Update on Percutaneous Local Ablative Procedures for the Treatment of Hepatocellular Carcinoma

Aktueller Stand zu perkutanen lokalablativen Verfahren beim hepatozellulären Karzinom

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ABSTRACT

Background Hepatocellular carcinoma (HCC) is the fifth most common tumor worldwide. Because many hepatocellular carcinomas are already unresectable at the time of initial diagnosis, percutaneous tumor ablation has become established in recent decades as a curative therapeutic approach for very early (BCLC 0) and early (BCLC A) HCC. The aim of this paper is to provide a concise overview of the percutaneous local ablative procedures currently in use, based on their technical characteristics as well as clinical relevance, taking into account the current body of studies.

Materials and Methods The literature search included all original papers, reviews, and meta-analyses available via MEDLINE and Pubmed on the respective percutaneous ablation procedures; the primary focus was on randomized controlled trials and publications from the last 10 years.

Results and Conclusions Radiofrequency ablation (RFA) and microwave ablation (MWA) are well-established procedures that are considered equal to surgical resection in the treatment of stage BCLC 0 and A HCC with a diameter up to 3 cm due to their strong evidence in international and national guidelines. For tumors with a diameter between 3 and 5 cm, the current S3 guidelines recommend a combination of transarterial chemoembolization (TACE) and thermal ablation using RFA or MWA as combination therapy is superior to thermal ablation alone in tumors of this size and shows comparable results to surgical resection in terms of overall survival. Alternative, less frequently employed thermal procedures include cryotherapy (CT) and laser ablation (LA). Non-thermal procedures include irreversible electroporation (IRE), interstitial brachytherapy (IBT), and most recently, electrochemotherapy (ECT). Due to insufficient evidence, these have only been used in individual cases and within the framework of studies. However, the nonthermal methods are a reasonable alternative for ablation of tumors adjacent to large blood vessels and bile ducts because they cause significantly less damage to these structures than thermal ablation methods. With advances in the technology of the respective procedures, increasingly good evidence, and advancements in supportive techniques such as navigation devices and fusion imaging, percutaneous ablation procedures may expand their indications for the treatment of larger and more advanced tumors in the coming years.

Key Points:

- RFA and MWA are considered equal to surgical resection as a first-line therapy for the curative treatment of stage BCLC 0 and A HCCs with a diameter of up to 3 cm.
- For HCCs with a diameter between 3 and 5 cm, a combination of TACE and RFA or MWA is recommended. This combination therapy yields results comparable to those of surgical resection in terms of overall survival.
- Due to insufficient evidence, alternative ablation methods have only been used in individual cases and within the

framework of studies. However, nonthermal methods, such as IRE, IBT, and, most recently, ECT, are a reasonable alternative for ablation of HCCs adjacent to large blood vessels and bile ducts because they cause significantly less damage to these structures than thermal ablation methods.

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ZUSAMMENFASSUNG

Hintergrund Das hepatozelluläre Karzinom (HCC) ist das fünfthäufigste Tumorleiden weltweit. Da viele HCCs bereits zum Zeitpunkt der Erstdiagnose nicht resektabel sind, haben sich in den letzten Jahrzenten perkutane Tumorablationen als kurativer Therapieansatz für das sehr frühe (BCLC 0) und frühe (BCLC A) HCC etabliert. Ziel dieser Arbeit ist es, einen kompakten Überblick über die aktuell zur Anwendung kommenden perkutanen lokalablativen Verfahren zu geben, basierend auf den technischen Besonderheiten sowie der klinischen Relevanz unter Berücksichtigung der aktuellen Studienlage.

Methode Die Literaturrecherche umfasste alle über MEDLINE und PubMed verfügbaren Originalarbeiten, Reviews und Metaanalysen zu den jeweiligen perkutanen Ablationsverfahren, hierbei wurde vor allem ein Fokus auf randomisiert kontrollierte Studien und Veröffentlichungen aus den letzten 10 Jahren gelegt.

Ergebnisse und Schlussfolgerung Die Radiofrequenzablation (RFA) und Mikrowellenablation (MWA) sind etablierte Verfahren, welche aufgrund ihrer starken Evidenz in internationalen und nationalen Leitlinien bei der Behandlung von HCCs im Stadium BCLC 0 und A mit einem Diameter bis zu 3 cm der chirurgischen Resektion gleichgestellt sind. Für HCCs mit einem Diameter zwischen 3 und 5 cm wird in den aktuellen S3-Leitlinien eine Kombination aus transarterieller Chemoembolisation (TACE) und Thermoablation mittels RFA oder MWA empfohlen, da bei HCCs dieser Größe die Kombinationstherapie der alleinigen Thermoablation überlegen ist und mit der chirurgischen Resektion vergleichbare Ergebnisse bezüglich des Gesamtüberlebens zeigt. Alternative, deutlich seltener eingesetzte thermische Verfahren sind die Kryotherapie (KT) und die Laserablation (LA). Zu den nicht thermischen Verfahren zählen die irreversible Elektroporation (IRE), die interstitielle Brachytherapie (IBT) und als neuestes Verfahren die Elektrochemotherapie (ECT). Aufgrund der noch nicht ausreichenden Evidenz kommen diese bis dato allerdings nur in Einzelfällen und im Rahmen von Studien zum Einsatz. Die nicht thermischen Verfahren stellen jedoch eine sinnvolle Alternative für die Ablation von HCCs in Nachbarschaft zu großen Blutgefäßen und Gallengängen dar, da sie diese Strukturen im Gegensatz zu den thermischen Ablationsverfahren nicht schädigen. Durch Fortschritte in der Technik der jeweiligen Verfahren, zunehmend gute Evidenz sowie Weiterentwicklungen bei unterstützenden Techniken wie Navigationsgeräten und Fusionsbildgebung könnten die perkutanen Ablationsverfahren in den kommenden Jahren ihre Indikationsstellung zur Behandlung größerer und weiter fortgeschrittener HCCs erweitern.

