Image-guided minimally invasive treatment of liver tumors

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Abbreviations

AJCC	-	American Joint Committee on Cancer
BCLC	-	Barcelona-clinic Liver Cancer
CLIP	-	Cancer of the Liver Italian Program
CUPI	-	Chinese University Prognostic Index
CT	-	Computer Tomography
cTACE	-	conventional transarterial chemoembolization
DEB	-	Drug-eluting beads
EM	-	Electromagnetic
EASL-EORTC	-	European Association for the Study of the Liver, European Organisation for Research and Treatment of Cancer
HVPT	-	Hepatic venous pressure gradient
HCC	-	Hepatocellular Carcinoma
HIFU	-	High-intensity focused Ultrasound
LA	-	Laser ablation
MR	-	Magnetic resonance
MWA	-	Microwave ablation
Nd-YAG	-	Neodymium-doped yttrium aluminium garnet laser
OLT	-	Orthotopic liver transplantation
OS	-	Overall survival
PEI	-	Percutaneous ethanol injection
PVA	-	Polyvinyl alcohol
PVT	-	Portal vein thrombosis
RFA	-	Radiofrequency ablation
TAE	-	Transarterial bland embolization
TACE	-	Transarterial Chemoembolization
TARE	-	Transarterial Radioembolization
US	-	Ultrasound
UNOS	-	United Network for Organ Sharing

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Summary

Hepatocellular carcinoma (HCC) is the 6th most common cause of cancer worldwide and contributes to 9% of the global mortality burden attributed to cancer. The limited options of classic systemic cancer therapies, the strict criteria for surgical resection and the global shortage of donor organs for transplantation have led to a search for alternative treatment modalities. Local image-guided, minimally invasive therapies have successfully filled the gap as therapeutic options for HCC, establishing themselves in practice guidelines across the world. Image-guided, minimally invasive therapies encompass local ablative modalities including Radiofrequency ablation (RFA), Cryotherapy, Microwave ablation (MWA), Laser ablation (LA) and High-intensity focused Ultrasound (HIFU) as well as intra-arterial treatment modalities such as transarterial chemoembolization (TACE), transarterial bland embolization (TAE) and transarterial radioembolization (TARE). Both ablative and transarterial therapies have revolutionized the management of HCC. This review article highlights some of the technical aspects of these therapies and provides up to date scientific evidence for their clinical use.

Naziv: Minimalno invazivno liječenje tumora jetre navođeno metodama slikovne dijagnostice.

Autor: Christopher Lambers

Sažetak

Hepatocelularni karcinom (HCC) je 6. po redu najčešći uzrok raka u svijetu i doprinosi do 9% globalnog tereta smrtnosti koja se pripisuje raku. Ograničene opcije klasičnih sistemskih terapija protiv raka, strogi kriteriji kirurških resekcija i globalni nedostatak donora organa za transplantaciju su doveli do potrage za alternativnim načinima liječenja. Lokalne minimalno invazivne terapije navođene slikom su uspješno ispunile prazninu u opcijama liječenja HCC, uspostavivši se u smjernicama za liječenje diljem svijeta. Minimalno invazivne terapije navođene slikom obuhvaćaju lokalne modalitete ablacije uključujući radiofrekventnu ablaciju (RFA), krioterapiju, mikrovalnu ablaciju (MWA), ablaciju laserom (LA) i ultrazvuk visokog intenziteta (HIFU) uz, također, intra-arterijske metode liječenja kao što su transarterijska kemoembolizacija (TACE), transarterijska bland embolizacija (TAE) i transarterijska radioembolizacija (TARE). Ablacijsko i transarterijsko liječenje su oba revolucionarizirali vođenje HCC. Ovaj pregledni članak naglašava neke od tehničkih aspetaka tih terapija i pruža najnovije znanstvene dokaze za njihovo kliničko korištenje.

1. Introduction

With increasing incidence in many parts of the world, liver cancer continues to be a major contributor to the global burden of disease in the 21st century.

Liver cancer makes up 6% of the global cancer incidence and 9% of the global mortality burden attributed to cancer. According to the WHO World Cancer Report, with an estimated 746,000 deaths in 2012, liver cancer is the second most common cause of cancer-related death, overshadowed only by lung cancer (1).

Hepatocellular carcinoma (HCC) is by far the most common primary liver cancer, encompassing 80% of all primary liver cancers and representing the 6th most common cancer worldwide, with an estimated 554,000 and 228,000 new cases in 2012 in men and women, respectively.

To this day, major risk factors for the development of HCC are chronic Hepatitis B and C infection as well as chronic fatty liver disease associated with long-term alcohol consumption. Additionally, non-alcoholic fatty liver disease associated with metabolic syndrome has come into focus in relation to its synergistic contribution to the development of HCC (2).

Despite the fact that the lowest rates are documented in North and South America and Northern Europe (10 in 100,000), an increase in HCV incidence has resulted in an increase in HCC in these regions. Furthermore, the increasingly apparent importance of metabolic syndrome and the increasingly significant rates of obesity and diabetes may contribute to this trend.

