

Postablation Immune Microenvironment: Synergy between Interventional Oncology and Immuno-oncology

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Semin Intervent Radiol 2019;36:334–342

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Abstract

Current tumor thermal ablation techniques rely on extreme temperatures to induce irreversible cellular injury and coagulative tissue necrosis. Ablation-induced cellular injury or death releases cancer neoantigens and activates the cancer-immunity cycle, potentially generating tumor-specific immune effectors. However, multiple negative regulatory modulators exist at each step of the cycle, mitigating meaningful and therapeutic anticancer effect provided by the immune system. Recent studies have focused on the introduction and testing of adjuvant immunotherapy combined with ablation to synergistically shift the equilibrium out of inhibitory immune modulation. This article reviews the immune microenvironment in relation to image-guided ablation techniques and discusses current and upcoming novel strategies to take advantage of antitumor immunity.

Keywords

- ▶ immune microenvironment
- ▶ ablation
- ▶ interventional oncology
- ▶ immunotherapy

Interventional oncology (IO) has seen remarkable progress over the last two decades to now offer a variety of locoregional cancer treatments. The minimally invasive nature of IO was the main driver for the specialty's emergence and growth, particularly as an alternative to traditional surgical and systemic treatments. With the degree of image resolution offered by current clinical imaging technologies, the efficacy of IO therapies is now well established at the tissue or organ level.

Recent advancements in immuno-oncology research have brought a new “magnifying glass” to IO, namely, one focusing on the immune microenvironment. The effect of IO therapeutics is now investigated at the cellular and molecular level with a focus on the immune system. A unique feature of IO therapy is particularly pertinent in these investigations: IO achieves in situ destruction, during which tumor-specific neoantigens are released and potentially inducing the so-called abscopal effect or in vivo antitumor vaccination.^{1,2} In addition, the spontaneous remission of distant malignant disease after focal thermal ablation has been reported occasionally, but the exact mechanism remains elusive.^{3–6}

Current tumor ablation techniques rely on extreme temperatures to induce irreversible cellular injury and result in tissue coagulative necrosis. The commonly used techniques include radiofrequency ablation (RFA), microwave ablation (MWA), and cryoablation, while the newer techniques such as laser and high intensity focused ultrasound (HIFU) have demonstrated promising results. While not based on thermal energy, irreversible electroporation (IRE) is also employed along with the aforementioned thermal ablation methods.

The aim of this article is to provide a review on the immune microenvironment in relation to current image-guided ablation techniques and to discuss current and upcoming developments of novel IO strategies to take advantage of antitumor immunity.

Cancer-Immunity Cycle

Antitumor immunity involves a series of events referred to as the cancer-immunity cycle⁷ (▶ Fig. 1). Oncogenic neoantigens expressed by tumor cells are processed by antigen-presenting cells (APCs) to prime and activate antigen-specific CD8+