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common tumor worldwide and the leading cause of death in patients with cirrhosis of the liver [1, 2]. The Barcelona Clinic Liver Cancer (BCLC) classification is the most common staging system of HCC in the cirrhotic liver and has proven to be the basis for recommending different therapeutic options. This classification, first published in 1999 and modified several times since, includes as variables tumor stage (defined by tumor size, number of tumor sites, vascular invasion, and metastases), liver function (defined by Child-Pugh stage, CPS A–C), as well as general health (defined by Eastern Cooperative Oncology Group/ECOG Performance Status, EPS 0–5) and links the stage of the disease to specific therapeutic strategies [1, 3].

In the current S3 guideline, percutaneous local ablative procedures were considered equivalent to resection for very early (BCLC 0: singular HCC < 2 cm, CPS A, PS 0 [1]) and early tumor stage (BCLC A: singular HCC > 2 cm or 2–3 foci ≤ 3 cm, CPS A, PS 0 [1]) in patients with tumors up to 3 cm. Locally ablative procedures are also recommended in the current S3 guideline for “bridging” to liver transplantation in patients with HCC within Milan criteria on the transplant waiting list and for “downstaging” in patients with HCC outside Milan criteria. Here, local ablative procedures are considered equal to resection on the one hand, and transarterial procedures such as transarterial chemoembolization (TACE) and transarterial radioembolization (TARE) on the other.

In principle, thermal (radiofrequency ablation; RFA, microwave ablation; MWA, laser ablation; LA, cryotherapy; CT) are distinguished from non-thermal procedures (irreversible electroporation, IRE; interstitial brachytherapy, IBT; percutaneous ethanol injection, PEI; electrochemotherapy, ECT). According to the S3 guideline, percutaneous ablations of HCC should be performed using RFA or MWA. For patients with tumors smaller than 3 cm in locations unfavorable for resection or with impaired liver function (i. e., at least CPS B), the primary goal should be thermal ablation (i. e., RFA or MWA) of the tumor. For lesions > 3 to < 5 cm, preserved liver function and low- or moderate-grade portal hypertension, transarterial chemoembolization should be performed beforehand if thermal ablation is planned. IRE, IBT, LA, CT, PEI, and ECT are to be used only in exceptional cases when neither resection, RFA, or MWA are appropriate [4].

The aim of this review article is to highlight percutaneous local ablative procedures available for the treatment of HCC with re-

gard to the exact mechanism of action, technical features and clinical relevance, taking into account the current S3 guideline as well as the current body of research. For this purpose, the MEDLINE database PubMed was searched for the term "hepatocellular carcinoma" in combination with the terms "percutaneous ablation," "radiofrequency ablation," "microwave ablation," "laser ablation," "cryotherapy," "irreversible electroporation," "interstitial brachytherapy," and "electrochemotherapy." Subsequently, all randomized controlled trials and cohort studies identified in this manner were identified and considered in the preparation of this review article. An overview of the current state of evidence is presented using randomized controlled trials shown in ▶ **Table 1**. The following will review the ablation procedures most commonly used in HCC.

Thermal Ablation Procedures

Radiofrequency ablation

Radiofrequency ablation (RFA) is currently the most widely used percutaneous ablation procedure for the treatment of HCC. In RFA, a radiofrequency electrode, consisting of an insulated metal shaft with one to six active electrode tips, is inserted percutaneously into the target lesion. Subsequently, a sinusoidal alternating current with frequencies between 375 and 480 kHz is applied to the radiofrequency electrode (synonym: ablation probe or applicator) via a radiofrequency generator which induces ionic movement around the electrode tips. The ionic motion in turn generates frictional heat, resulting in temperatures of more than 60° C in the target area, which leads to irreversible denaturation of proteins and thus coagulation necrosis [5]. Optimal target temperatures for RFA are considered to be 90–100 °C. In most systems, this is achieved by energy output control of the radiofrequency generators, which is based either on the permanently measured tissue resistance (impedance) or directly on the measured temperature in the target tissue. This prevents excessive temperatures in the target tissue and thus avoids charring of the tissue around the electrode tips. Currently, monopolar, bipolar and multipolar ablation systems are in use. In a monopolar ablation system, the current is discharged from the body via cutaneously applied neutral electrodes. In bipolar ablation systems, the current is derived between each of 2 active electrode tips of the ablation probe. Multipolar ablation systems simultaneously use two to six bipolar ablation probes. An additional lumen in newer ablation probes allows the application of liquid cooling with NaCl solution, which prevents charring effects around the active electrode tips.