Conversely, countries in South-east Asia, a region with some of the highest rates of HCC (20 in 100,000), have seen a decline in incidence. Contributors to this decline are an overall decrease in aflatoxin exposure, a major synergist in HBV infection, as well as successful vaccination and treatment attempts for HBV (3). A 2009 cohort study published in Taiwan reported a significantly lower incidence of HCC when comparing vaccinated and unvaccinated children (4).

The staging of cancer is necessary, as it serves a multitude of variables and goals, from accurately estimating prognosis and survival rate to recommending appropriate primary and adjuvant intervention. HCC is of particular interest with regard to tumor staging, as it not only emcompasses the malignant potential of the tumor and its extension, but also the presence of underlying cirrhosis, which is predictive of treatment efficacy and applicability. Currently there are eight different staging systems used to depict the state of the primary tumor and predict the outcome of intervention, none of which currently have universal acceptance.

Conventional systems, like the TNM staging that primarily focuses on variables related to tumor characteristics, have shown to be of poor predictive value in HCC patients undergoing surgical

treatment, in part because they do not take underlying hepatic function into account. In response, adjustments to the system have been made by proposing the introduction of a fourth stage, which indicates presence or absence of fibrosis. The TNM staging has since been endorsed by the American Joint Committee on Cancer (AJCC). Staging systems and scores like the Okuda staging system, the Chinese University Prognostic Index (CUPI) score, and the French classification have all been called into question due to the fact that all three lack a level of discrimination for early stages of HCC and therefore are of limited prognostic value for pre-advanced stage cancers. The Cancer of the Liver Italian Program (CLIP) Score has proven to be of a higher discriminatory value, but is limited in that it does not recommend appropriate therapy based on its scoring (5).

The Barcelona-Clinic Liver Cancer (BCLC) classification, officially endorsed by the European Association for the Study of the Liver and the European Organisation for Research and Treatment of Cancer (EASL–EORTC), accounts for variables regarding tumor status (size, number, invasion, N1, M1), liver function status (Child-Pugh's) and health status (ECOG) (6). By classifying HCC patients into five stages (0, A, B, C, D) it further allocates recommended treatment options to each stage. Research has shown BCLC to be superior in differentiating early-stage HCCs while recommending appropriate interventions including resection, orthotopic liver transplantation (OLT), and local ablation. Additionally, its variables include presence or absence of portal vein thrombosis (PVT), which, according to research, has shown decreased survival probability independently of other prognostic factors as it suggests vascular invasion. Lastly, particularly with regards to early-stage HCC, BCLC serves as a more detailed predictor of survival when compared to scoring systems such as CLIP or the Okuda staging system (7).

One of the prerequisites for a precise staging system for HCC, aside from the multiplicity of influencing factors such as cirrhosis or portal vein hypertension, is the lack of successful systemic chemotherapy or hormone therapy. No systemic therapy has thus far proven effective in demonstrating improved survival in HCC, with the exception of Sorafenib, an oral multi-tyrosine kinase inhibitor. Clinical trials have proven Sorafenib to increase overall survival (OS) rate by nearly three months in patients with advanced HCC. However, given the fact that patients have largely been chosen with well-preserved liver function (Child-Pugh class A), it is to be expected that in patients with more advanced liver failure (Child-Pugh class B, C) results would be significantly poorer (8). Therefore, Sorafenib is accepted as standard systemic therapy for advanced HCC (BCLC C), only in cases of Child-Pugh class A (6). Other attempts of systemic treatment for HCC with Brivanib or Everolimus have demonstrated no improvement over Sorafenib (9,10).

According to the clinical practice guidelines published by the EASL-EORTC, the main treatment of choice for solitary tumors with well-preserved liver function remains hepatic resection, which has an

estimated 5-year survival rate of 60-80%. Following the BCLC classification, the main indicators for surgical resection are single <2 cm HCC or carcinoma in situ (BCLC stage 0), with additional considerations in patients with multifocal tumors meeting the Milan criteria (≤3 nodules ≤3 cm) who are not suited for liver transplantation (6). Research has shown 5-year survival drops significantly with increased size of the primary tumor (66%, 52% and 37% for tumors ≤2 cm, 2-5 cm and >5cm, respectively) (11). Furthermore, multiple tumor resection has, until now, carried a considerably lower 5-year survival rate compared to single-tumor resection. However, newer research shows comparable survival rates in patients with multiple tumors and preserved liver function undergoing surgical resection, indicating that the main reason for contraindication to resection in these cases is higher recurrence rates (exceeding 70% at 5 years) (12). The assessment of liver functional reserve has of late shifted from the rather crude Child-Pugh classification to more detailed and refined procedures involving indocyanine green retention rate at 15 min or hepatic venous pressure gradient (HVPG) (13). Platelet count, however, remains the most accessible parameter when assessing HVPG. In reality, using proper selection criteria of patients with HVPG <10 mmHg or platelet count of <100,000/mm³ yields an overall rate of fewer than 10% of HCC patients eligible for resection.

Recommendations have been set to perform anatomical resections according to Couinaud with tumor margins of 2cm as this method has proven to yield better survival compared to narrow-margin resections of <1 cm. Narrow-margin resections should only be considered if a wide-margin resection is not advisable, either due to anatomic location or the severity of underlying cirrhosis (14).

As one of the major challenges in surgical resection remains the high incidence of tumor recurrence, attempts have been made to use Interferon as adjuvant therapy. However, research has not shown universally successful adjuvant therapy for HCC undergoing resection, with the exception of subgroups in which late-recurrences could be significantly reduced (15).