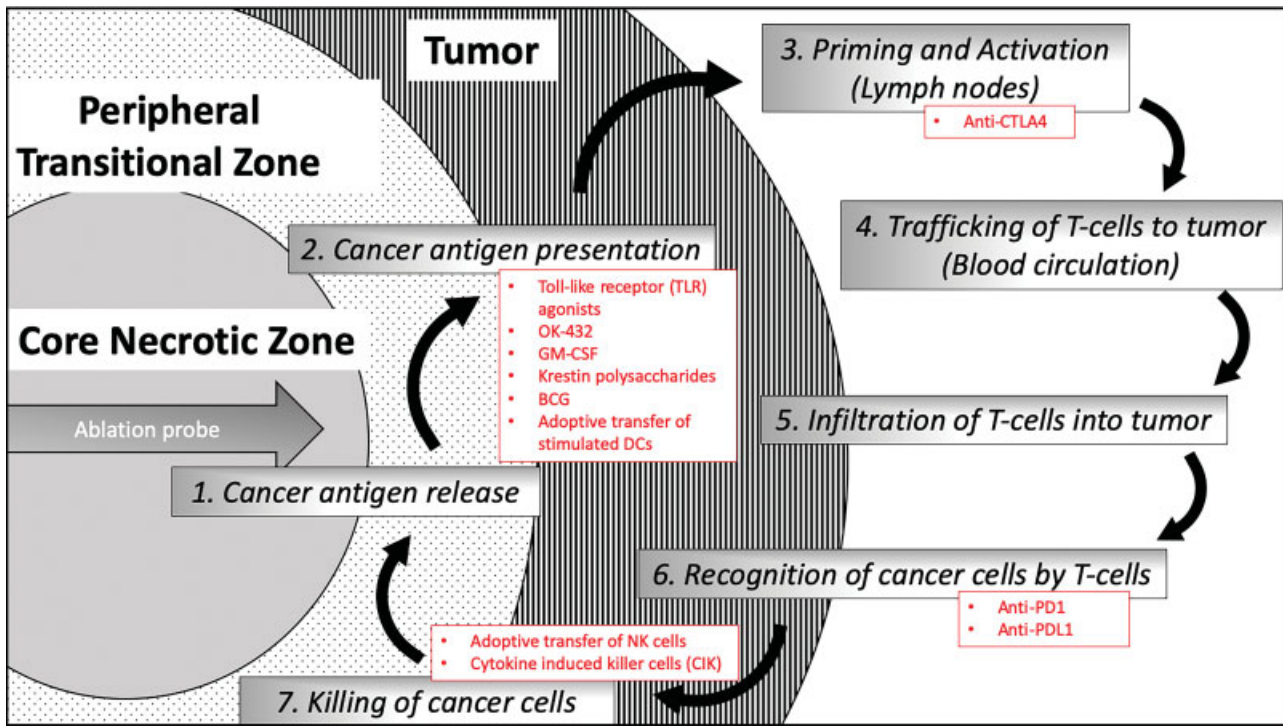


Fig. 1 Postablation immune microenvironment: cancer-immunity cycle. The area of thermal ablation can be divided into three different zones: central necrotic, peripheral transitional, and normal surrounding tissues. Cancer neoantigens released from cellular injury or death will activate the cancer-immunity cycle, generating tumor-specific immune effectors. These activated effector cells travel via systemic circulation and carry out their tumor-killing function when they encounter their specific antigen expressed within the tumor beds. However, there are multiple negative regulatory mechanisms at each step of the cancer-immunity cycle, preventing meaningful and therapeutic anticancer effect provided solely by the immune system. Multiple immunomodulatory strategies have been combined with image-guided locoregional ablation to synergistically shift the equilibrium out of inhibitory immune modulation (red boxes).

cytotoxic T-lymphocytes (CTLs) at tumor-draining lymph nodes (TDLNs). These activated effector cells travel via systemic circulation and carry out their tumor-killing function when they encounter their specific antigen expressed within the tumor beds.

Despite successful initial priming of CTLs,^{8,9} subsequent clonal expansion leading to an effector population rarely comes to completion.⁷ There are multiple negative regulatory mechanisms at each step of the cancer immunity cycle, preventing meaningful and therapeutic anticancer effects provided solely by the immune system. This can explain anecdotal reports of effective immunotherapy throughout the history of immuno-oncology including original observations by Fehleisen, Busch, and Coley.^{3-6,10-12} Additionally, the tumor cell population can escape the immune system's immunoediting, where tumor cells evade immune surveillance, by promoting the selective survival of the immune-resistant antigen cohort.^{13,14,22} The goal of cancer immunotherapy is to modulate negative regulatory mechanisms and induce an effective cancer elimination process without creating an overt autoimmune reaction or accelerating the immunoediting process. Recent successes in systemic immune checkpoint inhibitors such as anti-PD1 (programmed cell death protein 1), anti-PDL1 (programmed death ligand 1), and anti-CTLA4 (cytotoxic T-lymphocyte associated protein 4) therapies are examples of these efforts.

Cellular Injury and Immunogenicity of Thermal Ablative Therapy

Currently available ablative therapies, with the exception of IRE, rely on heat-based cellular destruction methods. RFA, MWA, HIFU, and laser ablation induce hyperthermic cellular damage, while cryoablation induces cellular injury by freezing. Regardless of the technique, thermal ablation can be divided into three zones: central necrotic, peripheral transitional, and normal tissue¹⁵⁻¹⁷ (→ Fig. 1). The central area is characterized by direct and immediate cellular injury achieved by lethal temperatures, that is, greater than 60°C in hyperthermic methods and below -20°C in cryoablation.^{15,16} The peripheral or transitional zone is a band-like area of thermal conduction between the central necrotic zone and surrounding normal tissue, characterized by a steep temperature gradient toward normal tissue temperature. Within the peripheral zone, different degrees of cellular injury will result in a mixture of necrotic, delayed/indirect, and reversible injury. This is also the area where most of the immune and inflammatory cellular infiltrates are found.^{15,18} Delayed or indirect cellular injury can manifest via many different mechanisms including apoptosis, ischemia-reperfusion, and innate and adaptive immune response.¹⁶

