies have compared conventional TACE to conservative management in HCC patients not candidate to curative options, and when analysed together in a meta-analysis, TACE demonstrated a significant superiority in terms of survival [129]. Also, TACE, such as conventional, DEB and radioembolization could be performed upon larger tumors than RFA and may simplify treatment of patients with multiple tumors. The main risks of TACE are linked to the ischemic insults of the embolisation. Patients with large lesions may develop a post embolisation syndrome due to tumour necrosis, with fever and abdominal pain. When a large area of liver parenchyma
has been embolised, patients are also exposed to the risk of liver failure and TACE should as a rule not be attempted in patients with decreased liver function (Child–Pugh C), except when an hyper selective TACE can be offered by expert hands. Finally, this procedure includes a small risk of arterial injury, estimated at 2% [130]. Another limitation is linked to the poor uptake of dye by hypovascular HCCs and these lesions may be better treated with RFA. For those who presented contradiction to TACE with progressing HCC, HAI with PCS was another option worth trying.

PEI was primary percutaneous treatment for HCC with cirrhosis, and now was almost replaced by percutaneous thermal ablation, i.e., RFA, WMA. The latter has proven to be as effective as resection in tumors < 5 cm and offers favorable results for tumors < 7 cm for patients without other treatment options. Complications from RFA are reported to be approximately 7% [131]. The most common complication is hemorrhage, but major hemorrhage requiring transfusion occurs in < 1% of cases. Other risks include injury to the liver, abscess (1%), pneumothorax (< 1%), and biliary injury (< 1%). These risks compare favorably to surgical resection, which has reported complication risks of 9% to 22% [132]. Cryoablation seems to present similar tumor responses compared with RFA, but the issue of increased complications needs attention with a comparative study. Due to limited radioactive range, brachytherapy could precisely kill the tumor cell with high dose of irradiation, and without damaging liver function.

HIFU is a novel technology that enables transcutaneous ablation effect without needle puncture [133,134]. While controlling the energy and focusing of US, successful HIFU results in necrosis of the tumor in the focal area with less damage of surrounding tissues. As some studies [118,133] showed insufficient ablation effects were observed, it remains to be solved whether HIFU is valuable as a reliable method for curative treatment of small HCC. Nonetheless, this non-invasive method is really expected to be used for HCC treatment, as an alternative to PEI or RFA.

Combination therapies with thermal ablation and conventional TACE have presented further increases survival rates in patients with HCC [135-139]. Improved tumor response appears to be helpful in prolonging the lives of patients, improving their lives qualities. Tailored treatment for each patient is required to prevent progression of disease in liver transplant candidates and to prolong survival in nontransplant candidates. The role of “interventional technologies” in the treatment to HCC is rapidly developing as to the high incidence of HCC all around the world and will continue to grow with knowledge increasing and technologies evolving.
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