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ADVANCES IN CLINICAL RADIOLOGY

Advances in the Ablative Management of Hepatocellular Carcinoma

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KEYWORDS

• Hepatocellular carcinoma • HCC • Ablation • Locoregional therapy • Radiofrequency • Microwave • Cryoablation • Irreversible electroporation • Radioembolizaiton • Stereotactic body radiotherapy • Ethanol • TACE • HIFU • Laser • Immunotherapy

KEY POINTS

- Ablation is recommended by international guidelines for the treatment of HCC.
- Ablative therapies have demonstrated outcomes comparable with resection for early HCC.
- The choice of therapy is a complex decision requiring evaluation of oncologic goals, tumor phenotype, hepatic functional substrate, and patient anatomy.

INTRODUCTION

Hepatocellular carcinoma (HCC) is a global health problem with an increasing incidence [1]. HCC commonly arises in the setting of liver cirrhosis, which results in an organ-wide preneoplastic environment compounded by functional deterioration. Liver transplantation addresses tumor and cirrhotic hazards, but many patients are ineligible at diagnosis [2,3]. Likewise, less than a third of patients are candidates for resection and more than half recur within 2 years of surgery [4]. In light of these challenges, ablation has emerged as a uniquely suited, minimally invasive, treatment of HCC because it balances curative intent therapy with preservation of hepatic tissue.

Ablation is the *in situ* transfer of energy, chemical, or bioactive implements that change the tumor and regional environment resulting in permanent disruption of cellular metabolism. Robust evidence in support of ablation generated over decades of research has led the American Association for the Study of Liver Disease, the European Association for the Study of the Liver, and the Barcelona Clinic Liver Cancer group to include ablative therapy as recommended curative treatments for very early stage HCC [2,5,6]. Patient selection requires the examination of a complex interplay of variables including performance status, oncologic goals, tumor phenotype and staging, hepatic functional substrate,

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and local anatomic involvement. Although radiofrequency ablation (RFA) is the benchmark and most widely acknowledged ablation technology, there are limitations to its safe use in certain tumors. Developments in multiple ablation modalities have expanded patient eligibility and enhanced the practice of interventional oncology. A survey of key points in the current application of ablative therapies for HCC is presented herein.

RADIOFREQUENCY ABLATION

RFA was the first thermal ablation technique to receive international societal guideline endorsement for curative HCC therapy. It carries the largest published experience and is the modality to which all other ablation technologies are compared. RFA uses high-frequency alternating electrical current to create ionic agitation and frictional heating, which leads to protein denaturation and coagulative necrosis. Ablation efficacy depends on temperature and time, with 4 to 6 minutes required to achieve cell death at 50°C and near instantaneous cell death at temperatures greater than 60°C [7].

RFA is well tolerated with an associated mortality of less than 1.2% and a morbidity of 3% to 7% [8,9]. In a low bias risk randomized controlled trial (RCT) of RFA versus partial hepatectomy for solitary HCC less than or equal to 5 cm, both groups had similar overall survival (OS) and disease-free survival with fewer and less severe complications with RFA [10]. A multicenter study of 544 patients undergoing RFA versus resection for HCC less than or equal to 3 cm demonstrated no significant difference in tumor recurrence or OS after propensity score matching [11]. A systematic review of variable quality RFA versus resection RCTs demonstrated no difference in 3-year survival, shorter hospitalization, but a higher risk for intrahepatic recurrence with ablation [12].

Despite its efficacy, there are several well-recognized limitations to RFA. Although successful treatment of tumors greater than 3 cm is achievable, the maximum benefit of RFA may be limited to 2 cm tumors or less [13]. Tumors in close proximity to central bile ducts and critical extrahepatic anatomy unamenable to ductal cooling or hydrodissection may not be eligible for treatment. Poorly defined tumors with limited visibility during image guidance are at risk for suboptimal ablation. Similarly, tumors with an infiltrative morphology or high-risk biology may require larger margins that cannot be safely provided with RFA. Perhaps of most significance, RFA treatment volumes are restricted by diminished electrical conductivity of desiccated tissue and lethal temperature thresholds are impeded by heat-sink effect near large vessels.

