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Review Article

Immunomodulatory effects of microwave ablation on malignant tumors

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Abstract: Image-guided thermal ablation (IGTA) is an important treatment modality for interventional oncology. It is widely used for the treatment of solid tumors, such as liver, lung, breast, kidney, and thyroid cancers. IGTA include radiofrequency ablation, microwave ablation (MWA), cryoablation, and laser ablation. Compared with other energy sources, MWA has the advantage of a large ablative volume, short ablative time, and a low heat sink effect. MWA can also induce antitumor immunity; however, only a minority of patients derive a clinical benefit from it. Based on these data, the combination of MWA and immunotherapy has emerged as a promising new direction for cancer treatment. This review article focuses on current research on the combination of MWA and immunotherapy. The status of immune activation and related studies involving MWA for the treatment of various malignant tumors are discussed.

Keywords: Microwave ablation, immunotherapy, cancers

Introduction

The incidence and mortality rates for malignant tumors have been increasing worldwide annually and are becoming one of the major threats to human health and life. Currently, there are various strategies for treating tumors, including surgery, radiation, medical oncology, and interventional oncology [1]. Interventional oncology is a subspecialty of interventional radiology, which focuses on treating cancer patients with minimally invasive, image-guided procedures [2]. Compared with traditional surgery, interventional therapy is safer, more convenient, minimally invasive, enables faster recovery, and requires no anesthesia.

Image-guided thermal ablation (IGTA) is a precision super minimally invasive treatment technology that uses the biological effect of heat or cold to directly cause irreversible damage or necrosis of tumor cells in a specific organ [3]. It is widely used for the treatment of solid tumors, such as liver, lung, breast, kidney, and thyroid cancers [3-9]. IGTA include radiofrequency ablation (RFA), microwave ablation (MWA), cryoablation, and laser ablation. Compared with other energy sources, MWA has the advantages of a larger ablative volume, good conductivity, short ablative time, low heat sink effect, and high controllability [3]. MWA can also induce antitumor immunity [3, 10]; however, only a minority of patients derive a clinical benefit from it.

Immunotherapy has revolutionized our approach to cancer treatment by introducing a fresh perspective on mobilizing and activating the body's immune system to kill tumors [11]. This has brought renewed hope for many cancer patients. Compared with traditional treatments, immunotherapy has many advantages, such as high specificity, long-lasting efficacy, and a low likelihood of developing drug resistance [12]. In recent years, the breakthrough in immune checkpoint inhibitors has significantly enhanced the effectiveness of immunotherapy. The discovery of immune checkpoints [13, 14] has also improved the specificity of immunotherapy,

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effectively activating the patient's own immune system and increasing the success rate of tumor treatment. However, because of the complexity of the tumor-immune microenvironment, immune-related adverse events and the multifactorial mechanisms affecting the immune response, immunotherapy as a monotherapy has not shown satisfactory efficacy for some clinical applications [15]. Therefore, immunotherapy should be combined with other treatments to improve the tolerance and response rate of immunologic agents, extend the response time, and strengthen control of tumor progression [16, 17].

IGTA combined with immunotherapy represents a promising new direction for cancer treatment [18, 19]. As a local treatment, MWA can not only achieve the destruction of tumors, but it also can release antigens from tumor cells in situ that act as immune modulators to activate immune the response and thereby increase the body's antitumor-immune function [10]. However, the specific underlying mechanisms remain unclear. This review focuses on current research related to MWA combined with immunotherapy. It summarizes the results of animal models and human studies, explores the relevant mechanisms of immune activation by MWA, and identifies potential mechanisms and strategies for the combined treatment of tumors.

Characteristics of MWA

MWA employs high-frequency electromagnetic waves for the purpose of generating active heat [20]. In practice, this involves the utilization of frequencies at 915 MHz or 2,450 MHz to create a microwave electromagnetic field through an intratumoral antenna [21]. This generates an electric field that drives the rapid oscillation of polar molecules within tissues with water and proteins being the primary constituents. This oscillation results in a surge in kinetic energy, triggering a cascade of molecular collisions and friction. The cumulative effect of these interactions is a swift and substantial elevation in temperature within the targeted tissue [22, 23]. This precise hyperthermia acts as a decisive mechanism for the annihilation of tumor cells.