In multiple studies, the efficacy of RFA was evaluated with respect to primary technique efficacy rate (PTER [6]), i. e., the complete eradication of the tumor tissue as shown in imaging, as well as overall survival (OS) compared with percutaneous ethanol injection (PEI) and surgical resection.

In both cohort studies and randomized controlled trials, RFA of HCC up to a maximum size of 5 cm has been shown to have a PTER between 90 % and 100 %, with OS varying between 60 % and 84.1 % at 3 years and 37.0 % and 75.0 % at 5 years, respectively, depending on the study [7–27].

Five randomized controlled trials and two meta-analyses with a total of 701 and 625 patients demonstrated superiority of RFA compared with PEI with respect to PTER as well as LTP and OS [7, 8, 10, 11, 13, 28, 29]. In recent years, this has led to RFA displacing PEI as the standard procedure for percutaneous local ablative therapy in most developed and emerging countries.

Compared with surgical resection, the only other primary curative therapy for HCC besides liver transplantation, the randomized controlled trials conducted to date have yielded inconclusive results. In some cases, better results were described for surgical resection [15, 17]; in some other instances RFA was identified as an equivalent alternative with potential advantages due to reduced invasiveness [12, 30], while other studies determined no significant differences in OS or recurrence-free survival (RFS) [24, 30]. Previous meta-analyses on this topic have also failed to demonstrate clear advantages for either method. Center expertise is also likely to have a non-negligible influence on the results of both therapy methods, although this influence is difficult to quantify scientifically and has therefore not yet been analyzed. However, primary resection apparently tends to ensure slightly better results with respect to OS and RFS, especially for tumors with a diameter greater than 3 cm [31, 32]. Studies comparing RFA and surgical resection tend to associate RFA with lower complication rates and shorter hospital stays than resection [12, 15, 17].

In addition to overall OS and RFS, many studies also addressed the identification of positive and negative predictors of treatment success. Relevant negative predictors generally included increasing tumor size, higher number of HCC masses, higher Child-Pugh stage, and higher serum alpha-fetoprotein (AFP) levels (especially above 200 ng/ml) [13, 14, 18, 22, 33–37].

In addition to the predictors mentioned above, other factors influencing the success of therapy and the safety of RFA also play a role. An important factor is the positional relationship to large and medium-sized hepatic veins as well as portal vein branches, since heat dissipation in the vessels attenuates the immediately adjacent RFA-induced heat generation, increasing the risk for incomplete ablation or early local recurrence. This phenomenon is known as the "heat sink effect" [38]. The heat generated by RFA can also cause damage to bile ducts, leading to serious complications such as cholangitis or cholangiosepsis, which is why a direct positional relationship of the HCC to the common bile duct is considered a contraindication for RFA [39]. Other possible complications of RFA requiring therapy are primarily injury to surrounding organs such as the kidney, adrenal gland, pancreas, stomach, intestines, gallbladder, pleura, lungs and heart, either from the radiofrequency electrode or from the generated heat. Additional complications may include bleeding, abscesses, and the spread of tumor cells along the stent canal, so-called tumor seeding, although overall the risk of major complications is at a low level of 1.0 % to 3.4 % [16, 19]. Comparatively, morbidity rates of 30.9 % to 41.7 % and major complication rates of 1.6 % to 24.5 % are reported for surgical resection [40, 41].

▶ **Table 1** Randomized controlled studies on percutaneous local ablative procedures for HCC 2012–2021.