MICROWAVE ABLATION

Microwave ablation (MWA) generates rapid heating of tissues through the electromagnetic wave-induced oscillation of water molecules rather than electrical current. This provides several advantages when compared with RFA by generating higher temperatures, larger ablation volumes, shorter treatment times, and reduced susceptibility to heat-sink effect [14,15]. Multiple MWA antennae are used with all devices and patient grounding pads are not required. Although these are recognized improvements, MWA shares several limitations with RFA, the most important of which is risk of thermal injury to adjacent critical structures.

Clinical studies have shown comparable safety and efficacy for MWA when compared with RFA with lesions up to 5 cm and trends that suggest an advantage for larger tumors [16]. A study of 220 patients with HCC treated with MWA demonstrated an OS of 95% and 89% and a progression-free survival (PFS) of 81% and 63% at 1 and 2 years, respectively [17]. Chong and colleagues [14] analyzed the use of MWA versus resection in patients with tumors less than 5 cm and showed a significantly better OS for ablation in patients with albumin-bilirubin scores of 2 or 3. In an RCT of MWA versus RFA for lesions up to 4 cm, no significant difference was found with 2-year target lesion progression of 6% and 12%, respectively [18]. Nevertheless, MWA has seen increased use because of its useful technical improvements over RFA.

CRYOABLATION

Cryoablation induces tumor necrosis by freezing tissues to −20°C to −40°C [16]. The expansion of high-pressure argon gas within a closed-circuit (Joule-Thompson effect) enables the noninsulated cryoprobe tip to centrifugally cool adjacent soft tissues resulting in a spheroid ablation. Cryoablation typically entails two 8- to 10-minute freeze cycles separated by a 5- to 8-minute thaw, with the lethal isotherm (−20°C) optimally extending 0.3 to 0.5 cm beyond the tumor to achieve a sufficient treatment margin.

Intraprocedural ice formation is easily monitored with computed tomography, MRI, and ultrasound (Fig. 1). This is advantageous when treating tumors

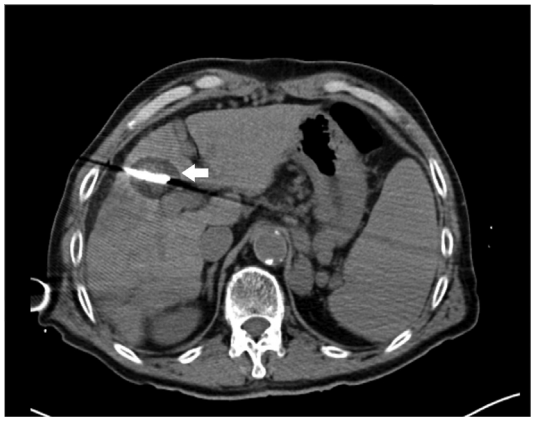

FIG. 1 A 79-year-old man with alcoholic cirrhosis presents for definitive management of a United Network for Organ Sharing (UNOS) 5A 1.8-cm HCC at the junction of hepatic segments 5 and 4b in direct contact with the central anterior division bile duct. Cryoablation generated visible ice ball formation (*arrow*) allowing for real-time noncontrast computed tomography (CT) monitoring of margin. Lesion demonstrated complete response at 13 months post-treatment with no biliary injury.

close to critical structures, allowing dynamic visualization to avoid nontarget thermal injury. Cryoablation creates large ablation volumes, with a 5.5 cm × 3.5 cm ice-ball typically achievable with a single 13G to 17G cryoprobe, and the potential for even larger volumes when multiple probes are used. Other advantages include decreased periprocedural pain and reduced vascular and biliary injury [19].

