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Title
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Journal
British Journal of Radiology, 95(1138)

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Publication Date
2022-09-01

DOI
10.1259/bjr.20211360

Peer reviewed

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BJR
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https://doi.org/10.1259/bjr.20211360

Received: 08 December 2021 | Revised: 20 May 2022 | Accepted: 27 May 2022 | Published online: 06 July 2022

Cite this article as:
Breuer JA, Ahmed KH, Al-Khouja F, Macherla AR, Muthoka JM, Abi-Jaoudeh N. Interventional oncology: new techniques and new devices. *Br J Radiol* (2022) 10.1259/bjr.20211360.

REVIEW ARTICLE

Interventional oncology: new techniques and new devices

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ABSTRACT

Interventional oncology is a rapidly emerging field in the treatment of cancer. Minimally invasive techniques such as transarterial embolization with chemotherapeutic and radioactive agents are established therapies and are found in multiple guidelines for the management of primary and metastatic liver lesions. Percutaneous ablation is also an alternative to surgery for small liver, renal, and pancreatic tumors. Recent research in the niche of interventional oncology has focused on improving outcomes of established techniques in addition to the development of novel therapies. In this review, we address the recent and current advancements in devices, technologies, and techniques of chemoembolization and ablation: thermal ablation, histotripsy, high-intensity focused ultrasound, embolization strategies, liquid embolic agents, and local immunotherapy/antiviral therapies.

INTRODUCTION

Image-guided interventional oncology is rapidly emerging as one of the four pillars of oncology. Ablation in hepatocellular carcinoma and colorectal liver metastases (CLMs) have been shown in prospective randomized trials to have similar overall survival as surgery for lesions smaller than 3 cm.[1,2] Transarterial embolization whether bland, conventional transarterial chemoembolization (cTACE), drug eluting embolics TACE (DEE-TACE) or radioembolization have been integrated in various guidelines (NCCN, BCLC) as therapeutic options in the management of liver only or liver dominant metastatic disease or primary liver cancer.[3–5] Despite these gains, much needs to be done to improve patient outcomes and survival. The goal of this review is to discuss newly developed devices, technologies and techniques in ablation and embolization including thermal ablation, histotripsy, high-intensity focused ultrasound, embolization strategies, liquid embolics, and local immunotherapies and antiviral therapies (Tables 1 and 2).

THERMAL ABLATION

Historically, percutaneous ablation was performed with ethanol injection (PEI).[3] However, recent advancements have led to PEI being replaced by thermal ablation. The latter induces cell death within the targeted tissue by hyperthermia with microwave or radiofrequency ablation or hypothermia with cryoablation (Figure 1). RFA induces coagulative necrosis by alternating electric current that agitate ions resulting in heat.[6] MWA utilizes electromagnetic waves emitted through a non-insulated area of antenna that agitate water molecules causing friction, heating and coagulative necrosis at 60°C.[7] Cryoablation is achieved by passing argon gas under extremely high pressure through the probe that freezes the surrounding tissue to induce cell death.[8] Multiple prospective randomized trials comparing RFA with hepatic resection for the management of small (<5 cm diameter) HCC showed that RFA had comparable survival rates to resection but with reduced complications and hospital stays.[1,9–11] In contrast, one trial found RFA to have higher recurrence rates at 5 years post-treatment compared with resection (63.48 and 41.74%, respectively, $p = 0.017$).[12] The reason for discrepancies between the trials is multifactorial including their inclusion criteria, patient characteristics and technique. For example, Huang et al which showed resection to be superior to RFA, however, the RFA cohort included participants that required laparoscopic

Table 1. Local ablation techniques including their mechanisms, indications in current/recent trials, and benefits and limitations

Technique	Mechanism	Trial indications	Benefits/Limitations
Percutaneous thermal ablation: RFA, MWA	Heat production via agitation of ions (RFA) or water molecules (MWA) resulting in tissue necrosis	Small hepatocellular carcinoma Colorectal liver metastases	Minimally invasive, localized therapy Curative for tumors up to certain size (5 cm diameter) Highest efficacy for lesions below 3 cm in diameter Heat sink (RFA more than MWA) Collateral damage form probe placement
Histotripsy	Cellular fractionation via production and ultrasound-mediated destruction of microbubbles	Primary liver tumors Calcified aortic valves BPH Liver metastases	No heat sink effect Pressure parameter modification preventing collateral tissue damage Release of tumor antigens, bolstering immunogenic responses (including checkpoint inhibitor therapies) Increased risk of damage in gaseous organs (*i.e.* lung) Risks of thrombosis & metastasis
HIFU	Ultrasound-mediated combination of thermal ablation and histotripsy mechanisms	Prostate cancer Uterine leiomyoma (fibroid) Bone tumors Breast cancer	Real-time tracking of tissue destruction when combined with MRI Urinary tract strictures, erectile dysfunction, rectal lesions in treatment of prostate cancer Effectiveness reduced by tissues that disrupt ultrasound waves (*i.e.* bone, gas) Precision sensitive to body movements (*i.e.* breathing)
IRE	Pulsatile electric field induced creation of nanopores in plasma membrane resulting in cell death	LAPC	Preserves extracellular matrix (does not destroy ducts and vessels) No heat sink effect Limited to tumors below 4 cm in diameter Possibility of strong muscle contractions (may require neuromuscular blockade) Nearby metal (*i.e.* stents) can disrupt electric current

BPH, benign prostatic hyperplasia; HIFU, high-intensity focused ultrasound; IRE, irreversible electroporation; LAPC, locally advanced pancreatic cancer; MWA, microwave ablation; RFA, radiofrequency ablation.