Following the BCLC guidelines, the second type of surgical intervention for HCC is liver transplantation. In line with the Milan Criteria, first introduced in 1996 by Mazzaferro et al., liver transplantation is indicated for either ≤3 nodules ≤3 cm, or single tumors ≤5 cm with advanced liver dysfunction (16). Still in use today, the Milan Criteria is recognised as a separate prognostic category, demonstrating favourable outcome after liver transplantation, resulting in a 5-year survival rate of 70% (17). However, the use of neoadjuvant therapy in liver transplantation has been the cause of further debate. With the current shortage of donors and consequent longer waiting time, an estimated 20% of HCC patients will drop out of the waiting list before receiving a liver transplant (6,18). The strategy behind the introduction of neoadjuvant therapy is to prevent disease progression and reduce wait-list dropouts. The choice of therapy depends on the degree of tumor invasion but all options involve a type of minimally invasive image-guided technique.

Aside from preventing disease progression, another implementation of neo-adjuvant therapy is based on the principle of downstaging: using local ablation or chemoembolization in HCC in order to fulfill the Milan Criteria for liver transplantation. Despite a few small promising prospective studies, there is an overall lack of large, well-designed research in this field (19,20). The EASL-EORTC panel does, however, recommend adopting downstaging interventions in specific cases, such as in HCC patients who have progressed beyond the Milan Criteria while awaiting liver transplantation (6).

The fourth and final treatment modality of HCC as outlined in the BCLC staging system is a number of local, image-guided, minimally invasive therapies. These techniques can be divided into tumor-ablative and image-guided, catheter based treatment modalities. The former technique uses either thermal or chemical destruction. Thermal ablation includes procedures such as radiofrequency, cryotherapy, microwave, laser, or high-intensity focused ultrasound ablation. Chemical ablation involves percutaneous injection of ethanol into the tumor. As indicated by the BCLC staging, tumor-ablative therapies are modalities mainly aimed at early-stage HCC, whereas image-guided catheter based intervention delivering embolic, chemoembolic, or radio-embolic agents intra-arterially are primarily indicated for intermediate-stage HCC.

The introduction of minimally invasive, image-guided therapeutic modalities has revolutionized the treatment of HCC. This review will provide an overview of all employed procedures and evaluate their scientific evidence and clinical use.

2. Tumor-ablation techniques

2.1 Chemical ablation

Introduced in the 1980s, percutaneous ethanol injection (PEI) is one of the oldest and most established loco-regional therapies for HCC (21,22). Despite advances in thermal ablation techniques, PEI is still included in the recommended treatment modalities for early stage HCC (BCLC 0, A) and is not suitable for surgery (6).

It is believed that injection of 95% ethanol into the primary tumor under US or CT guidance results in immediate dehydration of the neoplastic cells and denaturation of cellular proteins, ultimately culminating in coagulative necrosis. Additionally, local vascular thrombosis, the result of either endothelial damage due to the ethanol itself or due to the surrounding necrotic cells, may contribute to tumor destruction through ischemic tissue necrosis (23,24). Initial success rate of PEI for single

nodule HCC approaches 100% for nodules <2 cm, followed by 70% and 50% in nodules <3 cm and <5 cm, respectively (25). However, randomised control trials have shown PEI to require more sessions in order to achieve full tumor necrosis, with subsequent longer hospitalisation when compared to other local ablative therapies like radiofrequency ablation (RFA),(26,27). Overall 3, 5 and 7-year survival rates for HCC <3 cm are comparable across several studies, measuring 78%, 54% and 28%, respectively (28–30). The therapeutic effect of PEI has been shown to be largely dependant on tumor size, with frequency of microscopic portal invasion being significantly higher in HCC size 16-20mm (40%) compared to HCC size 11-15mm (25%) (31). As indicated in the previous discussion on the introduction of the BCLC scoring system, another major contributor to OS in HCC patients treated with PEI is liver function. Shiina et al. reported a significant decrease in survival rates with increased level of liver dysfunction (Child-Pugh class A-C). 3 and 5-year survival rates declined from 77% and 58% in Child-Pugh class A, to 54% and 36% in class B and 38% and 19% in Child-Pugh class C (32). However, the major pitfall for PEI in treatment of HCC is comparatively high recurrence rates. While there is no significant difference in *de novo* HCC development and extrahepatic metastasis incidence when comparing PEI and RFA, local recurrence rates are significantly higher in PEI. Several studies have reported cumulative local recurrence rates at 2 and 3 years between 16-23% and 34-45% (27,33). Shuichiro et al. reported an 88% smaller risk of local tumor progression in RFA compared to PEI (26). Nonetheless, with its low treatment costs and its comparable success rate for small HCC nodules <2 cm, PEI remains part of the standard care for patients with BCLC 0-A tumors not suitable for surgical resection (6). Furthermore, studies focusing on the recent introduction of multi-pronged needles with three retractable prongs, reporting successful eradication of HCC up to 5 cm in only 1-2 treatment sessions, demonstrate that PEI may still play an important role in HCC therapy in the future (34).