RFA, MWA, and cryoablation are the three ablation techniques commonly used practice for cancer treatment. Each ablative technique has its advantages and disadvantages. The selection and use of these techniques should consider the size and location of the tumor, the risk of complications, and the skill and expertise of the physician. Multipolar RFA has good conformability and may be adjusted to protect adjacent organs; however, it is more affected by blood flow and airflow [24]. Cryoablation is less likely to cause local pain and it has certain advantages for patients with tumors ≤ 1 cm away from the pleura or with bone metastases causing bone destruction [25]. However, the cryoablation procedure requires significant time and consumes platelets during treatment; thus, patients with poor coagulation function should avoid this treatment. Compared with RFA and cryoablation, MWA has the advantages of shorter procedure time, large ablative zone, low heat sink effect, and no platelet consumption [26-28].

MWA is a super minimally invasive procedure that offers significant advantages over conventional surgery. In additionally, it is a simpler process and eliminates the need for general anesthesia, reducing potential risks and relieving patients of the financial burden of surgery [29, 30]. Moreover, MWA exhibits high repeatability, enabling better disease control for patients with multiple tumor lesions or metastases. Another distinction is the ability of MWA to destroy tumor tissue in situ, which results in the continuous release of tumor-related antigens. The subsequent activation of an immune response contributes to a synergistic antitumor effect [31].

The role of MWA in the tumor microenvironment

The tumor microenvironment is a dynamic area consisting of multiple elements, including immune components, which play a central role in the development and progression of solid tumors [32-34]. If the tumor microenvironment lacks sufficient infiltrating immune cells (i.e., a "cold" state), the efficacy of immunotherapy will be greatly compromised [35]. MWA not only induces coagulation necrosis of tumor tissue in the ablative area, reduces tumor burden, releases antigens, and decreases the suppressive effect of tumor cells on the immune system, but it also activates surrounding immune