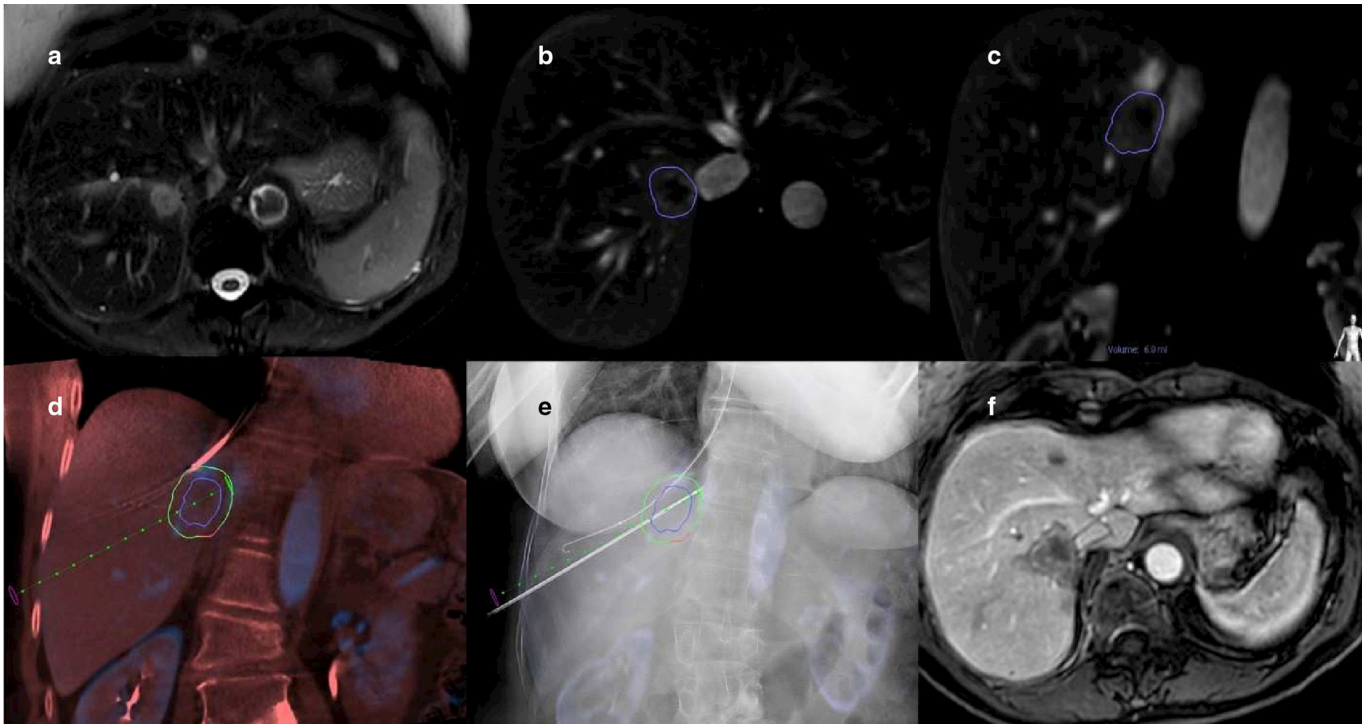
ablation due to unfavorable tumor location for a percutaneous approach. Moreover, Feng et al included tumors up to 4 cm, but it is well known that RFA's recurrence rate is greater for tumors larger than 3 cm. In general, MWA has been shown to be comparable with RFA in terms of overall survival (OS).[13–16] Studies have examined MWA and surgery finding similar outcomes in terms of OS, reduced hospital stay and complications but higher recurrence rates. MWA was also found to have higher local tumor progression-free survival compared to RFA for ablation of CLMs near hepatic vasculature since it is less susceptible to heat

Table 2. Mechanisms, discussed agents and their indications in current/recent trials for transarterial embolotherapies, liquid embolic agents, and oncolytic therapies

Therapeutic class	Mechanism	Agents	Trial indications
Transarterial embolotherapies	Directed intraarterial chemotherapy	TACE +sorafenib (VEGF inhibitor) Tirapazamine (free radical-producing prodrug)+TAE	HCC HCC
Liquid embolic agents	Tumor ischemia via complete casting of tumor microvasculature	Instylla HES™ hydrogel Silk-elastinlike protein (SELP-815K) PCL-PEG-SM hydrogel PCLA-PUSSM hydrogel	Hypervascular tumors (primarily HCC) None Liver tumor (rabbit) Liver tumor (rabbit)
Oncolytic therapies	Direct injection into tumor induces "danger signals" triggering innate immune response at local and distal tumors	T-vec (Talimogene laherparepvec) G47 δ Adenovirus CG0070 Reolysin ECHO-7 virus Rigvir virus BTV	Melanoma Glioblastoma Bladder cancer Head and neck cancers Renal cell carcinoma

BTV, Bluetongue Virus; HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization.

Figure 1. Patient with biopsy-proven cholangiocarcinoma who undergoes thermal ablation. (a-c) MRI images showing the lesion abutting the IVC and the right hepatic vein in axial and coronal planes. The lesion is segmented (purple in b-c). (d) CBCT image showing the lesion (purple) with a 1cm margin (green) as well as the projected trajectory of microwave probe. (e) Fluoroscopy images fused with CBCT and MRI planning showing the probe along the planned trajectory. (f) MRI 1month post-procedure confirms complete ablation. Patient has been disease free for over 1year



sink, which is the concept of heat dissipating due to perfusion-mediated cooling from blood flow in nearby vasculature. Particularly interesting was a 119-patient Phase II randomized clinical trial that investigated the clinical outcomes of systemic chemotherapy (oxaliplatin + 5-fluorouracil + leucovorin/folic acid, or FOLFOX) alone for CLMs *vs* FOLFOX + RFA ± resection. OS at 3, 5, and 8 year follow-up were 56.9% (95% CI = 43.3%–68.5%), 43.1% (95% CI = 30.3%–55.3%), and 35.9% (95% CI = 23.8%–48.2%), respectively for the combination group *vs* 55.2% (95% CI = 41.6%–66.9%), 30.3% (195% CI = 9.0%–42.4%), and 8.9% (95% CI = 3.3%–18.1%), respectively for chemotherapy group.[17]

All thermal ablations are limited by the ablation volume with the best results being for lesions below 3 cm.[18] Another limitation is heat sink.[18] Finally damage to adjacent organs or sensitive structures limit the use of thermal ablation such as proximity to bowel, cardiac structures, central bile duct or pancreatic duct.[18] To overcome these limitations, non-thermal ablative techniques have been investigated, including irreversible electroporation (IRE), high intensity focused ultrasound and histotripsy.