2.2 Radiofrequency ablation

nducing coagulative necrosis with the introduction of a local electric current, RFA is the most widely-used thermal ablative technique to date. During the procedure, a small electrode is introduced into the primary tumor percutaneously, laparoscopically, or via laparotomy. While running a high-frequency alternating current through the electrode, ionic movement in the adjacent tissue results in frictional heating and irreversible cellular injury at temperatures around 50° C. Following the procedure, the damaged tissue undergoes apoptosis resulting in the coagulative necrosis of the tumor cells (35). The efficiency of the treatment is ultimately limited by an increasing circuit impedance, as a result of tissue dehydration through water vaporization. A number of additional modalities have

been introduced in order to slow development of circuit impedance. These modalities include larger surface area of the electrode through multi-tined electrodes, pulsating power, and injections of saline (36). A major limiting factor to RFA is the "heat sink" effect, in which thermal ablative effects are dissipated due to local blood flow in vessels of at least 3 mm in diameter, thereby limiting its efficacy particularly near the liver hilum (37). RFA has proven effective in the treatment of small HCC tumors <3 cm in very early-stage and early stage disease (BCLC 0-A) and is recommended as the main ablative therapy in tumors <5 cm (6).

Despite recommendations outlined by the BCLC scoring system of prioritising surgical resection over RFA, recent studies have shown comparable results with regard to OS. In a randomized controlled trial, Lu et al. concluded 3-year survival outcome of RFA to be equivalent to surgical resection (38). Furthermore, Feng et al. reported no statistical difference in overall and recurrence free survival when comparing RFA and surgical resection in patients with hepatocellular nodules of <4 cm (39). This conclusion was further supported by a meta-analysis of 4 randomised controlled trials comparing RFA with surgical resection between 1990 and 2010, describing no statistically significant difference in OS between the two treatment modalities (40). Finally, Livraghi et al. concluded in their retrospective cohort study that RFA can be a treatment of choice for patients with tumors ≤2 cm, despite primarily being surgical candidates (41).

One of the inherent benefits of ablative treatment modalities like RFA is the minimally invasive nature of the procedure and the associated low incidence of complications. Based on their extensive literature review encompassing publications from January 1990 to December 2001, Mulier et al. reported of a mortality rate of 0.5% and an 8.9% incidence of major complications, concluding that the morbidity and mortality rates associated with RFA are higher than previously assumed (42). However, more recent research by Livraghi et al., Giorgio et al. and Chen et al. report rates as low as 0.9% to 5.2% for major complications, as well as mortality rates of 0.3% (43–45). The most common major complications include peritoneal hemorrhage, intra-abdominal infections ranging from hepatic abscess to sepsis, biliary tract damage, hepatic decompensation and neoplastic seeding (46). Needle-track seeding in particular has gathered much attention. In 2001, Llovet et al. demonstrated biopsy-proven needle-track seeding in 12.5% of their 32 patients (47). In line with their observations, a more recent study by Snoeren et al. confirmed viable tumor cells adherent to needle applicators after ablation in 26.7% of patients, concluding that a major independent risk factor is failure to perform track ablation (48). However, several researchers found the incidence of needle-track seeding to be much lower. Jaskolka et al. reported an incidence rate of 4%, Imamura et al. of 3.2% and Livraghi as low as 0.9% (49,50). Specific risk factors reported included poor degree of differentiation of the primary tumor, needle biopsy performed previous to RFA intervention, subcapsular location, as well as multiple sessions and lesions requiring multiple electrodes (49).

2.3 Cryoablation

Unlike the process of heating applied in RFA, Cryoablation utilizes the process of freezing and thawing by introducing an applicator percutaneously into the primary tumor. Freezing the applicator's surrounding tissue very quickly down to a range from -40°C to -60°C leads to intracellular ice crystal formation. This formation results in damage to cellular membranes and organelles, culminating in cell destruction. Any remaining viable cell after the first freezing will take up water from the surrounding hypotonic interstitium during thawing, which will in turn yield more crystal formation in subsequent freezing intervals (51). In addition, local microvascular collapse as a result of endothelial damage from ice crystals further contributes to tissue destruction through local ischemia (52). Despite research demonstrating that healthy liver cells can only resist temperatures of -15°C to -20°C, tumor cells have been shown to be more temperature-variable and resistant to freezing injury, which explains the use of much lower temperatures during Cryoablation (53).

In the past, Cryoablation for HCC was regarded critically due to severe complications involving "Cryoshock". Seifert et al. reported Cryoshock complications in 1% of performed hepatic cryotherapy patients. Furthermore, they associated Cryoshock with a high risk of death, contributing to 18.2% of perioperative mortality (54). In a more recent randomised controlled multicenter study, however, Wang et al. reported of incidents of Cryoshock and no treatment-related mortality (55). The authors further compared the efficacy of Cryoablation with RFA in patients with HCC ≤2 nodules measuring ≤4 cm each with underlying cirrhosis in Child-Pugh class A or B. OS rates at 1, 3 and 5 years were comparable between the two treatment modalities, being 97%, 67% and 40% for RFA and 97%, 66% and 38% for Cryotherapy, respectively. Additionally, the complication rate was similar at 3.9% for RFA and 3.3% for Cryotherapy. Similar 1 and 3-year survival rates have been reported by Shimizu et al. in 2009 (93.8% for 1-year and 79.3% for 3-year OS) (56). Contrary to the comparable complication rates reported by Wang et al., a meta-analysis conducted by Wu et al. points to a significantly higher risk of complications with cryotherapy, particularly with regards to treatment-related bleeding, thrombocytopenia, and renal impairment. Their explanation for the increased incidence of bleeding is the lack of electrocautery of the needle tract during cryoablation (57).