Cellular necrosis immediately releases immunogenic intracellular contents (such as DNA, RNA, and heat shock proteins [HSPs]) directly into the extracellular matrix. Unlike necrosis,

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apoptosis is a much more intrinsic process of cell death and is less immunogenic or inflammatory.¹⁹ The ratio between postablation apoptosis and necrosis may be a key modulator to achieving a maximally immunogenic microenvironment.¹⁵ Some authors also suggest that different immunogenic qualities can be achieved by modifying ablation protocols or parameters.^{18,20}

Postablation Inflammation: Immunogenic versus Prooncogenic

All image-guided ablative therapies create in situ tissue damage which induces not only an immunogenic response but also local wound healing and a systemic inflammatory response. Postablation inflammation is well established clinically, with symptomatic treatment generally being applied in a conservative manner. At the molecular level, tissue remodeling upregulates and releases many prooncogenic growth factors and cytokines.²¹ There is experimental and clinical evidence of worse outcomes of ablation therapy with accelerated local or off-target tumor progression,^{18,22–27} suggesting that a postablation microenvironment was potentially prooncogenic. In animal HCC model, RFA was associated with increased tumor burden and decreased survival compared with partial hepatectomy or sham controls.²⁷ Furthermore, this prooncogenic effect of RFA was attenuated by postablation systemic inhibition of c-met signaling.²⁷ In another animal study with breast cancer, RFA of the normal liver was associated with the growth of a distant tumor, which could also be suppressed by c-met inhibition.²² In a separate study, the same group also reported a tumorigenic effect observed with MWA which was attenuated by high-power, faster MWA protocol.¹⁸

Several efforts have been made to unfold the enigma of postablation inflammation by characterizing peripheral blood mononuclear cell (PBMC) samples. In a study with 193 patients with CRLM (colorectal liver metastases) treated with RFA, elevated lymphocyte–monocyte ratio (LMR) was identified as a significant negative predictor for recurrence and mortality.²⁸ Decreased post-RFA neutrophil–lymphocyte ratio (NLR) was associated with improved disease-free survival in 178 small hepatocellular carcinoma (HCC) patients,²⁹ while increased postablation NLR was associated with local recurrence and metastatic disease in patients with 185 renal cell carcinoma (RCC) patients treated with RFA.³⁰ Additionally, an increase in the number of interferon gamma (IFN- γ) producing cytotoxic natural killer (NK) cells was associated with longer disease-free survival after RFA in 37 subjects with HCC.³¹

Methods of Ablation and Immune Stimulation

As RFA is the oldest technique, there are many studies in the literature regarding the postablation immune reaction of this technique. Within hours or days after RFA, there is a local and systemic release of proinflammatory cytokines, including IL (interleukin)-1 β , IL-1 α , IL-6, IL-8, IL-18, and TNF α (tumor necrosis factor α).^{21,32–35} Intriguingly, anti-inflammatory cytokines such as IL-10 and transforming growth factor-beta

are also shown to be released and upregulated after RFA.^{35,36} Some studies have reported contradictory findings regarding the regulation of specific cytokines, reflecting the complex and dynamic nature of the process.^{33,36,37} Apart from cytokines, an important immune modulator found in the post-RFA microenvironment is the extracellular heat shock protein (HSP).^{38–41} HSP belongs to a group of endogenous molecules and is known as a “danger signal” released by necrotic cells. Extracellular HSP70 is a chaperone molecule facilitating the antigen presentation of APCs to T-cells^{42,43} and is upregulated in the tumor microenvironment.^{38–41} In a study with 22 posthepatic RFA subjects, serum HSP70 level was significantly elevated within 24 hours and was positively associated with survival benefits and time to disease progression.⁴⁴ Although it was first discovered in a post-RFA setting, HSP upregulation and release have also been identified in other ablative modalities.^{45–48} Additional danger signal molecules such as high-morbidity group box-1 (HMGB-1) are under investigation regarding their role in postablation immune reaction.^{49,50}