HISTOTRIPSY

Histotripsy is a non-invasive, non-thermal ablation technique that uses focused ultrasound pulses to break down tissue (Figure 2). Acoustic cavitation, a major principle in the mechanism of histotripsy, is defined as the generation and destruction of microbubbles present in tissue. These nanometer-sized pockets of gas, when stimulated by ultrasound pulses exceeding a threshold pressure expand and collapse, fractionating tissue at the cellular level.[19] The threshold required to cause acoustic cavitation is dependent on the intrinsic surface tension of the gas bubbles, which varies by tissue type.[20] Bubbles can grow from less than 5 nm in size to greater than 100 μm and then collapse, within the span of a 100 μs. This creates extreme stress on surrounding cells, causing mechanical disruption in the target tissue.[21]

Histotripsy has several advantages to thermal ablation techniques in a large part due to its non-thermal mechanism of action including a lack of heat-sink susceptibility and precise ablation margins.[22] The complete mechanism description is beyond the scope of this paper but in short acoustic cavitation is generated by delivering ultrasound microsecond length pulses resulting in the production of gas bubbles that grow from 2 to 5 nm to >100 um followed by their collapse. The expansion and collapse of the microbubbles results in strain to adjacent cells with fractionation. The boundary of histotripsy ablation zone *vs* surrounding viable cells is hundreds of microns.[23] In contrast, thermal ablation is negatively affected by a heat gradient, creating a transition zone where the level of heat applied to the target tissue diminishes directly with distance from the probe. In this transition zone, target tissue is heated but will fail to die resulting in a portion of the target tissue remaining viable. Moreover, collagen-based tissue or certain tissue with higher mechanical strength such as bile ducts, vessels, bowel require greater ultrasound pressure and the pulses than non-collagenous

Figure 2. Diagram of patient undergoing histotripsy for treatment of a liver tumor. (a) Placement of histotripsy probe over location of liver tumor. (b) Histotripsy machine with the probe and screen. (c) Illustration of the focused-ultrasound waves ablating a liver tumor

tissue (*i.e.* organ parenchyma or tumors) to induce cavitation. This threshold differential and the narrow ablation margin allow histotripsy next to critical structures.[24]

Histotripsy has the potential to be applied in a wide array of ablation contexts as evidenced from numerous pre-clinical animal experiments destroying *in vivo* tumors in a variety of different tissues.[25] Furthermore, a 2020 study showed that histotripsy cavitation causes the release of tumor antigens from acellular debris that can induce an immunogenic response, thus bolstering the impact of checkpoint inhibition immunotherapy.[26]

Three Phase I human clinical trials have been conducted to investigate the safety and feasibility of histotripsy in patients. In a 2019 trial conducted in Barcelona (NCT03741088), 11 hepatic tumors were treated with the VORTX Rx device with no adverse events and averaged 71.8% tumor contraction at 2 months follow-up, showing initial safety and efficacy of hepatic histotripsy.[27] Two Phase I primary and metastatic liver lesion ablation trials using histotripsy (Histosonic Edison) are currently ongoing in the USA and Europe since early 2021 with promising results leading to Breakthrough Designation by the US Food and Drug Administration (FDA), putting the device on an expedited fast track for approval.[28]

HIGH-INTENSITY FOCUSED ULTRASOUND

High intensity focused ultrasound (HIFU) is a local ablative technique that uses high energy ultrasound waves to alter the structure of target tissue through thermal and mechanical forces. The focused ultrasound waves can be absorbed by target tissue and this energy can be converted to internal temperatures of 70–100°C, ultimately leading to coagulative necrosis. These ultrasound waves can also create bubbles through negative pressure, which can collapse, causing mechanical damage to tissues.[29,30]

HIFU has been used for multiple pathologies. FDA-approved indications include prostate cancer, uterine leiomyoma ablation, and bone tumor pain. The largest review of the literature of prostate cancer HIFU treatment is by Warmuth et al, combining data from 20 studies including 3018 patients who underwent HIFU as primary (93%) or salvage therapy (7%).[31] Subjective outcomes included quality of life questionnaires pre- and post-HIFU treatment. Objective outcomes were biochemical disease-free survival rate, negative biopsy rate, OS rate, and prostate-cancer specific survival rate. Subjective measures were reported to be not significantly different between pre- and post-HIFU treatment. Biochemical disease-free survival rate ranged between 78–84%, 0–91%, 20–86%, 45–84%, and 69% at 1, 2, 3, 5, and 7 years respectively.[31] The negative biopsy rate was 86 and 80% at 3 and 15 months, respectively.[31] Overall survival and cancer specific survival rate were reported in only one study as 90 and 100% at 5 years and 83 and 98% at 8 years. Overall, this study did not make any conclusions on the superiority of radical prostatectomy *vs* HIFU, but reported the subjective and objective outcomes of HIFU treatment. Another study by Barret et al aimed to uncover the morbidity of focal therapy in 106 patients who underwent cryotherapy (47%), vascular-targeted photodynamic therapy (22%), HIFU (20%), and brachytherapy (11%) for prostate cancer treatment.[32] Overall, this study concluded that focal therapy like HIFU had a low complication rate and still provided successful treatment suggesting it could replace radical prostatectomy in the future. This study also recorded changes in PSA to determine therapeutic success and concluded equivalency between focal therapies at 3, 6, and 12 months. The median PSA level for all patients was 6.0 ng ml^{-1} at baseline and 2.7 ng ml^{-1}, 3.1 ng ml^{-1}, and 3.1 ng ml^{-1} at 3 months, 6 months, and 12 months, respectively.[32] Ahmed et al studied 41 patients with low, intermediate, and high-risk prostate cancer to determine whether HIFU can reduce complications specifically incontinence and erectile dysfunction seen post-radical prostatectomy. At 12 months, 100% of patients returned to full continence and 89% achieved satisfactory erectile function in addition to a reduction of the baseline median PSA from 6.6 to 1.9 ng ml^{-1}.[33] Overall, the study concluded that focal therapy like HIFU had a low complication rate and still provided successful treatment suggesting it could replace radical prostatectomy in the future. While HIFU has been shown to produce great results for prostate cancer treatment, there are some side-effects to be aware of such as urinary tract strictures and non-target ablation zones, erectile dysfunction, non-target rectal ablation, and local pain.