The only multicenter RCT of cryoablation versus RFA included 360 patients with HCC measuring less than 4 cm and showed equal safety and efficacy, similar 5-year survival rates, and a significantly lower local tumor progression for tumors greater than 3 cm in the cryoablation group. Complications for both were similar with a rate less than 4% [20]. A smaller study also showed significantly improved local control rates in HCC greater than 2 cm for cryoablation compared with RFA and MWA [21].

Disadvantages of cryoablation include increased treatment time and lack of hemostatic coagulation. Rarely, post-cryoablation multiorgan failure known as "cryoshock" has been reported, but its incidence is less than 1% [22].

IRREVERSIBLE ELECTROPORATION

Irreversible electroporation (IRE) is a nonthermal ablative technology that uses short, high-voltage, electrical pulses delivered between probes to create microscopic holes in tumor cell membranes while preserving extracellular matrix, blood vessels, and bile ducts within the liver. It may be safer to use when thermal ablation is not an option because of tumor location near critical structures and it is impervious to heat-sink effects.

There are increasing IRE data suggesting similar outcomes in small (<3 cm) tumors when compared with thermal modalities [23,24]. Additionally, studies have demonstrated safe ablations that involved the intrahepatic bile ducts and it may be better tolerated than MWA [25,26].

Disadvantages to IRE include the need for general anesthesia with paralysis and the necessity for placing multiple parallel probes with minimal convergence or divergence [27]. Ablations are susceptible to the interaction of several electrical fields and variable tissue impedance factors. Bipolar IRE probes are currently under development, which will likely improve these circumstances. Although IRE has been cleared by the Food and Drug Administration (FDA) for the ablation of soft tissue, it currently does not carry a disease-specific indication, which can preclude reimbursement and create barriers to routine clinical use.

TRANSARTERIAL RADIOEMBOLIZATION

Transarterial radioembolization (TARE) is a form of vascular brachytherapy that implants microscopic yttrium-90-containing particles that emit ionizing β-radiation to a limited range of tissue (2–11 mm). TARE is now included within American Association for the Study of Liver Disease recommendations for the treatment of Barcelona Clinic Liver Cancer stage A, B, and C HCC with level 2 and 3 evidence, but retrospective data from highly variable practices and dosimetry has limited further endorsement [5].

Similar to definitive radiotherapy used in other malignancies, ablative TARE relies on precisely delivering high radiation doses to tumor and an expendable margin of liver within an arterially perfused volume, or hepatic angiosome (Fig. 2). Usually reported as radiation segmentectomy or lobectomy, this approach is generally accomplished by administering sufficient particle radioactivity and number to achieve a greater than 190 Gy Medical Internal Radiation Dose.

Retrospective analyses of ablative TARE for early HCC have demonstrated tumor complete pathologic necrosis (CPN) rates of 100% and greater than 90% in 52% and 48% of patients, respectively, and responses equivalent to thermal ablation [28,29]. A single institution, high-volume, practice has reported 5-year ablative