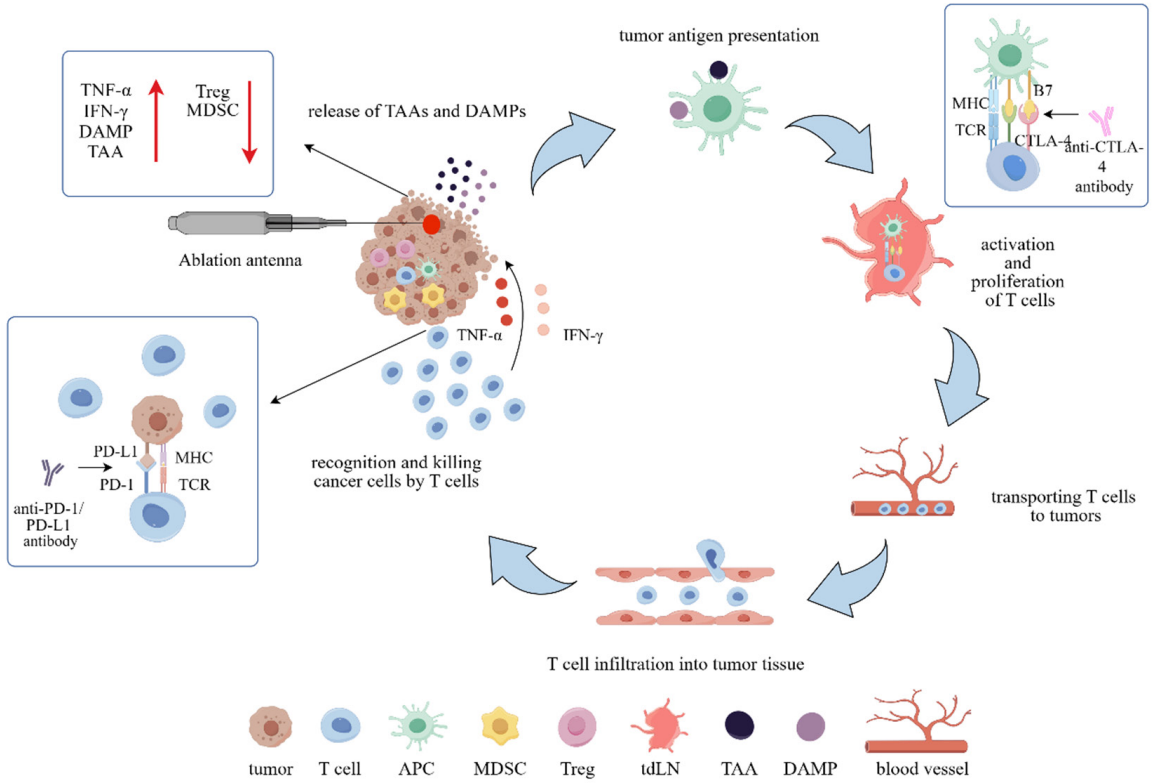

Figure 1. Immune effects following MWA. (1) MWA locally disrupts tumor cells, releasing TAAs and DAMPs; (2) Antigen-presenting cells take up TAAs and DAMPs for antigen presentation; (3) In tumor-draining lymph nodes, mature APCs activate T cells, leading to their proliferation; (4) Peripheral blood vessels transport cytotoxic T lymphocytes (CTL) to the tumor tissue; (5) Numerous CTLs infiltrate, recognize, and subsequently target and destroy the tumor. DAMP, damage associated molecular patterns; TAA, tumor-associated antigen; Treg, regulatory T cell; MDSC, myeloid-derived suppressor cells; MHC, major histocompatibility complex; TCR, T cell receptor; PD-1/PD-L1, programmed death receptor 1/programmed death ligand 1; CTLA-4, cytotoxic T lymphocyte-associated antigen-4.

cells through various mechanisms, to stimulate innate and adaptive immune responses [36]. Ultimately, the tumor microenvironment changes from a "cold" to a "hot" state to achieve an antitumor effect (**Figure 1**) [37, 38].

Increased release and presentation of tumor antigens

Antigen expressed on the surface of tumor cells, such as glycoproteins and lipoproteins, are generally protected by the cell membrane, rendering them difficult for the immune system to detect. During MWA, however, high-frequency electromagnetic energy directly acts on the tissue, causing severe friction and energy conversion, which results in an increase in tissue temperature. Tissue structures, such as the cell membrane, cytoplasm, and organelles, are damaged, which results in changes in cell and tissue molecular structures. The tumor barrier is destroyed and the protein and sugar molecules on the tumor cell membrane are released into the microenvironment. This results in antigen release, which may be recognized by the immune system as "foreign", thus activating the immune system and triggering an immune response [31]. Immune cells, such as macrophages and dendritic cells, are attracted to the treatment site, to phagocytose and present tumor antigens, and initiate the immune response of specific T cells. The release of tumor antigens by MWA can also induce tumor cell apoptosis and necrosis, further enhancing the expression and presentation of tumor antigens and promoting the release and presentation of intracellular antigens of tumor cells [39].

When tumor cells are destroyed, not only do they release tumor-associated antigens (TAA), but the central area of ablation also releases damage-associated molecular patterns

(DAMPs) [40], including DNA, RNA, high mobility group protein 1 (HMGB1), heat shock proteins, and adenosine triphosphate (ATP), which act as danger signals that are recognized by the pattern recognition receptors of the immune system. These substances may be captured by dendritic cells, thereby activating the surface molecules of dendritic cells and other immune cells, such as CD80 and CD86, to enhance T-cell activation and proliferation. DAMPs can also act on receptors, such as Toll-like receptors, to stimulate the inflammatory response and antigen presentation process. In addition, DAMPs can attract, activate, and proliferate different types of immune cells, such as T cells, natural killer cells, and monocytes, thereby enhancing their killing effect [41].

Activating the innate and adaptive immune response and improving the effectiveness of immunotherapy

During MWA, the destroyed tumor cells release a substantial number of tumor-specific antigens, which are taken up by dendritic cells. This stimulates the maturation of dendritic cells, resulting in the activation of surface molecules on dendritic cells, such as CD80 and CD86. Subsequently, the dendritic cells present the antigens to $CD4^+$ T cells and $CD8^+$ T cells, thereby initiating the activation of tumor-specific T-cell responses. Furthermore, non-specific cytotoxic cells, such as natural killer (NK) cells, are also activated and migrate to the tumor ablation site to exert cytotoxic effects against the tumor. In certain tumor ablation scenarios, the role of NK cells can even surpass that of $CD8^+$ T cells [42].