HIFU can also be used for palliation of pain for patients with bone pain. A study by Lin et al did a meta-analysis of 28 studies and 717 patients. Their analysis found that the rate of technique success of HIFU ablation was 93% in patients with bone lesions.[34] They found that the rate of technical efficacy for HIFU ablation was 77%, and the minor and major complication rate of HIFU ablation was 12 and 2%, respectively.

HIFU has been paired with MR imaging, called MR-HIFU, to accurately measure and monitor the temperature changes in the target tissue and surrounding structures. Since information about the local tissue destruction occurs in real time, users can adjust therapy at the time of treatment. MR-HIFU has been explored in pediatric pathologies because it is a less invasive technique. Sharma et al performed a Phase I clinical trial of MR-HIFU for painful Osteoid Osteoma in children and early results found it to be a feasible, well tolerated procedure with similar results to commonly used CT-RFA without the radiation in this pediatric population.[35] Ghanouni et al demonstrated in a cohort of 15 pediatric patients, that MR-HIFU can be used in the setting of desmoid tumor to reduce tumor volume and pain.[36] Further research is ongoing in pediatric solid tumors with great promise.[35]

Non-FDA approved applications for HIFU include the treatment of hepatic tumors, fibroadenomas, and breast tumors.[29] Wu et al performed a study with 22 patients who underwent ultrasound-guided HIFU for treatment of breast cancer. Results showed a 5 year disease-free survival and recurrence free survival rate of 95 and 89% respectively.[37]

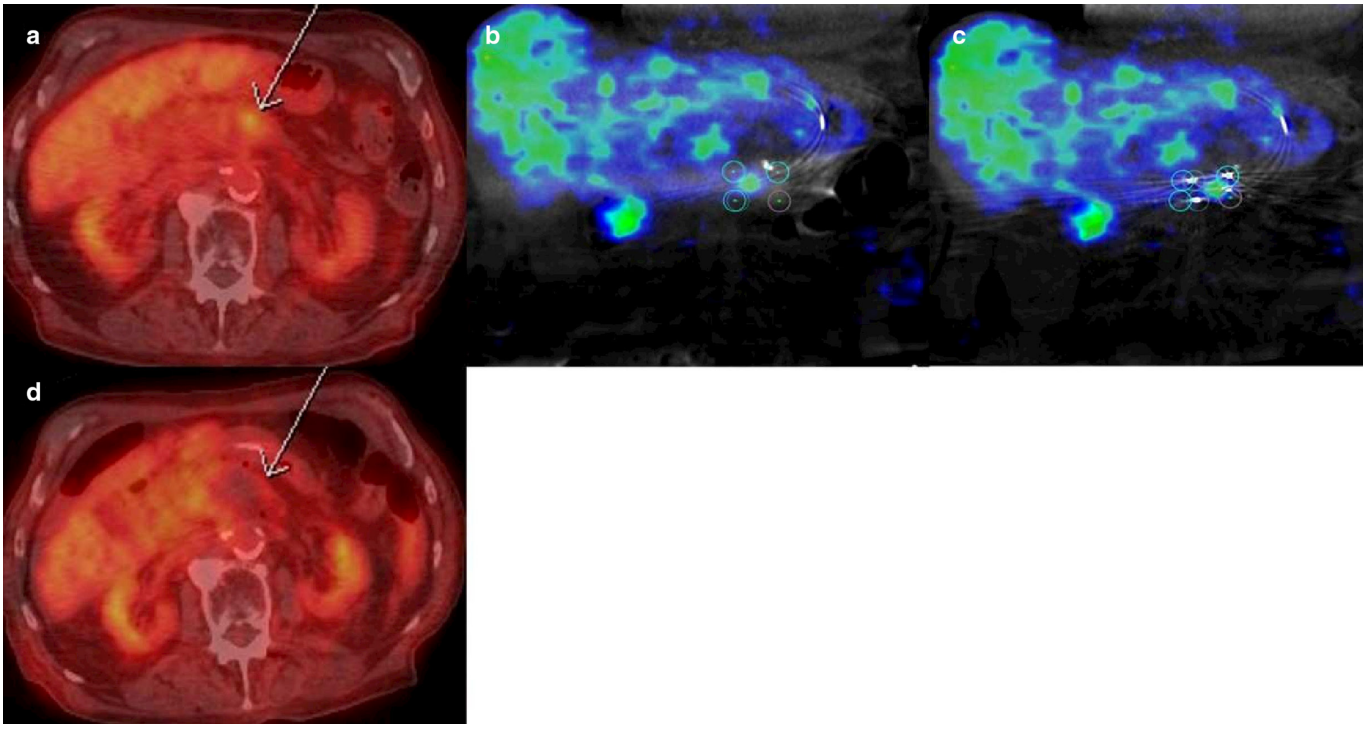
HIFU is a versatile ablative technique that has been primarily proven to be used for prostate cancer, uterine fibroids, and bone lesions in adults and children.