Randomized control study	Number of included patients	Number and size of HCC	Region	Endpoint	Results
RFA vs. resection					
Feng et al. 2012 [17]	168	Max. 2 HCC, < 4 cm diameter	China	OS and RFS (3 years)	OS 67.2 % vs. 74.8 % (p = 0.342), RFS 49.6 % vs. 61.1 % (p = 0.122)
NG et al. 2017 [24]	218	Within Milan criteria	China	OS and DFS (5 years)	OTR 81.7 % vs. 71.3 % (p = 0.092), OS 66.4 % vs. 66.5 % (p = 0.531), DFS 33.6 % vs. 41.5 % (p = 0.072)
Xia et al. 2019 [25]	240	Within Milan criteria	China	OS and RFS (5 years), CR	OS 38.5 % vs. 43.6 % (p = 0.17), RFS 30.2 % vs. 36.2 % (p = 0.09), CR 7.3 % vs. 22.4 % (p = 0.001)
Kudo et al. 2021 [23]	302	Max. 3 HCC, < 3 cm diameter	Japan	OS and RFS (5 years)	OS 70.4 % vs. 74.6 % (HR 0.96; 95 %CI 0.64–1.43; p = 0.828), RFS 50.5 % vs. 5.7 % (HR 0.90; 95 %CI 0.67–1.22; p = 0.498)
MWA vs. RFA					
Qian et al. 2012 [49]	42	1 HCC, < 3 cm diameter	China	PTER, LTP (approx. 5 months)	PTER 95.5 % vs. 95 %, LTP 18.2 % vs. 15 %
Abdelaziz et al. 2014 [48]	111	Max. 3 HCC, ≤ 5 cm diameter	Egypt	PTER and LTP, OS (2 years)	PTER 96.1 % vs. 94.2 % (p = 0.6), LTP 3.9 % vs. 13.5 % (p = 0.04), OS 62 % vs. 47.4 % (p = 0.49)
Yu et al. 2017 [50]	403	Max. 3 HCC, ≤ 5 cm diameter	China	PTER; OS, DFS und LTP (5 years), CR	PTER 99.6 % vs. 98.8 % (p = 0.95), OS 67.3 % vs. 72.7 % (p = 0.91), DFS 36.7 % vs. 24.1 % (p = 0.07), LTP 11.4 % vs. 19.7 % (p = 0.11), CR 3.4 % vs. 2.5 % (p = 0.59)
Vietti Violi et al. 2018 [47]	144	Max. 3 HCC, ≤ 4 cm diameter	France, Switzerland	LTP (2 years)	LTP 6 % vs. 12 % (HR 1.62; 95 %CI 0.66–3.94; p = 0.27)
Kamal et al. 2019 [46]	56	Max. 3 HCC, ≤ 5 cm diameter	Egypt	LTP (1 year)	LTP 9.1 % vs. 9.1 % (p = 1.000)
Chong et al. 2020 [45]	93	Max. 3 HCC, ≤ 5 cm diameter	Hong Kong	PTER; OS (5 years), DFS (3 years)	PTER 95.7 % vs. 97.8 % (p ≥ 0.99), OS 42.8 % vs. 56.7 % (p = 0.899), DFS 24.1 % vs. 22.7 % (p = 0.912)
LA vs. RFA					
Orlacchio et al. 2014 [61]	30	1 HCC, ≤ 4 cm diameter	Italy	PTER, LTP (1 year)	PTER 87 % vs. 93 %, (p = insignificant) LTP 46 % vs. 14 % (p = 0.083)
Di Costanzo et al. 2015 [62]	140	Within Milan criteria	Italy	PTER, TTLP, OS (3 years)	PTER 95.7 % vs. 97.4 % (p = 0.5), TTLP 46.7 vs. 42 months (p = 0.591), OS 80 % vs. 89 %

▶ **Table 1** (Continuation)

Randomized control study	Number of included patients	Number and size of HCC	Region	Endpoint	Results
CT vs. RFA					
Wang et al. 2015 [66]	360	Max. HCCs, ≤ 4 cm diameter	China	LTP (3 years) OS and DFS (5 years) CR	LTP 7.7 % vs. 18.2 % (p = 0.041), OS 40 % vs. 38 % (p = 0.747), DFS 35 % vs. 34 % (p = 0.628), CR 3.9 % vs. 3.3 % (p = 0.776)
PEI* and IRE/ECT**					

RFA = radiofrequency ablation, MWA = microwave ablation, LA = laser ablation, CT = cryotherapy, IRE = irreversible electroporation, IBT = interstitial brachytherapy, PEI = percutaneous ethanol injection, ECT = electrochemotherapy, TACE = transarterial chemoembolization. OS = overall survival, DFS = disease-free survival, RFS = recurrence-free survival, OTR = overall tumor recurrence, LTP = local tumor progression [6]), TTLP = time to local progression, TTUP = time to untreatable progression, TTP = time to tumor progression, PTER = primary technique efficacy rate [6]), CR = complication rate, CI = confidence interval.

* PEI for local therapy of HCC has been superseded by thermal ablation procedures, so a presentation of the current body of studies has been omitted.

** Currently there are no randomized controlled studies on IRE/ECT.

Microwave ablation

Microwave ablation (MWA) has become common as an alternative hyperthermal procedure for ablation of HCC in recent years. Clinical MWA is based on the emission of electromagnetic waves in the frequency range between 915 and 2450 MHz into the tumor tissue. Electromagnetic waves are generated by a microwave generator and emitted into the surrounding tissue starting from the active center of a microwave antenna placed in the target lesion. Microwaves generate an alternating electromagnetic field whose polarity changes about 109 times per second. Dipole molecules align their charge with this alternating field. Since the water molecule (H_2O) is the main dipole for hyperthermal ablation, tissues with high water content are particularly sensitive to MWA. The water molecules are excited by the periodically changing orientation of their charges in the alternating electromagnetic field, which increases the kinetic energy of the water molecules and thus leads to heating of the tissue [42].