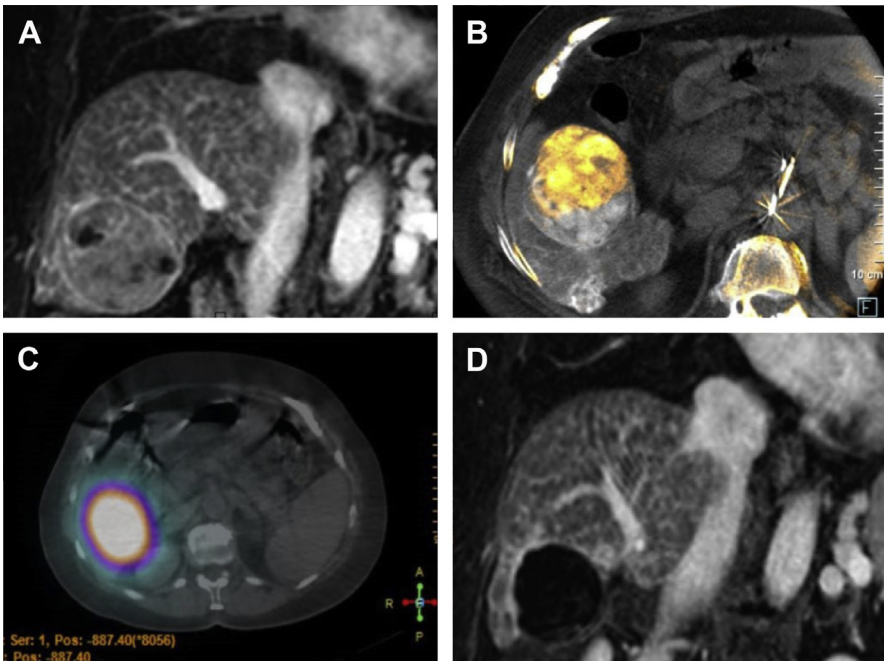

FIG. 2 (**A**) A 73-year-old woman with primary biliary cirrhosis presents for downstaging of a UNOS 5X, 6.7 cm right hepatic lobe HCC. (**B**) Cone beam CT fusion of hepatic segments 5 (orange) and 6 (white) within the target angiosome encompasses the tumor. (**C**) Bremsstrahlung single-photon emission CT fusion post ablative TARE demonstrates conformal activity within the tumor. (**D**) Portal venous phase subtraction MRI at 12 months shows complete response per mRECIST. Patient underwent liver transplantation 13 months post ablative TARE with complete pathologic necrosis of tumor in the explant.

TARE survival rates for early HCC that are comparable with established curative standards [30].

Ablative TARE advantages include treatment of tumors that are anatomically unamenable to thermal ablation, ablation of tumor thrombus, lack of cumulative whole-liver dose with repeat treatment, dose conformality of brachytherapy, and minimal treatment toxicity usually accomplished in one or two sessions. Uniquely, ablative TARE can safely devitalize large volumes of liver, including an entire lobe, which can be applied to future resection sites as a surgical neoadjuvant or in tumors necessitating large margins [31]. The foremost limitation of ablative TARE is its dependence on favorable vascular conduit to the target lesion.

STEREOTACTIC BODY RADIOTHERAPY

Stereotactic body radiotherapy (SBRT) is a valuable option for the treatment of select HCC [32–34] when thermal or transarterial therapies are not applicable [35]. The use of hypofractionated photon or proton SBRT under image-based stereotactic guidance is required to maximize safety and efficacy. Doses for photon-based SBRT typically range from 24 to 60 Gy in three to six fractions, and up to 67.5 Gy in 15 daily fractions for proton-based SBRT (Fig. 3) [36].

SBRT local control rates for HCC less than or equal to 5 cm are 85% to 93% in 1 to 3 years with OS rates ranging from 43% to 72% [32–34]. A retrospective 10-year study of patients with HCC bridged for transplant using SBRT and RFA yielded CPN rates of 13% and 49.2%, respectively [37]. For radiation-naive patients with Child-Pugh class A and B-7 status, SBRT is well-tolerated, with grade 3 or higher toxicity rates less than 13% [38]. The risk for complications increases substantially with worsening liver comorbidities, tumors greater than 5 cm, central location, and previous history of liver-directed therapies. The development of radiation-induced liver disease occurs in approximately 25% or less of patients, but is tolerated in subjects with a Child-Pugh score of 7 or less [39].