IRREVERSIBLE ELECTROPORATION

IRE is a local ablative technique that uses high voltage electrical energy to destroy local tissue structures. The mechanism leading to cell death is explained by the creation of nanopores in the cell membrane bilayer from the pulsatile electrical field. These nanopores allow for the disruption of intracellular homeostasis and ultimately results in a controlled apoptosis of the target cells (Figure 3).[38–41]

The primary indication and research focus of IRE is the treatment of non-metastatic locally advanced pancreatic cancer (LAPC). The current standard of care for LAPC includes chemotherapy with stereotactic body or external beam radiation therapy. Ablation techniques have been attempted including RFA and MWA. Thermal ablation techniques were associated with high mortality and morbidity.[38] The biggest advantage of IRE compared to these other ablative techniques is that it preserves the extracellular matrix therefore preserving the pancreatic duct and vascular structures.[38] It is also not prone to heat sink. Although IRE is limited to tumor smaller than 4 cm, the literature has shown this

Figure 3. Patient with locally advanced pancreatic adenocarcinoma showing progression despite chemotherapy and SBRT referred for irreversible electroporation. (a) PET avid focus in pancreatic body. (b) Coronal view of the fusion image of the previously obtained PET and intraprocedural CBCT with four planned probes trajectories. (c) Same projection as b, but the probes have been inserted. (d) PET post-procedure showing no FDG uptake. CBCT, cone beam CT; PET, positron emission tomography; SBRT, stereotactic body radiation therapy.



procedure to have strong promise as an adjuvant therapy for LAPC.[38]

Current literature on clinical outcomes is fairly limited for IRE but has demonstrated benefits in OS, which is the duration of patient survival from the time of treatment initiation and progression-free survival (PFS), which is the time from treatment initiation until disease progression (Hess).[38] Martin et al performed a retrospective study comparing outcomes of IRE patients (n = 54) to those who underwent chemotherapy and/or radiation therapy (n = 85) for LAPC. His study showed that the IRE group had an improvement in OS from 11 to 20.2 months (p = 0.03), PFS from 6 to 14 months (p = 0.01), and distant PFS from 9 to 15 months (p = 0.02) when compared to the chemoradiation group.[42] In that study, the PFS was defined as local progression per RECIST or hypermetabolic activity (increased FDG uptake) on PET if tumor was hot. Distant PFS is local progression at a remote site from primary tumor or extrapancreatic metastasis. Lafranceschina et al performed a systematic review of 15 studies including 691 patients with unresectable LAPC who underwent IRE. This study aimed to discuss the overall safety of IRE and the oncological results, measured by OS. This review found that the median OS after IRE ranged from 10 to 27 months. Overall morbidity rate was 30% (up 59% if laparoscopic) and overall mortality rate was 3%.[43]

A prospective, multi-institution assessment by Holland et al under the American Hepato-Pancreato-Biliary Association (AHPBA) used 152 patients who underwent open IRE technique. This study found OS and PFS to be 30.7 months and 22.8 months respectively as well as a recurrence rate of 21% and IRE-associated mortality below 1%.[44] The PANFIRE Phase I trial demonstrated percutaneous IRE in 25 patients to be associated with event-free survival of 8 months and OS of 11 months from IRE and 17 months from diagnosis.[45] This study also uncovered no change in pain perception and quality of life 6 weeks after IRE. The biggest concern from this trial was the number of complications from IRE which included infection, vascular damage, and biliary leaks.[45] The promising results of the PANFIRE Phase I trial led to PANFIRE Phase II trial which enrolled 50 patients with LAPC or local recurrence. They found that percutaneous IRE resulted in median OS of 17 months after diagnosis and 16 month PFS.[46] This Phase II trial also found a high complication rate of 58% and deemed IRE as a high-risk procedure. A strong recommendation was given to have patients undergo four cycles of FOLFIRINOX before IRE to downstage the tumor. Currently, the PANFIRE Phase III trial (NCT04612530) is underway evaluating the safety and efficacy of IRE with Nivolumab, an immune checkpoint PD-1 inhibitor, and CpG.[47]

IRE has now been utilized in the treatment of CLMs. The COLDFIRE-2 trial was a large Phase II, two-center, single-arm clinic trial that investigated the efficacy and safety of IRE for the management of CLMs ≤ 5 cm that were not suitable for resection or thermal ablation because of proximity to a critical structure. A total of 51 patients with 62 CLMs underwent IRE. For the primary endpoint to be met, 50% of patients had to alive without local tumor progression. The study end point was met since at 12 months, 34 of 50 patients showed no local tumor progression (LTP). Likewise, 79% of total tumors demonstrated no LTP at 12 months with no significant difference in LTP between small (<3.0 cm) and medium (3.1–5.0 cm) sized tumors. Mean survival in the study population was 2.4 years post initial IRE treatment of CLMs and 4.8 years post resection of the original colorectal tumor. With regards to safety, 44% of the 51 patients experienced adverse events with only 3 patients experiencing Grade 4 (n = 2) and Grade 5 (n = 1). The latter was a an infected biloma resulting in death 50 days post IRE. The two Grade 4 adverse events consisted of damage to the right hepatic artery branch in one patient with an ICU admission, and a wound infection with bacteremia in another patient who underwent IRE during surgery.[48]

In conclusion, IRE seems to have a lot of promise in treating LAPC when looking at the OS. Currently, a prospective randomized controlled trial is underway in the United States assessing the safety and efficacy of IRE and chemotherapy *vs* chemotherapy alone for unresectable Stage 3 pancreatic adenocarcinoma (NCT03899636)[49] In addition, a prospective registry is ongoing examining IRE in unresectable Stage 3 LAPC (NCT03899649).[50]

LOCAL EMBOLICS & NEW DEVICES

Embolization of arteries supplying hepatic tumors has been a staple of HCC and metastatic liver tumors. Local embolization causes a local ischemic and/or hypoxic environment, which theoretically will slow/stop tumor growth. Various forms of transarterial embolotherapy exist such as bland transarterial embolization (TAE), conventional transarterial chemoembolization (cTACE), drug-eluding embolization (DEB-TACE) and transarterial radioembolization. These strategies are integrated in the guidelines for the treatment of primary and metastatic liver cancer.[3,4] Embolic material that can occlude smaller vessels in the vascular tree results in greater ischemia compared to more proximal embolization. In clinical practice, hypoxia has been noted post embolization rather than ischemia.[51,52] However, hypoxic states have been shown to upregulate hypoxia inducible factor 1 (HIF-1α) as well as vascular endothelial growth factor (VEGF).[53] These factors have the potential to induce neovascularization and metastatic potential.[54] As a result, there has been research into the addition of antiangiogenics to local embolic agents.