Unlike monopolar RFA, which uses high-frequency alternating current, MWA does not require a neutral electrode for a closed circuit, thus allowing simultaneous use of multiple ablation probes. Some systems support the synchronous use of up to three ablation probes, which increases the achievable ablation zone and allows it to be reached in a significantly shorter time compared to the sequential use of a single ablation probe [43]. Operating the probes phase-synchronously exploits the synergy effect of constructive interference, leading to more efficient tissue heating and higher temperatures, resulting in larger, homogeneously contiguous ablation areas [42].

There are some technical advantages over RFA since MWA does not depend on the transmission of an electrical current in the tissue. With MWA, a larger ablation area can be achieved in a shorter time than with RFA. In addition, MWA is less susceptible to the heat sink effect than RFA [44].

PTER and the OS of the MWA are rated as equal to the RFA in retrospective controlled studies as well as randomized controlled studies and two meta-analyses [45–53]. OS varied from 81.6 % to 97.9 % at one year, 50.5 % to 81.9 % at 3 years, and 36.8 % to 67.3 % at 5 years in the previously mentioned studies, with a PTER between 94.9 % and 99.7 %. A meta-analysis with a total of 774 patients showed that MWA achieved a significantly longer RFS compared with RFA in HCC with a larger tumor diameter (odds ratio 0.46; 95 % CI 0.24–0.89; p = 0.02), if only studies were considered that also included treated tumors with a diameter of more than 3 cm [53].

The complication rates of MWA appear to be similarly low to those of RFA, with the spectrum of potential complications including, as with RFA, primarily injury to surrounding heat-vulnerable structures, hemorrhage, abscesses, and tumor seeding.

Due to the increasingly good data situation regarding oncological efficacy, MWA has been placed on an equal footing with RFA as a curative procedure for first-line therapy in the current S3 guidelines [4].

Laser ablation

Laser ablation (LA, synonym: laser-induced thermotherapy, interstitial laser thermotherapy) is a procedure based on local heating by laser energy and was introduced in the early 1990 s for the treatment of liver tumors [54, 55]. After puncturing the target lesion with a coaxial needle, a translucent, thermostable sheathed catheter together with a laser applicator is inserted. A Nd:YAG laser (neodymium-doped yttrium aluminum garnet laser) with a wavelength of 1064 nm is typically used for tissue ablation; this works in the low-energy range (maximum 20 watts) and leads to slow heating with subsequent destruction of the tissue.

There are hardly any current data available for HCC in the treatment of primary liver malignancies, but the studies performed to

date have offered thoroughly positive results. Several retrospective cohort studies have demonstrated a PTER of 82 %–97 % for LA in patients with HCC [56–59]. A retrospective multicenter study demonstrated cumulative 3- and 5-year survival rates after LA of 61 % and 34 %, respectively. Remarkably, in a subgroup analysis of patients with Child-Pugh stage A and tumors ≤ 2 cm in diameter, 5-year survival was increased up to 60 % with a median survival of 63 months [60]. The latter findings are confirmed by a randomized controlled trial in which LA demonstrated comparable results to established RFA in terms of PTER and RFS in tumors ≤ 2 cm, with lower complication rates [61]. Another randomized controlled trial with a total of 140 patients with HCC within the Milan criteria (either a tumor focus < 5 cm or a maximum of 3 tumor foci with a diameter of < 3 cm), demonstrated comparable results between LA and RFA [62]; thus in synopsis of the above results, LA is a potential alternative in patients with liver cirrhosis and smaller hepatocellular carcinomas. In addition, a recently published retrospective case-control study demonstrated the superiority of LA over transarterial chemoembolization for solitary unresectable tumors ≥ 4 cm [63]; however, the results still need to be confirmed by randomized controlled trials.

Despite the promising results, LA is not mentioned in the current S3 guideline, partly because of the high level of required equipment; however, it is rarely used and has been superseded in many centers by MWA or RFA in particular.

Cryotherapy

In contrast to hyperthermal ablation procedures, cryotherapy (CT) relies on the formation of ice crystals in the target tissue using the Joule-Thomson effect. For this purpose, the inert gas argon is pressed under high pressure into an expansion chamber within the currently available cryoablation systems introduced percutaneously into the target lesion. There it expands and extracts energy from the surrounding tissue in the form of temperature with consecutive formation of an ice ball and associated irreversible cell damage.

The oncological efficacy of percutaneous CT for the treatment of HCC has been repeatedly demonstrated within the last decade. CT is an effective ablation procedure for patients with HCC within the Milan criteria with 1-, 3- and 5-year survival rates of 98.6 %, 80.6 % and 60.3 %, respectively [64]. A propensity-matched population study with a total of 3239 patients with localized HCC (i. e., American Joint Committee on Cancer (= AJCC) stages 1 and 2) showed no difference between CT and RFA with respect to OS and so-called liver cancer-specific survival (i. e., cause of death HCC-related) [65]. A randomized, controlled, multicenter study of 360 patients with HCC ≤ 4 cm and Child-Pugh stage A or B also demonstrated comparable results between CT and RFA with respect to OS and tumor-free survival, but with significant advantages in favor of cryotherapy with regarding local tumor progression rate in HCC > 3 cm (7.7 % vs. 18.2 %, p = 0.041) [66]. The latter results were confirmed in a retrospective analysis between CT and RFA or MWA in patients with HCC < 5 cm, in which CT showed a significantly improved local recurrence-free 2-year survival rate (hazard ratio 0.3; CI: 0.1–0.9; p = 0.02) [67].