Currently, SBRT is limited to centers with advanced imaging and tumor motion tracking capabilities. The placement of fiducial markers to guide therapy may

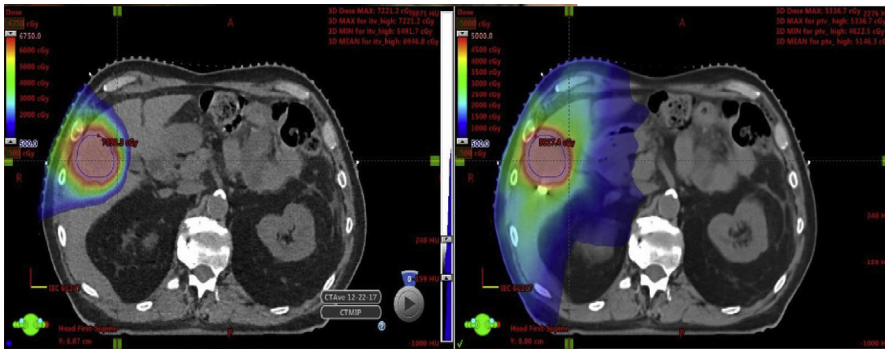

FIG. 3 The dosimetric advantage of proton beam radiotherapy, versus photon-based SBRT, is shown. (*Left*) A patient's plan with a prescription dose of 67.5 Gy in 15 daily fractions, by intensity-modulated proton therapy. (*Right*) The same patient's anatomy was used for photon-based SBRT planning, with a prescription of 50 Gy in 5 daily fractions. Despite a higher-dose prescription plan, the dose fall-off to the surrounding organs at-risk structures and also the rest of the liver are better for intensity-modulated proton therapy. The patient was eventually treated by proton therapy.

diminish the noninvasive advantage of SBRT [40]. Cumulative dose limitation remains a barrier to retreatment, but has become less restrictive with proton therapy [41,42]. Intrahepatic progression is the major mode of treatment failure, and increased efforts have been devoted to combining SBRT with other therapies. As more proton centers are built throughout the country, the use and understanding of proton therapy will undoubtedly increase accordingly.

ETHANOL THERAPY

Ethanol exhibits strong tissue ablative properties while minimizing the negative immune responses and angiogenesis related to ischemia-based therapies, such as transarterial chemoembolization (TACE). This includes reduced production of cytokines interleukin, interleukin-8, and vascular endothelial growth factor, elevations of which are associated with poor tumor response, distant metastases, and decreased OS [43]. It causes necrosis primarily by oxidative stress, alteration of membrane integrity, and denaturation of proteins by disrupting side-chain intramolecular hydrogen bonding.

As one of the first recognized ablative therapies for HCC, percutaneous ethanol injection (PEI) is practical and inexpensive, but efficacy is highly operator-dependent and subject to tumor visibility. It is further limited by tumor architecture that may not allow adequate diffusion, and the unreliable treatment of liver margin that may harbor microscopic disease. PEI is less effective than RFA, but provides a low morbidity option for small lesions in high-risk anatomy with poor blood supply [44,45].

Ethanol can also be delivered intra-arterially as a lipiodol/ethanol mixture (LEM) and is best accomplished with superselective wedged or balloon-assisted catheterization. LEM regionally infiltrates arterioles, sinusoidal spaces, peribiliary plexuses, and portal venules, and penetrates into tumor cells. This multicompartmental distribution provides a superior margin over single-compartment arterial embolizations and may increase efficacy with angioinvasive tumors (Fig. 4) [46]. LEM is limited by its dependence on tumor vascularity, need for occlusive superselective arterial catheterization, and failure to adequately saturate tumor before excessive reflux occurs.

Phase I data suggest that LEM versus conventional TACE results in significantly improved rates of complete response (CR) by European Association for the Study of the Liver criteria, time-to-progression, and CPN [47]. An RCT of 90 patients favored LEM over TACE with median time-to-progression of 34.6 versus 26.1 months ($P = .028$). CR at 6 months favored LEM over TACE (73% vs 54%; $P = .012$). The OS for LEM and TACE (24.3 vs 20.1 months) was not significantly different because extralesional progression and worsening cirrhosis were independent of therapy [48].