Trials combining TACE and systemic VEGF inhibitors such as sorafenib have shown mixed results. The SPACE trial, a prospective randomized trial, did not show survival benefit with sorafenib, however there were criticisms about the design.[53] Other trials have shown a survival benefit but were retrospective.[55,56] One study found that PFS of TACE *vs* TACE + sorafenib increased from 13.5 to 25.2 months, respectively (p = 0.006).[55] However, sorafenib was replaced by the combination of atezolizumab and bevacizumab since the combination demonstrated improved overall and progression free survival in the IMBRAVE-150 trial which was maintained long term.[57] Currently, ongoing as of 2022 is the DEMAND trial to evaluate the efficacy of atezolizumab and bevacizumab in combination with or prior to TACE in patients with intermediate HCC.[58] A recently completed trial comparing atezolizumab and bevacizumab to the tyrosine

kinase inhibitor sunitinib for the treatment of metastatic renal cell carcinoma has shown increased OS.[59] The TACTICS trial was a randomized, multicenter prospective trial that examined 80 patients treated with TACE plus sorafenib *vs* 76 patients treated with TACE alone for unresectable HCC. They identified that median PFS was significantly longer for the TACE plus sorafenib group than TACE alone group (25.2 *vs* 13.5 months, $p < 0.01$).[60] The LAUNCH trial is an ongoing multicenter, Phase 3, randomized trial comparing the efficacy of lenvatinib with TACE in 170 patients *vs* lenvatinib alone in 168 patients with advanced HCC.[61] Both median OS and PFS for the lenvatinib with TACE group was significantly longer than for the lenvatinib alone group (OS 17.8 *vs* 11.5 months [$p < 0.001$], PFS 10.6 *vs* 6.4 months [$p < 0.001$]).

Several trials have attempted to determine whether the addition of chemotherapeutic drugs to the embolization is beneficial. A trial by Brown et al compared drug eluting bead TACE (DEB-TACE) *vs* bland beads (TAE) in patients with unresectable HCC. In this single-center, randomized trial, PFS via RECIST (Response Evaluation Criteria in Solid Tumors) and OS were compared between 51 patients who underwent TAE *vs* 50 patients who underwent DEB-TACE with doxorubicin-eluding beads.[62] They found no significant difference in average PFS (6.2 months *vs* 2.8 months for TAE *vs* DEB-TACE, respectively, $p = 0.11$). Furthermore, there was no significant difference in overall survival between the two groups with an OS of 19.6 months for TAE *vs* 20.8 months in the DEB-TACE ($p = 0.64$). Another study by Meyer et al examined 41 patients treated with TAE using PVA particles *vs* 44 patients treated with TACE cisplatin and PVA for unresectable HCC. There was no significant difference in response or PFS (6.9 *vs* 7.8 months) nor OS (16.2 *vs* 15.9 months).[63] Multiple meta-analyses have been conducted comparing bland TAE with single-agent cTACE for HCC. Guo et al identified six randomized controlled trials and found no significant difference in response rates between bland TAE and single-agent TACE groups.[64] Furthermore, Katsanos et al identified 51 randomized controlled trials comparing cTACE, DEB-TACE, and TARE (trans-arterial radioembolization with radiation-eluting beads) with bland TAE and found no significant survival benefit for the former treatment groups over bland TAE.[65]

Agents with complementary mechanisms to embolization are being explored. One example is a hypoxia activated agent tirapazamine (TPZ) in HCC. Indeed, Tirapazamine is a prodrug that forms a free radical damaging DNA in a sustained hypoxic environment (Figure 4).[66] A Phase I trial using intraarterial administration of TPZ followed by embolization was performed in 27 patients with unresectable HCC. The average tumor size was 6.53 cm with median of 2 target lesions per patient prior to treatment. This trial showed a CR of 60% and ORR of 84% per mRECIST. Additionally, the maximal dose tolerated and dose limiting toxicity were not reached.[67] Further investigation with Phase II trials of TPZ are required to determine efficacy in a larger population.