A feared complication of CT, especially during ablation of large liver tumors, is cytokine-mediated cryoshock syndrome, in which the transfer of cellular debris from the ablation site into the system circulation can lead to ARDS (acute respiratory distress syndrome), renal failure or disseminated intravascular coagulation, among other complications. However, the complication rate of CT, especially in smaller hepatic lesions (i. e., < 4 cm), is considered to be rather low with a concomitant high technical success rate of up to 96.6 % [68, 69]. However, it should be noted that there are still no prospective randomized studies on the effectiveness and safety of CT compared to surgical procedures or on the combination with systemic immune or chemotherapy with regard to the increasingly multimodal-based therapy of HCC [70]. For this reason, CT is not represented in the current S3 guideline.

Combination of Hyperthermal Ablation Techniques with Transarterial Procedures

For tumors with a diameter between 3 and 5 cm, surgical resection tends to achieve better results than RFA alone with regard to OS and RFS; however, multiple studies have shown that a combination therapy of TACE followed by thermal ablation improves both OS and RFS compared to thermal ablation or TACE alone, and lower LTP (local tumor progression) rates can be achieved [71–74]. This applies to both RFA and MWA. As an example, a randomized, controlled study with 189 patients demonstrated both an improved OS and RFS in patients with a combination therapy of conventional Lipiodol-based TACE (= cTACE) and RFA compared to RFA alone with a 1-year OS 92.6 % vs 85.3 % and 3-year OS 66.6 % vs 59 % (hazard ratio 0.525, 95 % CI 0.335–0.822, p = 0.002) [72]. A current meta-analysis with 1892 patients from a total of 9 retrospective and randomized controlled studies also observed a comparable OS after one (odds ratio 1.71, 95 % CI 0.966–3.02, p = 0.07), 3 (odds ratio 0, 94, 95 % CI 0.57–1.57, p = 0.82) and 5 years (odds ratio 0.84, 95 % CI 0.66–1.07, p = 0.15) for surgical resection and combination therapy of TACE and RFA with lower complication rate for combination therapy (p = 0.0001) [75]. Based on these results, the current S3 guidelines for the treatment of HCC in tumors between 3 and 5 cm recommend the combination therapy of TACE and thermal ablation if resection is not possible [4].

It has become increasingly possible to treat larger tumors due to the synergistic effects of TACE and thermoablation, as well as further developments of already known ablation procedures. For example, a retrospective study of 43 patients with HCC and preserved liver function with a mean tumor diameter of 8.8 cm (SD 2.8 cm) using combination therapy of cTACE followed by multi-antenna MWA demonstrated an OS of 64.0 % at one year and 46.8 % at 2 years [76].

However, the following should be considered critically with regard to the combination therapy of TACE and hyperthermic ablation: that the patient collectives of the above-mentioned studies were exclusively from the Asian region with a correspondingly higher proportion of viral hepatitis-induced liver cirrhosis and HCC. There are currently no corresponding studies in European and American patient cohorts with predominantly nutritive toxic genesis of liver cirrhosis and HCC.

Non-thermal Ablation Procedures

Irreversible electroporation

Irreversible electroporation (IRE) is a relatively new, non-thermal ablation procedure based on the principle of electroporation [77]. IRE employs multiple electrodes with an insulated shaft and a non-insulated tip that are placed in parallel around the target lesion. It is important that the distances between the individual electrodes are in the range of 0.7 to 2.0 cm. Electrical fields are then generated between the individual pairs of electrodes by repeated, short current pulses. For each electrode pair, 70 to 100 pulses are emitted with a voltage between 1650V and 3000V and a duration of 90µs each. The electric field thus generated leads to irreversible formation of nanopores in the double lipid layer of the cell membranes in the ablation region, resulting in cell death by apoptosis [78]. One advantage of this ablation technique over thermal ablation methods is that the electroporation effect influences cell membranes, but much less so tissue architecture. Thus, blood vessels, bile ducts and liver capsule, but also adjacent diaphragm, are damaged to a much lesser extent [79, 80]. This makes IRE a potential curative therapeutic option for nonresectable tumors that are immediately adjacent to central hepatic vessels or major bile ducts.

To prevent cardiac arrhythmias such as atrial fibrillation caused by the high-voltage pulses, individual pulses are delivered ECG-synchronized in the absolute refractory phase of the cardiac muscle cells. In addition, patients must be completely muscle relaxed during IRE to avoid involuntary contractions during ablation; therefore IRE can be performed only under full anesthesia. It is also worth mentioning that unlike hyperthermic ablation procedures, IRE does not allow ablation of the puncture tract. Whether this leads to an increased occurrence of so-called tumor seeding along the insertion paths of the electrodes has not yet been scientifically investigated.