EMERGING THERAPIES

Less frequently used but promising modalities in HCC ablation include high-intensity focused ultrasound (HIFU) and laser ablation (LA). HIFU is typically performed within a specialized motorized gantry that directs high-energy external compression waves onto a single focal point in the liver. Compared with TACE,

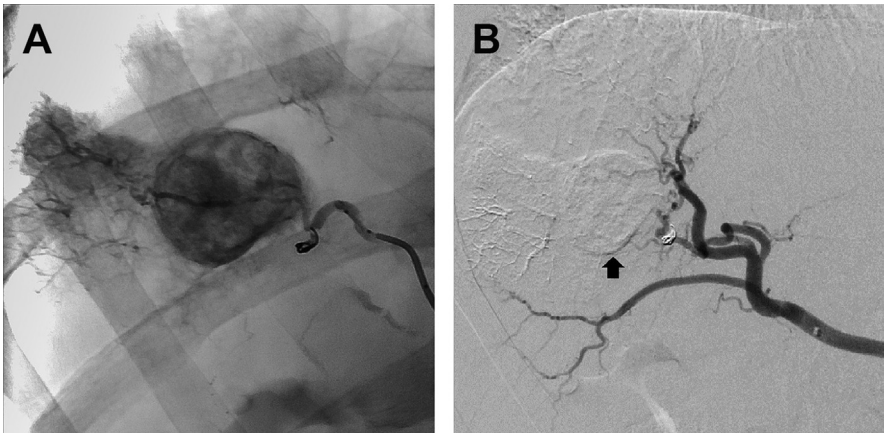

FIG. 4 A 64-year-old man with hepatitis C cirrhosis and a UNOS 5B 3.7-cm HCC presenting for bridging therapy in preparation for liver transplant. (**A**) Radiograph obtained during balloon-occlusion delivery of lipiodol/ethanol 2:1 mixture shows saturation of the tumor and extension into the portal system. (**B**) Post-LEM digital subtraction arteriogram shows a small vessel supplying the inferior margin, which was initially not recognized. The tumor demonstrated greater than 95% necrosis at explant with trace viability in the inferior margin. Five years after transplantation, the patient has no evidence of tumor recurrence.

HIFU demonstrates increased CR rates and improved 1-, 3-, and 5-year survival (84.6%, 49.2%, 32.3% vs 69.2%, 29.8%, 2.3%, respectively) for larger HCCs (3–8 cm) [49]. HIFU requires lengthy procedure times in excess of 5 hours and is limited by patient motion and reflective tissue, such as ribs, within the irradiation path [38].

LA causes tissue necrosis via the conversion of absorbed infrared light into heat through coaxially placed optical fibers in multiple 21G needles. Infrared energy penetrates up to 15 mm, but ablations can be larger because of conducted heat. Compared with TACE in a pilot case-control study, LA demonstrated improved CR (63.4% vs 19.5%), 36-month survival (55.4% vs 48.8%), and recurrence (75% vs 19.5%) for lesions greater than 4 cm [50]. Benefits to LA include the low-profile needles required for placement and low cost when compared with RFA and MWA [51]. Disadvantages are few compared with other thermal therapies, but there is limited representation in the literature.

TRANSARTERIAL CHEMOEMBOLIZATION COMBINATION THERAPIES

Ablation is often curative for small HCC, but efficacy decreases as tumor size increases beyond 3 cm. Ischemia via transarterial embolization (TAE) or TACE as an adjuvant to thermal ablation has been shown to improve outcomes in animal models and clinical studies increasing the size of tumors that can be treated with curative intent.