2.4 Microwave ablation

Microwave ablation (MWA) achieves local tissue destruction in a similar fashion to RFA. After introduction of a MWA probe into the primary tumor under US guidance, an electromagnetic (EM) field emitted by the probe results in the oscillation of water molecules in the surrounding tissue. Depending on the effective conductivity of the specific tissue, a fraction of the EM field is absorbed and converted to heat. Tissue destruction as a result of heating is comparable to the processes occuring in RFA. One seemingly important difference to RFA, however, is that EM energy propagation is not negatively influenced by increasing impedance of the charred tissue surrounding the probe, allowing for larger ablative zones without the need of additional modalities like saline injections. In addition, multiple simultaneously-introduced probes in MWA, when positioned correctly, allow for increased tissue heating in overlapping EM field areas. By comparison, multi-probe application in RFA only allows one probe to be active at a time. In summary, MWA allows for the faster heating of larger ablation zones as compared to RFA (58,59).

Seki et al. observed significantly higher 5-year survival rates in patients with moderately to poorly-differentiated HCC $\leq$2 cm when treated with MWA as compared to with PEI. This observation was shared in the group with well-differentiated HCC (60). Considerably more research has been done with the aim of comparing MWA to RFA, resulting in no significant differences with regard to OS. In 2005, Lu et al. reported 1, 2, 3, and 4-year cumulative survival rates for MWA of 81.6%, 61.2%, 50.5% and 36.8%, respectively. They concluded that both modalities are equally valuable with regard to local tumor control and complication rate (61). Conversely, Ohmoto et al. concluded that RFA is superior to MWA due to the need for fewer treatment sessions, lower local recurrences, and higher cumulative survival rates. They also reported a higher incidence of minor complications such as pain and fever and pointed out several serious complications including bile duct injuries, intraperitoneal bleeding, and hepatic infarctions that were associated with MWA treatment (62). However, in line with results compiled by Lu et al., more recent research by Ding et al. and Abdelaziz et al., show that RFA and MWA are of similar clinical value for the treatment of HCC (63,64).

2.5 Laser ablation

Laser ablation (LA) as a treatment modality for the ablation of tumors was first introduced by Bown et al. in 1983 (65). In current practice, a neodymium-doped yttrium aluminum garnet laser (Nd-YAG) with a wavelength of 1064 nm or a diode laser is introduced under combined US and CT or MR guidance. Light in the near infrared spectrum emitted from the fiber tip permeates into the surrounding tissue resulting in partial reflection and absorption. Absorbed energy is converted into heat, ultimately resulting in coagulative necrosis, comparable to the process described in RFA. With a single tip application, a maximum spherical lesion of 12-16 mm in diameter can be achieved. In order to achieve larger ablation zones of >5 cm, multiple fibres have to be placed at 2 cm distance to each other (66–68). According to data collected by Gough-Palmer et al., the ideal criteria for LA in HCC have been described as <3 cm in diameter, deep in the liver parenchyma, while severe liver disease (Child Pugh Class C) and coagulopathy have been considered relative contraindications (69). Meanwhile, Pacella et al. concluded in their retrospective analysis that tumors should not exceed 2 cm in size with normal liver function as represented by serum albumin levels >3.5 g/dl. They further describe achieving complete ablation in 79.6%, with the highest rates in nodules ≤2 cm (85.1%). 3 and 5-year cumulative survival rates were recorded at 61% and 34%, respectively. Lastly, via Cox analysis, Pacella et al. identified serum albumin >3.5 g/dl, complete tumor ablation and age <73 years as independent predictors of survival. (70) Interestingly, according to a retrospective study conducted by Giampiero et al. analyzing 182 HCC nodules ≤4 cm in 164 patients, tumor location does not affect safety, effectiveness, or local tumor progression. After dividing patients into high-risk and standard-risk groups based on the location of the nodule, the researchers reported no significant difference between the two groups in respect to initial ablation rate, major complication rate, cumulative incidence of local tumor progression or local tumor-free survival (71). Comparing LA and RFA, a recent randomised controlled trial conducted by Di Costanzo et al. points to no significant difference between the two treatment modalities in respect to proportion of complete tumor ablation, time to local tumor progression, and OS. In their conclusion, the researchers suggest that LA be considered as an alternative to thermal ablation in small nodule HCC (72). Lastly, with the application of multifibre LA under a newly designed US needle guidance system, researchers have been able to achieve 91.7% complete ablation of nodules ≤5 cm (73).