Compared with RFA and MWA, as well as the other percutaneous ablation procedures, the body of studies on the oncological efficacy of IRE is deficient. Previous studies mostly addressed other tumor entities besides HCC, but showed promising results. A recent meta-analysis evaluated a total of 15 prospective and 10 retrospective single-arm studies involving a total of 776 patients with liver tumors of all entities for OS, progression free survival (PFS), and safety [81]. For IRE, this meta-analysis reported an OS of 81.3 % at 12 months, 61.5 % at 2 years, and 40.9 % at 3 years; PFS was reported as 64.2 % at 12 months and 49.1 % at 2 years. Of note, HCC as a treated tumor entity was identified as a statistically significant predictor of prolonged OS ($p = 0.0176$ at 12 months and $p = 0.0094$ at 3 years). Overall, complications were observed in 23.7 % of ablations; however, in only 6.9 % of patients were complications that required treatment and thus were considered a major complication. However, the relatively high rate of major complications compared to thermoablative procedures (6.9 % vs. 1.0–3.4 %) is striking [16, 19]). This circumstance may be due, among other things, to the fact that IRE is used in the vast majority of cases for tumor lesions that are not suitable for thermal ablation or resection due to their location relative to heat-vulnerable structures or large vessels, and thus entail higher complication rates due to their high-risk location.

Despite the promising initial data, IRE is currently not recommended in German and international guidelines for the treatment of HCC due to the overall still low level of evidence, if resection, RFA or MWA is possible instead [4]. IRE is largely performed only at specialized centers and for smaller-diameter HCC due to the technically complex and potentially challenging technique involved in the parallel placement of multiple electrodes, mostly near major hepatic vessels and major bile ducts.

Interstitial brachytherapy

Interstitial brachytherapy (IBT) is a local high-dose irradiation procedure (usually performed using the afterloading technique) and, along with the thermal ablation procedures RFA and MWA, is part of the current ESMO guidelines as an alternative treatment option for patients with stage BCLC 0-A HCC [82]. It should be mentioned that according to the current S3 guideline, no general recommendation for this can be derived from the literature on IBT. Similar to LA, the target tissue is punctured using a coaxial needle and then a sheath catheter for the radiation source (usually iridium-192) is inserted. After consultation with the radiotherapists, multiple catheters may be placed depending on tumor size and geometry to acquire an optimal irradiation model. Subsequent cross-sectional imaging using computed tomography (CT) or magnetic resonance imaging (MRI) is used for individualized pre-therapeutic radiation planning. Advantages of IBT within the liver are the steep dose fall-off from the radiation source to the periphery and a concomitant sparing of peritumoral tissue, as well as the better predictability of dose exposure to structures at risk (unlike the more or less uncontrolled heat propagation with RFA/MWA). If the known tolerance values are exceeded during planning, the irradiation geometry can be adjusted or the target dose can be reduced (while accepting a lower effectiveness). Further advantages are the lack of limitation regarding the tumor size to be treated as well as the independence of cooling effects of large vessels in contrast to thermal ablation methods [83, 84].

Excellent local tumor control rates ≥ 90 % at a follow-up of ≥ 12 months have been demonstrated for IBT in recent years in predominantly retrospective cohort studies in patients with carcinomas up to 12 cm in diameter [85–88]. A recently published randomized single-center phase 2 trial demonstrated a better outcome' of IBT in a total of 77 patients with unresectable HCC compared to transarterial chemoembolization with respect to the endpoints TTUP (time to untreatable progression, hazard ratio: 0.49), TTP (time to progression, hazard ratio: 0.49), and OS (hazard ratio: 0.62) [89]. According to the BCLC classification, patients in stage BCLC-B and -C in particular benefited (hazard ratio for OS: 0.55 and 0.52, respectively), so that in summary of the results, according to the authors, the prerequisites for a phase 3 trial are given. However, to clarify the ultimate value of IBT among percutaneous local ablative procedures, further comparative prospective randomized trials versus established therapies RFA/MWA and transarterial chemoembolization are needed.

Electrochemotherapy

Like IRE, electrochemotherapy (ECT) utilizes the principle of electroporation [90]. For this purpose, several electrodes are placed in

parallel around the target lesion. The technical design of the electrodes is identical to IRE consisting of an insulated shaft and a non-insulated tip. In contrast to IRE, however, only 8 current pulses with a frequency of 1000 Hz and a pulse length of 100 µs and a voltage of up to 3 kV are applied, resulting in electroporation in the ablation region. In contrast to IRE, the effect of electroporation in ECT is reversible due to the shorter duration of electroporation and the lower electrical field strengths. The reversibly created nanopores in the cell membranes in the ablation region allow molecules that would otherwise not cross the double lipid layer of the cell membranes to cross to intracellular in significantly increased concentrations. This effect is used to achieve a local cytotoxic concentration of a chemotherapeutic agent without resulting in a systemic effect. Bleomycin and cisplatin have been established as chemotherapeutic agents for ECT. For bleomycin, 100–5000-fold increased local concentrations are achieved, and for cisplatin, 1.8–12.2-fold increased concentrations are reached [91]. Bleomycin may be administered either locally into the tumor at a concentration of 1000 I/ml or intravenously at a dosage of 15 000 IU/m² body surface area; cisplatin may only be administered locally at a concentration of 1 mg/ml [92].