LIQUID EMBOLICS

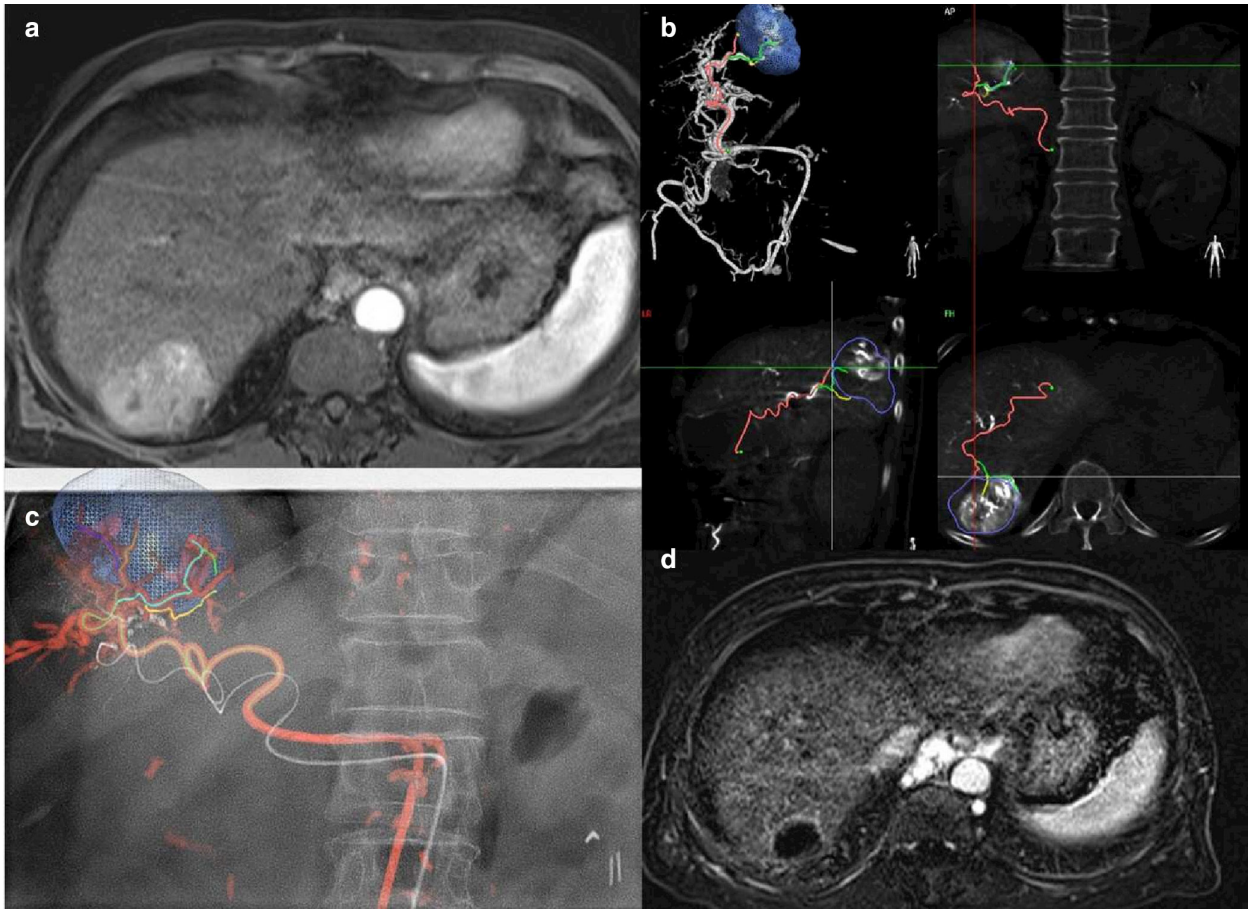
Historically, liquid embolics were used for the embolization of intracranial arteriovenous malformations.[68,69] However this class of embolic agents has a growing popularity due to their potential ability to penetrate deeply into targeted tissues. Liquid embolic agents solidify during administration under physiologic conditions, forming a cast that molds the vessels, impedes blood flow inducing a state of ischemia in the targeted tissue.[70] The degree of penetration can be controlled with the viscosity or with properties of the embolic to delay or speed solidification. Liquid embolics do not rely on thrombus formation for complete occlusion unlike other classes of embolic agents. Liquid embolics are beneficial for patients with clotting disorders.[71]

Lipiodol is a well-established agent utilized in TAE. Its hydrophobic properties allow it to serve as an emulsifier for drugs, penetrate and retain well in tumor microvasculature, and importantly serves as a contrast agent for fluoroscopy.[72–74] Current research on lipiodol has focused on widening its clinical applicability. For example, Burgio et al has demonstrated that lipiodol retention pattern can be utilized to predict tumor response in cTACE. Tumors with lipiodol retained throughout the entire volume of the tumor resulted 30% tumor progression (per mRECIST) as compared to 94% in tumors where lipiodol retention was incomplete.[75] Chen et al successfully combined lipiodol with indocyanine green (ICG), a dye frequently used as an intraoperative tumor marker when visualized under near-infrared fluorescence, into a combination agent labelled super-stable homogenous iodinated formulation technology (SHIFT).[76] Furthermore, the authors utilized SHIFTs for TAE in a rabbit VX2 HCC tumor model where the ICG could be taken up into tumor tissue directly from embolized microvasculature. They conclude that this highly specific labeling of tumor tissue post TAE could allow for precise surgical resection of HCC.

Hydrogel (Instylla HES) consists of a polymer and initiator precursor that solidify when combined in adequate concentrations in blood. Both precursor and polymer also have low viscosity which allows them to be administered via microcatheters into vasculature. Preliminary rabbit studies comparing unilateral renal artery embolization with the hydrogel *vs* 40 µm microspheres demonstrated in 0% *vs* 38% recanalization respectively ($n = 14$ and $n = 8$, respectively, $p = 0.036$).[77] Moreover, histological analysis revealed viable renal tissue in 14% of hydrogel embolized renal tissue *vs* 63% in microsphere group ($p = 0.052$) and penetration of embolic material in vessels as small as 10 µm with the hydrogel. A 150-patient, randomized, multicenter randomized controlled-trial utilizing the hydrogel (Instylla HES NCT04523350) is currently underway.[78,79] The primary aim of this trial is to compare the efficacy of the hydrogel with TAE/transcatheter arterial chemoembolization in the treatment of hypervascular tumors, primarily HCC. This trial is ongoing, and results are highly anticipated.

The efficacy of silk-elastinlike protein polymer (SELP) liquid embolic agent for the TAE has recently been studied. SELP gelation process is temperature regulated. Embolization with SELPs was first tested *in vivo* in Poursaid et al in 2015 in right or left

Figure 4. 79-year-old female with hepatitis B and HCC diagnosed by typical imaging characteristics and elevated AFP who was treated with Tirapazamine embolization. (a) Large hypervascular tumor on arterial phase in segment 7. (b) CBCTreconstructions shows segmented tumor (blue shape) and the feeding vessels in all places. (c) Fusion CBCT and fluoroscopy images demonstrated the microcatheter in the feeding vessel, (d) Follow-up MRI demonstrates no enhancement and significant decrease in size of the lesion. AFP, alpha fetoprotein; CBCT, cone beam CT; HCC, hepatocellular carcinoma.



rabbit hepatic arteries. Histological examination of liver sections from three rabbits embolized with SELP-815K demonstrated complete casting of targeted arterioles with no SELP-815K identified in the hepatic veins, only a reduction of RBC in the latter compared to hepatic veins in the control group.[80] Moreover, the utilization of SELP resulted in fewer non-target embolization in the pulmonary circulation compared to the microspheres group. In a follow-up study, the authors successfully incorporated both doxorubicin and sorafenib into SELP-815K gels *in vitro*, finding that they were able to achieve drug concentrations at therapeutic levels.[81] Further studies need to be performed to evaluate the clinical translation of SELP.