Data are developing to support the synergy of TACE with multiple modalities (Fig. 5). In an RCT for solitary HCC less than 7 cm comparing TACE plus RFA with RFA alone, OS at 1 and 4 years favored TACE + RFA at 92.6% and 61.8% versus 85.3% and 45.0% ($P = .002$), respectively. Recurrence-free survival (RFS) was superior for TACE + RFA at 79.4% and 54.8% versus 66.7% and 38.9% at 1 and 4 years ($P = .009$) [52]. Similarly, a single-center RCT comparing cryoablation and TACE + cryoablation in 60 patients with unresectable stage III or IV HCC showed improved OS and PFS in the TACE + cryoablation group [53].

A meta-analysis of 19 RCTs comparing TACE with or without PEI demonstrated higher survival rates at 1, 2, and 3 years, lower local tumor recurrence rates, and improved tumor response with TACE + PEI combination therapy [54]. An RCT comparing TACE with and without HIFU for HCC greater than 5 cm found TACE + HIFU is more effective than TACE monotherapy with a 31.8% versus 2.8% 3-year OS, respectively ($P<.01$) [55,56]. A retrospective study found that TAE/TACE plus SBRT is more effective than SBRT monotherapy for large HCC (>5 cm). The reported 5-year OS was 46.9% versus 32.9% ($P = .047$) and significantly favored the TAE/TACE plus SBRT [57].

The available data do not elucidate which therapeutic combinations offer optimal outcomes and safety profiles.

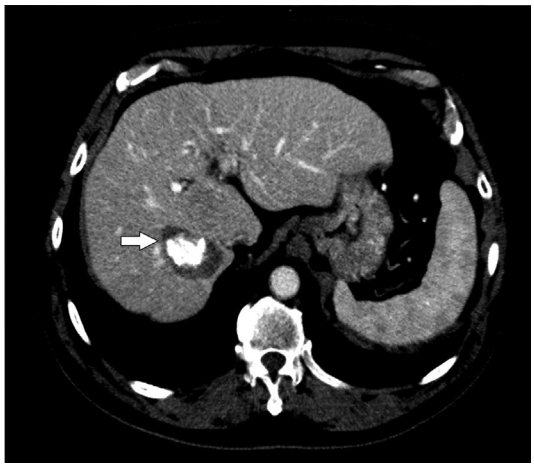

FIG. 5 A 68-year-old man with nonalcoholic steatohepatitis cirrhosis presents for definitive therapy for a UNOS 5B 3.4-cm right hepatic lobe HCC. Portal venous phase CT at 3 months post-TACE plus MWA demonstrates lipiodol-stained tumor (*white arrow*) within the treated ablation margin.

ABLATIVE-SYSTEMIC COMBINATION THERAPIES

Although there is rationale for combining ablation with a systemic tumor growth inhibitor, data exploring this notion have been negative thus far. The STORM trial randomized patients with HCC to adjuvant sorafenib versus placebo after resection or ablation and showed no difference in median RFS of 33.3 versus 33.7 months (hazard ratio [HR], 0.940; $P = .26$) [58]. In the subgroup undergoing ablation, median RFS was 19.6 versus 22.1 months (HR, 0.97).

The HEAT study randomized patients with HCC up to 7 cm to RFA with and without a peripheral infusion of lysothermosensitive liposomal doxorubicin. Although the overall study population end point of improvement in PFS was not met (HR, 0.96; 95% confidence interval, 0.79–1.18; $P = .71$), a subset analysis of patients with greater than or equal to 45-minute RFA dwell times suggested improved efficacy (HR, 0.63; 95% confidence interval, 0.41–0.96; $P<.05$) [59].

Although sorafenib was the sole standard-of-care for locally advanced systemic therapy in the past decade, there has been a rapid expansion of FDA-approved systemic agents for HCC. First-line therapy now includes sorafenib and lenvatinib, and second-line therapy has been established with regorafenib and nivolumab [60,61]. Although all but four of the agents are multiple kinase inhibitors, the immuno-oncologic mechanism of nivolumab is of particular interest as an adjunct to ablation. This potential, in addition to the interplay between the immune system and ablation, is discussed in the following section.