2.6 High-intensity focused ultrasound

Despite the principle behind being rather old, High-intensity focused ultrasound (HIFU) is one of the latest modalities with regards to treatment of HCC. With the use of an extracorporeal transducer, this treatment option is, in theory, completely non-invasive. At a frequency of 0.8-3.5 MHz, US waves can be bundled at a particular distance from the transducer with a local tissue temperature increase beyond 60°C, ultimately resulting in coagulative necrosis in the tumor focus (74). In 2004, Wu et al. conducted a non randomised clinical trial involving 51 patients with an average tumor size of 8.14 cm. OS was reportedly at 86.1%, 61.5% and 35.3% for 6, 12, and 18 months, respectively. In conclusion Wu et al. describe HIFU as an effective, safe and feasible treatment modality for HCC (75). However, prior to the use of HIFU, half the trial population had been treated with transarterial chemoembolization (TACE) and rib resections had been performed on 14 patients. The purpose and effect of rib resection was the subject of another study conducted by Zhu et al. In their study, 16 patients with HCC at a mean diameter of 7.0 cm were treated with HIFU. All patients previously underwent rib resection in order to minimize US reflection. According to Zhu et al., US reflection not only reduces efficacy of HIFU but also increases the chance of complications of soft tissue and skin burns. Survival rates at 1, 2, 3, 4, and 5 years were reported as 100%, 83.3%, 69.4%, 55.6% and 55.6%, respectively (76). Nonetheless, prior rib resection in order to create an improved acoustic pathway for US beams, while effective, renders the feasibility and non-invasive nature of HIFU into question. Experimental measurements introducing segmented transducers for HIFU, however, promise to avoid the need for rib resection in the future (77). More recent research has been done with a focus on using HIFU as a bridging therapy for HCC prior to liver transplantation. In 2013, Cheung et al. compared response rates and dropout rates among prospective transplant recipients treated with transarterial chemoembolization (TACE) and HIFU. Of the limited number of patients receiving HIFU, 90% had complete response as compared to 3% in the TACE group. In their conclusion, the researchers describe HIFU as safe and effective and propose a possible reduction in dropout rates (78). In a pilot study, Chok et al. compared TACE, HIFU and no bridging therapy. Their results pointed to no significant difference between patients who had received TACE or HIFU, however both were superior to no bridging therapy at all. Still, with the inclusion of HIFU as an alternative to TACE for bridging to liver transplantation, adoption of pre-transplant therapy has increased from 39.2% to 80.4%, thanks in part to the eligibility of HIFU in severe liver disease (Child-Pugh C) and in patients contraindicated to receive TACE (79).

3. Intra-arterial interventions

Intra-arterial interventions for HCC, both primary and metastatic were first introduced in the late 1970s. Allison et al. reported symptomatic relief after treating patients with multiple hepatic carcinoid metastases by embolising the hepatic artery with an absorbable gelatin sponge (80). However, the particular physiological feature of HCC the therapy utilizes is based on was first described back in 1954. After injecting a solution containing ink into the portal vein and into the hepatic artery of several animal test subjects as well as postmortem human livers, researchers noticed a significant difference in patterns of pigment distribution throughout the livers. Portal vein injections resulted in colour uptake throughout the liver parenchyma with tumors remaining largely colourless. In contrast, tumor and adjacent tissue colourisation occured after injecting pigment solution into the hepatic artery. Breedis et al. therefore concluded that blood supply to all malignant tumors in the liver were almost exclusively arterial (81).

During intra-arterial interventions for HCC, a catheter is introduced into the hepatic artery or one of its lobar or segmental subsidiaries. Through this catheter, an embolic agent either alone or in combination with a highly concentrated dose of a chemotherapeutic- or radiotherapeutic agent is delivered into close proximity of the tumor. There are several types of intra-arterial interventions based on the combination of agents used, including transarterial chemoembolization, transarterial bland embolization (TAE) and transarterial radioembolization (TARE) (82).

3.1 Transarterial chemoembolization

TACE is regarded as the gold standard for patients meeting BCLC B staging criteria. These intermediate-stage HCC include inoperable multinodular asymptomatic tumors with no signs of vascular invasion or extrahepatic spread and adequate liver function (Child Pugh class A, B) (6). During TACE, a chemotherapeutic agent is mixed with an oil-based radiopaque contrast agent- most commonly lipiodol- and delivered trans-arterially to the tumor site. Following the administration of the chemotherapeutic-lipiodol emulsion, an embolic agent is infused. The resulting arterial occlusion serves twofold by reducing blood supply, thereby inducing ischemic tumor damage, and by reducing washout of the chemotherapeutic agent and consequently prolonging cytotoxic tumor exposure (83). Globally, the most commonly used chemotherapeutic agent is Doxorubicin. However, cisplatin, epirubicin, mitomycin and other cisplatin derivatives have been used, too. In general, no consensus has been achieved on which chemotherapeutic agent is superior for application in TACE. Several

studies have been conducted comparing cisplatin-based emulsions with emulsions containing epirubicin or miriplatin, with no obvious answer as to which is the optimal chemotherapeutic agent (84).