Cryoablation has been shown to induce a more robust systemic immune reaction compared with hyperthermic ablative methods in multiple experimental and clinical studies.^{21,32,51,52} Furthermore, postablation systemic or remote inflammatory organ injuries, the so-called cryoshock, have been reported after large-volume cryoablation.^{53–56} The hyper-immunogenicity of cryoablation is hypothesized to be due to the relative preservation of tumor neoantigens during freezing cell injury compared with hyperthermal ablation techniques. In cryoablation, osmotic changes across intra- and extracellular compartments induce cellular injury without affecting the potential intracellular tumor antigens including DNA, RNA, or proteins. Conversely, hyperthermal ablation denatures and degrades proteins, erasing part of the critical tumor immunogenic footprints.

MWA appears to induce the least magnitude of immune or inflammatory reaction. In the animal liver, a significantly lower level of inflammatory cytokines (IL-1 β and IL-6) and HSP70 in peripheral blood samples was observed after MWA compared with RFA or cryoablation.^{32,48} In another animal study, the level of proinflammatory cytokines after MWA was similar to that of the surgical resection group that did not have any ablation.²³ Thus, eventually, the low inflammatory characteristic of MWA enables it to achieve a successful larger volume hepatic ablation without collateral inflammatory remote organ injuries.^{48,57} Nevertheless, despite these reproducible observations, the exact mechanism for minimal immune or inflammatory response after MWA remains unknown.

HIFU destroys cells mechanically by acoustic cavitation and histotripsy.^{58–60} Acoustic cavitation results from the repeated growth and collapse of micro gas bubbles within the tissue under the influence of high-pressure sound waves. Mechanical fractionation combined with a boiling process enables histotripsy which eventually generates an emulsified acellular homogenate surrounded by very thin, less than 1 mm, margins, with minimal fibrosis.^{58–60} This liquefied lesion is absorbed rapidly by the surrounding tissue and easily infiltrated by immune cells. In a clinical study with 48

breast cancer subjects, HIFU-treated lesions were removed by mastectomy and demonstrated markedly increased immune cell infiltrates compared with surgical specimens not treated with HIFU.⁶¹

Laser ablation has had limited use in tumors and little data are available on its immune stimulation. Similar to other hyperthermal techniques, a postablative increase of proinflammatory cytokines in peripheral blood has been observed.⁶² In preclinical animal experiments, tumor-specific immune cell generation has also been observed after laser ablation.^{63,64}

IRE is the newest ablation technique and does not incorporate thermal energy. IRE selectively disrupts the lipid bilayer cellular membrane via the electrical induction of permanent nanopores. Preliminary microscopic studies in animal samples treated with IRE demonstrated minimal damage in extracellular structures as well as minimal fibrotic or inflammatory margins.⁶⁵ In an osteosarcoma animal model, IRE generated increased peripheral T-lymphocytes compared with surgical resection.⁶⁶ In a recent study employing an animal pancreatic cancer model, IRE exhibited a twofold increase in CD3+ T cell infiltrates compared with cryoablation.⁶⁷

In summary, non-hyperthermal ablation modalities such as cryoablation, IRE, and HIFU appear to generate a more robust immune response compared with hyperthermal modalities, possibly to the greatest degree with IRE. Regardless of ablative techniques, it is clear that proinflammatory cytokines and the danger molecule signaling pathway are activated in the immediate postablative period. The remaining and important question is if this translates into a therapeutically immunogenic or prooncogenic environment and which factors modulate the balance between them.

Investigating the postablation immune response is a challenging process. With varying ablation devices, heterogeneous parameters and protocols at each center, and various types of tumors treated, it is difficult to perform a standardized multicenter trial or to compare studies across centers or countries. Investigations are further challenged by the varying baseline individual immune function at the time of treatment. No optimal time point for sampling or quantifying the immune response has been determined. Finally, investigations may require additional invasive sampling of the treated area. Hence, to date, most investigators have chosen to look at the systemic immune response based on PBMCs as discussed earlier,^{28–31} and immunopositron emission tomography has been investigated for the possible noninvasive monitoring of immune response.^{68,69}

Combination Therapy: Ablation and Immunotherapy

It is established that a tumor-specific immune-stimulatory effect is generated after image-guided locoregional ablation. However, given that this rarely translates into robust effector clonal expansion or tumor killing, many recent studies have focused on the introduction and testing of adjuvant immunotherapy combined with ablation to synergistically shift the equilibrium out of inhibitory immune modulation (– Fig. 1).