ABLATION AND IMMUNOTHERAPY

Immune activation via exposure of tumor antigens seems to explain occasional tumor responses distant to an ablation site, a phenomenon referred to as the abscopal effect [62]. Unlike resection, antigenic exposure during ablation could stimulate immunologic responses that, if properly exploited, may generate sustainable immune-mediated disease control [63]. Durable tumoricidal responses require complex interactions between antigen recognition and presentation, T-cell activation, T-cell relevance in the setting of continuous tumor genetic mutation, and circumvention of suppression mechanisms. With the recent advent of FDA-approved immunotherapy agents for cancer, considerable research is underway on how to augment its effects with ablation.

The CheckMate 9DX study (NCT03383458) is evaluating RFS in 530 patients at high risk of recurrence receiving nivolumab versus placebo following complete resection or ablation. A National Cancer Institute trial is exploring the combination of durvalumab and tremelimumab with TACE, RFA, and cryoablation for HCC and biliary tract cancers (NCT02821754). There are numerous trials examining TARE plus immunotherapy in the United States, Europe, and Asia (NCT02837029, NCT03380130, NCT03033446).

Although heat-based ablation that denatures protein has been shown to elicit the abscopal effect [64], nonthermal modalities that preserve antigens (eg, IRE, cryoablation, TARE, and SBRT) are of particular interest as immune stimulators [65]. IRE may generate a larger immune response than cryoablation [66], and when used in conjunction with allogenic natural killer cells has demonstrated an increased median OS in stage IV HCC when compared with IRE alone [67,68].

Oncolytic virotherapy is a developing modality with demonstrated efficacy in preclinical models and phase 2 studies [69]. It involves the local injection of viruses that selectively target and replicate within tumor cells, providing cytoreduction while stimulating a host immune-mediated antitumor response. A randomized phase II study using vaccinia intratumoral injections in patients with advanced HCC showed acceptable safety and a significant OS benefit related to administered viral load (14.1 months vs 6.7 months for high and low dose, respectively; HR, 0.39; $P = .020$) [70].

Development of tailored viral vectors is an active area of research and phase 3 data is currently accruing. Comparisons with other ablative modalities are unavailable at this time.

FUTURE CONSIDERATIONS

The fortunate abundance of ablation technologies has strengthened options for many patients with HCC and allows for treatment allocation based on tumor presentation. Efforts to improve response and mitigate disadvantages to the discussed modalities require continuous refinement. Technical success is further improved by adopting enhanced imaging guidance techniques, such as fusion of ultrasound and computed tomography/MRI, contrast-enhanced ultrasound, and electromagnetic probe tracking [71,72]. Interstitial injection of saline, dextrose solutions, or hydrogels are used to protect critical structures [71,73]. Combining ablation technologies, even treating portions of the same lesion with different modalities, may ultimately be required to optimally eliminate tumor while preserving essential liver tissue [71,74].

It has been observed that inadequate locoregional treatment may generate several negative alterations to tumor biology. Both suboptimal embolic or ablative therapy can result in rapid progression of residual disease, promotion of distant tumor growth, and early nodal recurrence after transplantation [75–77]. Operators should strive for CPN of a targeted lesion and eschew perceptions of subtotal tumor ablation as an acceptable end point. Much like resection, successful ablations remain subject to the inherent limitations of staging because serologic, imaging, and histologic assessment lack the sensitivity to detect the entirety of disease. As such, there is opportunity for future alliance with adjuvant molecular and biologic agents to approach absolute tumor eradication.

Ablation has secured its role as an indispensable instrument for the treatment of HCC. As institutional and operator experiences with ablation continue to mature, patient selection and outcomes will undoubtedly benefit. Treatment protocols are evolving to more comprehensively reflect tumor and patient factors outside of conventional staging systems and consequently allocate personalized ablation regimens that maximize safety, efficacy, and quality of life.

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