The essential studies establishing its importance in the treatment of HCC were conducted in the early 2000s. In 2002, Llovet et al. published their results on survival probabilities after treatment with arterial embolization, chemoembolization and conservative treatment. Researchers reported OS at 1, 2 and 3 years. While results of embolization were higher than the conservative group (75%, 50% and 29% OS compared to 63%, 27% and 17%, respectively), TACE proved to be significantly superior over conservative treatment (82%, 63% and 29% OS at p=0.009). Of note, Llovet et al. only included patients with adequate liver function as represented by Child-Pugh class A and B (85). In the same year, Lo et al. reported similar OS rates at 1, 2 and 3 years when comparing TACE with conservative treatment (57%, 31% and 26% compared to 32%, 11% and 3%, respectively). In their conclusion, the researchers point out a major limiting factor for the application of TACE is the presence of unilobar portal vein obstruction, estimating a threefold increased risk of death (86). In 2011, a cochrane meta-analysis called into the question the benefits of chemoembolization. According to the authors, research into TACE lacked evidence of improving survival in patients with unresectable HCC (87). However, this article has been criticized by experts over their decision of excluding trials that showed benefit in survival after TACE as well as including trials focusing on TAE rather than TACE (88,89) . Lastly, a recent systematic review aimed at identifying efficacy and safety of TACE was conducted by Lencioni et al. In their data collection, including 10,108 patients treated in 101 studies, researchers reported a longer median survival and higher 3-year OS when comparing studies conducted until 2002 and after (90).

As described by the treatment criteria issued by EASL-EORTC, degree of liver dysfunction plays a critical part in patient selection. More specifically, absolute contraindications for TACE include decompensated liver cirrhosis (Child-Pugh B $\geq$8), extensive tumor replacement of both liver lobes as well as severely reduced portal vein flow (6,91).

Novel approaches in order to increase exposure time of cytotoxic agents to tumor cells while minimizing systemic side effects have been made. Drug-eluting beads (DEB) consist of nonresorbable polyviniyl alcohol (PVA) polymeric microspheres or acrylic copolymer microspheres that are capable of reversibly binding to polar molecules the likes of doxorubicin (92). This approach of drug delivery allows for fixed and gradual release of chemotherapeutic agents with significantly lower plasma concentrations when compared to conventional TACE (cTACE) (83,93,94). Furthermore, compared to cTACE, DEB-TACE has proven to provide improved tolerability with significant reduction in serious liver toxicity (95,96). With regard to local tumor control and OS, research has shown no significant benefit of DEB-TACE over cTACE. Recchia et al. reported statistically insignificant

results of median OS of 11.4 and 18.4 months for cTACE and DEB-TACE, respectively (97). In 2014, Golfieri et al. released their results of 1- and 2-year survival rates, illustrating similar insignificant differences between the two procedures with regards to survival (86.2% and 56.8% after DEB-TACE and 83.5% and 55.4% after cTACE) (98).

3.2 Transarterial bland embolization

TAE or transcatheter arterial embolization follows the same principle previously described under TACE: blockage of hepatic arterial flow to the tumor with a vascular occlusion agent. Agents commonly used include Gelfoam, polyvinyl alcohol or calibrated microspheres (82). Despite TACE largely replacing TAE as the prefered treatment modality for BCLC B HCC tumors, evidence of any superiority of TACE in terms of OS or recurrence-free survival is lacking. In a 2014 retrospective case-controlled study, Kluger et al. compared percentage of achieved complete necrosis, 3-year OS and 3-year recurrence-free survival between 25 and 50 patients treated with TAE and TACE prior to liver transplantation, respectively. At 1- and 3-year OS rates of 96% and 78% for TAE versus 94% and 74% for TACE, respectively, no significant difference between the two modalities could be established. The same could be observed in recurrence -free survival at 1 and 3 years, with neither therapy proving to be significantly superior to the other (91% and 72% for TAE, 92% and 68% for TACE, respectively) (99). In another recent small-scale trial, researchers compared embolization using microspheres alone with microspheres loaded with doxorubicin 150mg. Brown et al. confirmed no significant difference between the two treatment modalities with regard to progression-free survival (6.2 months versus 2.8 months) and OS (19.6 months versus 20.8 months) (100). In fact, in a 2007 published meta-analysis, Marelli et al. question the efficacy of any chemotherapeutic agent utilized in TACE, accounting its therapeutic effect on the embolization aspect of the therapeutic intervention (101). However, with some research stipulating that embolization could potentially result in hypoxia-induced angiogenesis and consequently tumor growth promotion, combining TAE with antiangiogenic agents rather than chemotherapeutic agents could prove beneficial (102,103). The first early studies combining TAE with antiangiogenic agents in the treatment of rat liver tumors show promising results (104,105).

3.3 Transarterial radioembolization

Delivery of high dose radiation through intraarterial injection of microspheres loaded with a radioactive agent is the basis of TARE. Radioactive agents typically used include Yttrium-90 or lipiodol-labeled iodine-131 (106). Therapeutic effect is based on both embolic effects exerted by the microspheres as well as brachytherapy. However, compared to TAE or TACE, due to the smaller diameter of the delivering microspheres, ischemic effects from embolization contribute far less to the overall therapeutic effect (107). Moreover, the lack of macro-embolization increases safety potential for patients with portal vein thrombosis- a clear contraindication for both TACE and TAE (106,108).
Research surrounding TARE focuses either on treatment of intermediate HCC (BCLC B) with comparison to TACE or as an alternative for downstaging treatment modalities prior to resection or transplantation. Several studies comparing TACE and TARE with focus on tumor response and OS have found no significant difference between the two treatment modalities (109–112). Salem et al. pointed out, despite median survival times not being significantly different, time-to-progression was longer after TARE compared to TACE (13.3 months compared to 8.4 months) (111). Furthermore, Fouly et al. reported a significantly lower number of treatment sessions, associated total hospitalization time and incidence of adverse events after TARE treatment (112). Another aspect in focus of research is the possibility of utilizing TARE as a mean of downstaging or bridging HCC until curative treatment is possible or transplantation is available. In 2009, Lewandowski et al. reported significantly longer event-free survival after TARE compared to TACE (17.7 months compared to 7.1 months, respectively). Additionally, successful downstaging to United Network for Organ Sharing (UNOS) T2 transplant criteria was achieved in 58% of TARE patients opposed to 31% of TACE patients (113). In another small retrospective study, Iñarrairaegui et al. reported successful downstaging in 6 of 21 patients with UNOS T3 stage, with varying median OS between patients who were treated radically after successful downstaging compared to patients who received palliative treatment only. The researchers conclude that successful downstaging with TARE followed by radical therapy would provide long-term survival for patients with UNOS T3 stage (114).