Ablation combined with immune checkpoint inhibitors has demonstrated a potential positive synergistic effect on tumors elsewhere in the body in multiple studies (– Table 1). In animal studies, the combination of anti-CTLA-4 and cryoablation⁷⁰ or anti-PD1 and RFA⁷¹ slowed tumor growth and increased effector T cell infiltration of distant tumors. In a pilot clinical study in 18 metastatic breast cancer patients, cryoablation combined with anti-CTLA-4 (ipilimumab) revealed a sustained increase of IFN- γ , effector T cells, and the ratio of effector T cells to regulatory T cells (Treg) in peripheral blood samples.⁷² In another pilot study,⁷³ 12 Barcelona clinic liver cancer stage C patients with metastatic HCC who failed sorafenib treatment underwent percutaneous RFA and chemoablation therapy combined with anti-CTLA-4 (tremelimumab). The investigators of that study reported that the patients had 7.4 months median time to progression and 10.1 months median overall survival without any severe treatment-related toxicity. The patients also had favorable objective treatment responses with increased active CD8+ CTL infiltration in the distant untreated lesion. Additionally, case reports have described the successful treatment of colorectal lung metastasis using MWA/anti-PD-1 (pembrolizumab)⁷⁴ and metastatic clear cell RCC using cryoablation/anti-PD-1 (nivolumab) combinations.⁷⁵

Positive modulation of the antigen-presentation process by dendritic cells (DCs) has been combined with ablation, showing promising results. In animal studies combining intratumoral injection of activated DC with RFA⁷⁶ or cryoablation,⁷⁷ significant growth inhibition on distal untreated tumors and increased effector immune cell infiltrates were demonstrated. Similarly, in animal studies combining RFA or cryoablation with intratumoral stimulation of native DC by using toll-like receptor (TLR) agonists,^{78–80} OK-432,⁸¹ granulocyte-macrophage colony-stimulating factor (GM-CSF),⁸² krestin polysaccharide,⁸³ and BCG,⁸⁴ a favorable response in untreated tumor burden was demonstrated. Some of these preclinical models were successfully reproduced in a few clinical studies. Thakur et al⁸⁵ and Si et al⁸⁶ confirmed robust tumor-specific CTL function in untreated tumors in patients with metastatic RCC and prostate cancer when treated with cryoablation and GM-CSF injection. Niu et al retrospectively reviewed 106 patients with metastatic pancreatic cancer⁸⁷ and demonstrated significantly improved median survival when cryoablation was combined with adoptive transfer of GM-CSF stimulated DCs compared with cryoablation only, immunotherapy only, or chemotherapy only (13, 7, 5, and 3.5 months, respectively). The authors applied the same strategy in 45 patients with metastatic HCC,⁸⁸ revealing significantly improved overall survival with cryo-immunotherapy compared with cryoablation only (32 vs. 17.5 months).⁸⁸

NK cells are cytotoxic effector lymphocytes within the innate immune system. They play an important role in cancer immune surveillance and are able to induce rapid immune responses against malignant cells in an antigen-independent manner.⁸⁹ Adoptive transfer of allogenic NK cells has been combined with ablative therapies in preclinical and clinical studies, demonstrating potential efficacy and safety. In a pilot clinical study of cryoablation and NK cell therapy in 48 patients with treatment-resistant metastatic breast cancer,

Table 1 Currently available human clinical data on the combination of immunomodulation and ablation as of June 2019