Lym et al[82] and Nguyen et al[83] recently investigated the efficacy of two new sulfamethazine-based, pH sensitive liquid embolic agents for use in TACE, PCL-PEG-SM and PCLA-PUSSM. Both agents undergo gelation based on pH-changes. Both agents were able to successfully release doxorubicin from PCL-PEG-SM and PCLA-PUSSM hydrogels after 4 weeks (65 and 25%, respectively).[82,83] TACE performed with doxorubicin loaded PCL-PEG-SM in a rabbit liver tumor model also demonstrated successful vessel occlusion 5 h post-embolization, while an identical procedure using PCLA-PUSSM achieved 48% tumor reduction by volume at 2 weeks post embolization.

LOCAL IMMUNOTHERAPIES & ANTIVIRAL THERAPIES

The field of immunotherapy is rapidly evolving. Immune check inhibitors such as CTLA-4 blockers (Ipilimumab) and PDL-1 blockers (pembrolizumab, nivolumab) are standard of care for the treatment of melanoma and lung cancer.[84] Although these agents have been associated with improved OS in some histologies, they have a low or non-existent objective response rate (ORR), no OS or PFS improvement in others.[84] Soft tissue tumors are not normally invaded by T cells, explaining the relative resistance to immunotherapy.[85] Induction of a T-cell inflammatory response may elicit the immune response required and has led to exploring intralesional oncolytic virus.

Oncolytic viruses are either wild type or genetically engineered viruses that are selected to replicate in cancer cells without harming normal human cell.[84–89] T-Vec (Talimogene Iaherparepvec), an intralesional oncolytic herpes simplex virus type-1,was the first oncolytic immunotherapy to be approved by the

FDA in 2015 for the treatment of unresectable Stage III, and IV melanoma.[84,89] It is an oncolytic virus that lyses tumor cells and thus releasing "danger signals" that are taken up by antigen presenting cells. These signals stimulate innate immune response locally and at distant untreated tumors.[84,85,87,90]

During its Phase III clinical trials (OPTiM), 436 patients with Stage IIIB, IIIC or IVM1 melanoma were randomized into 2:1 to receive intralesional T-Vec injections or subcutaneous GM-CSF.[84,85,90] The durable response, which was defined as a complete response (CR) or partial response (PR) lasting greater than 6 months was observed to be significantly higher in the T-vec arm (16.3%) compared to the GM-CSF arm (2.1%).[84,85,88,90] Both the ORR and rates of completed responders were also significantly higher in the T-vec arm (26.4 *vs* 5.7% and 10.8 *vs* 1%, respectively).[85,90] In addition, the median OS significantly favored T-vec arm (23.3 *vs* 18.9 months; hazard ratio 0.79; 95% CI, 0.62–1.00; $p = 0.051$).[85] As previously observed in both Phase I and Phase II trials, T-vec was associated with mild adverse effects.[84,85,90] In addition, the use of some oncolytic intratumoral therapy may be associated with additional benefits. Studies by et al Ricca showed that the presence of pre-existing immunity to oncolytic Newcastle Disease Virus (NDV) augmented its efficacy through creation of stronger antitumor effects.[91] Following the success of T-Vec in the treatment of melanoma, other oncolytic immunotherapy agents have been studied. In Japan for example, a Phase II clinical trial for G47 Δ for the treatment of glioblastoma is ongoing.[90] Vaccinia oncolytic virus JX-594 for HCC failed but is being examined for the treatment of metastatic renal cell carcinoma. Adenovirus CG0070 is being studied in bladder cancer, while reolysin (naturally occurring oncolytic virus) is being tested in head and neck cancers.[90] Renal cell carcinoma, a type of cancer that has shown significant resistance to chemotherapy and other agents, has been shown to respond well to treatment with oncolytic viral agents like ECHO-7 virus, Rigvir and the Bluetongue Virus (BTV).[92,93] Combination immunotherapy with T-Vec and ICIs, and/or radiation or chemotherapy are also being studied and preliminary results of the studies are promising.[85,87,88,90,94,95]

The downstream effect of intralesional therapy activates innate immunity, several clinical studies have shown that a subset of patients benefit from Toll Like Receptor nine agonists, Pro-inflammatory cytokines such as IFN-alpha, IL-2, IL-12, and stimulator of Interferon genes agonist.[85,87,90,94,95] Another area of interest is the combination of T-vec with other immune targets such as Toll-like receptors, proinflammatory cytokines to name a few.[85,87,90,94,95]

CONCLUSION

Several new technologies and devices are upcoming in interventional oncology that are potentially groundbreaking. Thermal ablation is a well-established therapy for small, unresectable HCC and CLMs with new evidence suggesting ablation (specifically MWA) in combination with chemotherapy is more effective than chemotherapy alone for treatment of CLMS (Figure 1). Histotripsy is being explored as a completely non-invasive alternative to ubiquitous thermal ablation technologies (Figure 2). HIFU and IRE are expanding the indications of ablation in prostate and pancreatic cancers (Figure 3). In the field of embolization, agents whose mechanisms is synergistic with the downstream effects of embolization are being studied. Indeed, hypoxia activated agents showed promising results in response rates and duration of response (Figure 4). Liquid embolics are being developed with the hopes that improved penetration into the tumor vessels can lead to ischemia instead of hypoxia and may also increase drug delivery if liquid embolic is loaded with therapeutic agents. Future studies including combinations of different intratumoral agents to optimize cancer immunotherapy are anticipated. Moreover, combination of loco-regional therapies and systemic immunotherapies are underway.

COMPETING INTERESTS

A-J has declared conflict of interests with the following entities: she is the principal investigator on research grants and/or clinical trials at University of California that are sponsored or have received financial support from Philips Medical Systems Inc, Teclison Limited Inc, Guerbet SA, Sillajen Inc, Instylla HES Inc, BlackSwan Vascular Inc, Sirtex Medical Ltd. Dr Abi-Jaoudeh has served on advisory boards with Genentech F. Hoffmann-La Roche Ltd, QED Therapeutics Inc, Eisai, Innova Vascular Inc, and Pfizer. She serves as a consultant for Johnson and Johnson as well as Medtronic Inc.

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