4. Combination therapy

Despite not being explicitly defined in the EASL-EORTC guidelines for treatment of HCC, some studies have focused on improving the efficiency of local therapies by combining them with other local or systemic therapies. One particular combination, local ablative therapy in conjunction with transarterial embolization techniques, has been the subject of a number of studies. As mentioned previously, one factor limiting the extent and efficacy of RFA is the process of "heat sink", which results from peri-tumoral vascularization and consequent loss of temperature into the circulation (37). Prior TACE should, in theory, reduce the effect of "heat sink" by occlusion of the vessels surrounding and feeding the tumor. Recent studies have shown promising results (115–117). In 2012, Peng et al. compared sequential TACE and RFA with RFA alone with regards to OS, recurrence-free survival in 139 patients with recurrent HCC ≤5 cm. The researchers reported better OS and recurrence-free survival in tumors >3 cm, concluding higher efficacy for sequential TACE-RF ablation compared to RFA alone for this subpopulation (117). Moreover, in a recent meta-analysis involving 8 randomised controlled trials, Ni et al. compared 305 patients treated with RFA plus TACE as opposed to 292 patients treated with RFA alone. In their analysis, OS at 1, 2, and 3 years was significantly better after combination therapy compared to monotherapy. Similar results were reported in recurrence-free survival at 3 and 5 years. Lastly, Ni et al. report significant improval of survival rates in tumors >3 cm only, which is in line with results reported by Peng et al. (117,118).

Another approach to combination therapy that was subject to studies is the combination of systemic Sorafenib chemotherapy with intra-arterial intervention modalities, either TARE or TACE for advanced HCC. In 2014, Chow et al. published their findings of a Phase II trial involving TARE with Sorafenib in 99 patients with BCLC B (38%) or BCLC C (62%) HCC. The researchers report a median survival of 20.3 and 8.6 months for BCLC B and BCLC C, respectively, signifying potential efficacy of sequential TARE-Sorafenib therapy with manageable toxicity (119). The latter observation is further confirmed by a 2015 European multicentre trial comparing safety and toxicity of TARE plus Sorafenib versus Sorafenib alone. Ricke et al. point out similar tolerability between the two study arms (120). Lastly, a recent small trial involving 19 patients with BCLC B or C HCC who were treated sequentially with TARE and Sorafenib reported an OS of 19.52 months and progression-free survival of 6.63 months (121). Combination of TACE with Sorafenib has as well been subject to multiple studies. Qu et al. compared this combination of therapy in 45 patients with BCLC B (36%) and BCLC C (64%) with a control group receiving TACE only. Alongside significantly less frequent

TACE interventions for symptomatic relief, the researchers demonstrated a significant difference in median OS between the combination group and the control group (27 months median OS versus 17 months, respectively), irrespective of the presence of PVT (122). In 2013, Choi et al. compared TACE with Sorafenib to Sorafenib only in a retrospective analysis in a total of 355 patients with advanced HCC (BCLC C). With a median time to progression of 2.7 months and 2.1 months (P= 0.011) and a median OS of 9.1 months and 6.7 months (P= 0.21) for combination therapy and monotherapy, respectively, they demonstrated the combination of TACE with Sorafenib is superior to Sorafenib only with regards to time to progression (123).

5. Conclusion

Image-guided, minimally invasive therapies play a key role in the management of HCC. On one hand, there are the tumor ablative techniques, which offer potential long-term survival for patients with early-stage HCC who are unable to undergo surgical intervention. Aside from RFA, other ablative therapies have proven their worth in studies. The choice of treatment should be based on the individual characteristics of the tumor, the location of the tumor, the residual liver function, as well as the patient's overall well-being. Lastly, with the introduction of HIFU, a new form of intervention has emerged that provides a completely non-invasive treatment modality for HCC that may further revolutionize this field of interventional radiology.

On the other hand, intra-arterial intervention techniques have solidified their key role in the treatment of intermediate HCC, a stage in which no other treatment modality has shown a comparably significant benefit. With novel approaches such as microspheres labeled with radioactive components or filled with chemotherapeutic agents, precision of radiotherapy and chemotherapy in the field of interventional radiology has reached new levels. Considering the dismal survival rates for late-stage HCC, further studies will need to evaluate whether combining minimally-invasive therapies with systemic therapies can indeed yield better results than our current treatment options.

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8. Biography

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