ECT has been used since 1991 for the treatment of cutaneous and subcutaneous metastases of various tumor entities [93]. Due to the good tolerability as well as local tumor control rates, ECT is, among others, integrated in the current S3 guideline for the diagnosis and therapy of malignant melanoma [94].

As with IRE, ECT causes very little damage to blood vessels, bile ducts, as well as liver capsule and other adjacent structures. Potenzial advantages of ECT over IRE are shorter ablation times due to the lower number of pulses (8 pulses per electrode pair vs. 70–100 per electrode pair) and the fact that electrodes can be placed farther apart in percutaneous ECT than in IRE (3.0 cm vs 2.0 cm), allowing ablation of much larger tumors without repositioning of the electrodes. Potenzial disadvantages of ECT are side effects due to the chemotherapeutic agents used, although these are expected to be much less common compared to systemic use due to the much lower dosage. A potential and feared side effect of bleomycin is drug-induced pulmonary fibrosis; this occurs more frequently at cumulative doses of 300 mg (300 000 IU) and above [95]. However, assuming an average adult body surface area of 1.8 m² and a bleomycin dose of 15 000 IU/m², the threshold of 300 000 IU would not be exceeded until the 12th ECT treatment.

Initial case series and pilot studies of intraoperative ECT of liver metastases and HCC showed promising results with complete ablation rates ranging from 55 % to 88 % [96–99]. As of 2021, there are only two case reports for percutaneous ECT of HCC [100, 101]. Due to the lack of supporting evidence for the effectiveness of percutaneous ECT, it is not mentioned in the current S3 guidelines for the diagnosis and treatment of HCC.

Summary and Outlook

Over recent decades, percutaneous tumor ablation procedures have become an integral part of the treatment algorithm for hepatocellular carcinoma. Due to good data, RFA and MWA are now considered equal to surgical resection as first-line local therapy in Germany for stage BCLC 0 and A HCC with a diameter of ≤ 3 cm. For tumors with a diameter between 3 and 5 cm, the current S3 guidelines recommend a combination of transarterial chemoembolization (TACE) and thermal ablation using RFA or MWA as combination therapy is superior to thermal ablation alone in tumors of this size and shows comparable results with surgical resection in terms of overall survival.

Another factor in achieving better therapeutic outcomes is the use of navigation systems which allow more accurate treatment planning and probe placement, especially when treating large and complex lesions using multiple probes or electrodes. In recent years, several navigation applications for CT-guided ablation have been developed and evaluated with promising results. Benefits to both patients and interventionalists include, more precise probe placement, shorter intervention times and reduced radiation exposure. Both robotic and stereotactic systems as well as tracking systems are currently available on the market [102–108]. New techniques such as augmented reality could also be used in the future to navigate during percutaneous ablations [109].

Hard-to-see or undetectable lesions can be a problem for image-guided ablations using ultrasound, CT, and more recently MRI. Advances in fusion of complementary image data sets from CT, MRI, ultrasound, as well as contrast ultrasound examinations make it possible to effectively and safely ablate difficult-to-visualize tumors [110].

In addition to advances in the technology of established RFA and MWA ablation methods, alternative ablation methods such as CT, LA, IRE and IBT continue to evolve. Although study results to date have been largely positive for these procedures, according to the S3 guideline, there is currently insufficient evidence to support their standard implementation in the treatment algorithm for HCC. Nevertheless, these procedures already represent a useful addition to the local ablative arsenal in individual cases and could assume a more prominent role in the near future.

Finally, electrochemotherapy (ECT), a procedure already known from dermatology for the treatment of cutaneous and subcutaneous tumors, has been further developed in recent years for the nonthermal percutaneous ablation of liver metastases. ECT has been known in dermatology for decades and is a widely used procedure due to strong evidence, both in the treatment of melanoma and metastases [111]. Similar to IRE, ECT is a nonthermal procedure in which multiple electrodes are placed around the target lesion. However, unlike IRE, reversible rather than irreversible electroporation is produced by the applied current fields. This results in high concentrations in the target area of a chemotherapeutic agent injected intravenously or locally immediately before electroporation (in most cases bleomycin, more rarely cisplatin), which leads to cell death [112]. As with IRE, ECT is a procedure that spares blood vessels and bile ducts. However, unlike IRE, ECT allows the electrodes to be placed much further apart, theoretically allowing larger target lesions with diameters greater than 5 cm to be treated curatively. Initial case reports and a small case series from recent years show the potential of ECT [100, 101, 113]; however, no studies with larger case numbers are yet available.

On the whole, the aforementioned technical and procedural advances are expected to further solidify the indication for percu-

taneous tumor ablation of hepatocellular carcinomas in the future and enable the treatment of larger and more complex tumors.

Conflict of Interest

The authors declare that they have no conflict of interest.

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