Methods of immunomodulation	Studies	Phase	Immunomodulators	Ablative methods	Disease (no. of subjects)	Impact of combinatory therapy
Immune checkpoint inhibitors	McArthur et al ⁷²	I, II	Ipilimumab (anti-CTLA4)	Cryoablation	Breast cancer (19)	↑ IFN- γ , ↑ effector T cells, ↑ effector T cells/regulatory T cells ratio in peripheral blood
	Duffy et al ⁷³	I, II	Tremelimumab (anti-CTLA4)	RFA + chemoablation	HCC (12)	7.4-mo median time to disease progression, 10.1-mo median overall survival, ↑ in-situ CD8+ cells in treatment responders
	Bäcklund and Freedman ⁷⁴	Case report	Pembrolizumab (anti-PD1)	MWA	Colorectal lung metastasis (1)	Complete response at 8 mo
Intratumoral injection of GM-CSF	Soule et al ⁷⁵	Case report	Nivolumab (anti-PD1)	Cryoablation	Renal cell carcinoma (1)	Decreased size and FDG uptake in osseous metastatic disease in 1 mo
	Thakur et al ⁸⁵	I, II	GM-CSF	Cryoablation	Renal cell carcinoma (6)	↑ Tumor-specific IFN- γ (+) effector T cells, ↑ Th1/Th2 ratio in peripheral blood of treatment responders
	Si et al ⁸⁶	I, II			Prostate cancer (12)	↑ Tumor-specific effector T cells in peripheral blood
Adoptive transfer of activated allogenic immune cells	Niu et al ⁸⁷	Observational	GM-CSF stimulated allogenic DCs	Cryoablation	Pancreatic cancer (106)	↑ Median overall survival with combinatory treatment
	Niu et al ⁸⁸	Observational			HCC (45)	↑ Median overall survival with combinatory treatment
	Liang et al ⁹⁰	I, II	Stimulated allogenic NK cells	Cryoablation	Breast cancer (48)	↑ IFN- γ , ↑ effector T cells in peripheral blood with combinatory treatment
	Lin et al ⁹¹	I, II		Cryoablation	Renal cell cancer (60)	↑ Th1 cytokines, ↑ effector T cells in peripheral blood with combinatory treatment
	Lin et al ⁹²	I, II		Cryoablation	NSCLC (60)	↑ Th1 cytokines, ↑ effector T cells in peripheral blood with combinatory treatment
	Yang et al ⁹³	I, II		IRE	Primary liver cancer (40)	↑ Overall survival, ↑ progression-free survival, ↑ Th1 cytokines, ↑ effector T cells in peripheral blood with combinatory treatment

Abbreviations: DCs, dendritic cells; FDG, fluorodeoxyglucose; GM-CSF, granulocyte-macrophage colony-stimulating factor; HCC, hepatocellular carcinoma; IFN, interferon; IRE, irreversible electroporation; MWA, microwave ablation; NK, natural killer; NSCLC, non-small cell lung cancer; RFA, radiofrequency ablation.

increased immune effector T cells and Th-1-type cytokines in the peripheral blood was demonstrated in the combinatory treatment group ($n=16$), although the increment in progression-free survival was not statistically significant compared with the cryoablation-only group ($n=16$).⁹⁰ Of note, this study also included a triple-combination group ($n=16$, cryoablation, allogenic NK cells, trastuzumab) demonstrating a significant increase in immune response and progression-free survival compared with the aforementioned two groups. Two prospective clinical studies combining cryoablation with allogenic NK cell immunotherapy of metastatic RCC ($n=60$)⁹¹ and non-small cell lung cancer ($n=60$)⁹² also revealed enhanced effector immune cell quantity as well as Th-1-type cytokines in the peripheral blood. However, these studies did not report any clinical outcomes regarding progression-free survival or regression of distant untreated tumor. Lastly, one study using a combination of IRE and allogenic NK cell therapy for primary liver cancer patients demonstrated survival benefits and increased immune response compared with IRE therapy only.⁹³

Future Directions

As of June 2019, there are 22 ongoing or planned clinical trials for various combinatory regimens of locoregional ablative therapy and immunotherapy registered in the *clinicaltrials.gov* database (► **Table 2**). Additionally, there are also trials investigating the efficacy and safety of immunotherapy combined with other locoregional IO therapies such as chemoembolization or radioembolization. In addition to these preliminary outcome-based studies, there are many important questions to be answered.⁹⁴ Most importantly, the timing, sequence, number, and type of combinatory therapy should be determined to optimize the synergistic efficacy.

There is a great potential in the combination of locoregional therapy and immunotherapy. The synergy between interventional radiology and immuno-oncology with their different philosophies and approaches will enhance our understanding of cancer biology in general. Many innovative, minimally invasive locoregional IO therapies have been developed, demonstrating similar safety and efficacy profiles between them albeit the great heterogeneity in techniques and application.

Table 2 Locoregional ablative therapy combined with immunotherapy: ongoing and planned registered trials as of June 2019

Trial no.	Ablative modality	Immunotherapy	Disease (no. of subjects)	Phase	Expected study completion dates (mm/yyyy)
NCT02851784	MWA	CIK cells	Hepatocellular carcinoma (50)	II, III	12/2017
NCT03101475	SBRT or RFA	Durvalumab (anti-PDL1) + Tremelimumab (anti-CTLA4)	Colorectal liver metastasis (70)	II	01/2023
NCT03695835	Cryoablation or RFA	Anti-PD1 + anti-CTLA4 + GM-CSF	Prostate adenocarcinoma (18)	Observational	12/2025
NCT03864211	MWA or RFA	Toriplimab (anti-PD1)	Hepatocellular carcinoma (120)	I, II	03/2021
NCT03753659	MWA or RFA	Pembrolizumab (anti-PD1)	Hepatocellular carcinoma (30)	II	09/2022
NCT02678013	RFA	CIK cells	Hepatocellular carcinoma (210)	III	01/2022
NCT02849366	Cryoablation	NK cells	Soft-tissue sarcoma (30)	I, II	07/2019
NCT02849379	Cryoablation	NK cells	Tongue cancer (30)	I, II	07/2019
NCT02849353	Cryoablation	NK cells	Ovarian cancer (30)	I, II	07/2019
NCT02849340	Cryoablation	NK cells	Cervical cancer (30)	I, II	07/2019
NCT02849314	Cryoablation	NK cells	Laryngeal cancer (30)	I, II	07/2019
NCT02849327	Cryoablation	NK cells	Hepatic metastatic disease (30)	I, II	07/2019
NCT02844335	Cryoablation	NK cells	Breast cancer (30)	I, II	07/2019
NCT02843607	Cryoablation	NK cells	Renal cell carcinoma (30)	I, II	07/2019
NCT02843815	Cryoablation	NK cells	Non-small cell lung cancer (30)	I, II	07/2019
NCT02849015	Cryoablation	NK cells	Primary liver tumor (10)	I, II	07/2018
NCT01853618	Cryoablation or RFA or TACE	Tremelimumab (anti-CTLA4)	Primary liver tumor (61)	I, II	12/2020
NCT03008343	IRE	NK cells	Primary liver tumor (20)	I, II	12/2019
NCT00891475	RFA	Sunitinib (tyrosine kinase inhibitor) or IFN- α	Renal cell carcinoma (114)	I, II	01/2011
NCT03949153	Cryoablation	Ipilimumab (anti-CTLA4)	Cutaneous melanoma (15)	I, II	12/2021
NCT03939975	RFA or MWA	Pembrolizumab or nivolumab or JS001 (anti-PD1)	Hepatocellular carcinoma (50)	II	05/2023
NCT03237572	HIFU	Pembrolizumab (anti-PD1)	Breast cancer (15)	I	11/2021

Abbreviations: CIK, cytokine-induced killer; HIFU, high intensity focused ultrasound; IFN, interferon; IRE, irreversible electroporation; MWA, microwave ablation; NK, natural killer; RFA, radiofrequency ablation; TACE, transarterial chemoembolization.

Further understanding of the tumor immune microenvironment may also shed light on mechanisms to differentiate and tailor IO therapies toward more personalized cancer therapy.

Conclusion

Locoregional tumor ablative techniques induce tumor-derived immunogenic activation at local and systemic levels, which may ultimately translate into beneficial therapeutic effects in local and remote tumors. To overcome the body's innate negative immune modulation in the cancer-immunity cycle and to optimize the immunogenic response, ablative therapy has been combined with various immunotherapy regimens, resulting in promising outcomes, although these findings remain preliminary. Understanding the tumor microenvironment will help advance our knowledge of existing IO procedures, as well as aid in the development of innovative, personalized oncologic care.

Disclosure Statement

The authors declare that they have no conflicts of interest.

Source of Funding

This article was funded in part through the NIH/NCI Cancer Center Support Grant P30 CA008748.

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