MWA also induces the formation of a local inflammatory environment, leading to the infiltration of neutrophils and monocytes into the surrounding tumor tissue. These cells also release various cytokines and chemical substances that further activate tumor-specific T cells. Following MWA, a series of changes occur in the surrounding tissue of the tumor, such as hypoxia and cell death, which also activate the response of tumor-specific T cells and other immune cells [43, 44]. Meanwhile, the damage to the surrounding normal tissue of the tumor also causes some antigens to be released into the local environment, which can be presented to T cells, thus activating a response. Finally, MWA can also enhance adaptive immune response by affecting the function of immune cells. Some studies have shown that following MWA, cytokines and chemical substance levels in the surrounding tissue of the tumor increases [45], which can affect the activity and function of T cells and other immune cells, thereby enhancing adaptive immune response.

Increased immune cell infiltration

Infiltration of immune cells is an important aspect of tumor immunotherapy. Generally, the degree of immune infiltration in tumors is associated with prognosis [46]. Increasing immune cell infiltration can improve the efficacy of immunotherapy. Studies have shown that microwave ablation therapy increases immune cell infiltration in the peritumoral region [47]. The most common types of immune cells are $CD8^+$ T and $CD4^+$ T cells. $CD8^+$ T cells are the main component of tumor-specific T cells, which play an antitumor role by recognizing and killing tumor cells. $CD4^+$ T cells promote immune cell activation and regulate the immune response. In addition, MWA also induces the production and release of chemokines and inflammatory cytokines. The enrichment of chemokine signaling pathways, particularly the CXCL10/CXCR3 axis, can increase immune cell infiltration. The activation of this pathway is one reason for the increased infiltration of immune cells following MWA, especially when combined with ICB [48]. Inflammatory cytokines can cause local inflammation and attract immune cells to the lesion site. During tumor treatment, these inflammatory cytokines attract and increase immune cell infiltration and activate DC cells. This enhances the capture and presentation of TAA, thereby further promoting the activation of tumor-specific T cells and immune-mediated tumor cell killing.

Influencing the expression of tumor-immune-related genes

MWA can promote the expression of immune-related genes, such as PD-1 [48] and PD-L1 [49], within tumor cells, thereby enhancing immune recognition of the tumor cell and increasing the effectiveness of immune checkpoint inhibitor therapy. In addition, MWA can induce apoptosis, pyroptosis, and necrosis of tumor cells, which can affect the expression of related genes. Apoptosis [50] and pyroptosis,

and are two different types of programmed cell death, whereas necrosis [51] is a non-programmed form of cell death. The manner of cell death can cause changes in various cell signaling pathways, resulting in changes in the expression of related genes. Moreover, MWA can destroy the membrane and organelles of tumor cells, as well as the blood vessels in the tumor tissue, resulting in local ischemia, hypoxia, and metabolic changes. Specifically, MWA affects the three main metabolic pathways of tumor cells [52], including glycolysis, the tricarboxylic acid cycle, and oxidative phosphorylation.

Reversal of the suppressive immune microenvironment

The main inhibitory factors of the T-cell immune response in the tumor-immune microenvironment are regulatory T cells (Tregs) [53] and myeloid-derived suppressor cells (MDSCs) [54]. The function of Treg cells is to suppress the immune response and the activity of immune cells, whereas MDSCs can inhibit cell-mediated immune responses. These cells inhibit T-cell function by producing various inhibitory molecules, such as CTLA-4, PD-1, and LAG-3, thereby allowing the tumor to evade immune surveillance. Single MWA results in decreased numbers of Treg cells and MDSCs, thereby overcoming an immunosuppressive microenvironment. MWA combined with immunotherapy can reverse the inhibitory immune microenvironment [55, 56].

MWA as an immunomodulator in various organ tumors

Liver cancer

Hepatic malignant tumors are a major global health threat, with hepatocellular carcinoma (HCC) being the most common malignant tumor of the liver. The liver is one of the first organs to be used for MWA [57] and a complete treatment system was established. During early clinical application, many researchers were exploring the immunological effects of MWA. Dong et al. [58] conducted an analysis of 89 nodules from 82 patients treated with MWA and found that microwave ablation exhibited significantly increased immune cell infiltration in the tumor site compared with the control group, including T cells, NK cells, and macrophages, and was associated with the tumor recurrence rate. Patients with high immune cell infiltration had a lower recurrence rate following treatment. This indicated that MWA has an effect on the immune system in the liver, and innate and adaptive immune cells are activated to varying degrees; however, the specific role of each immune cell type remains unclear. In the study, Yu et al. [59] found that MWA combined with immunotherapy induced extensive changes in the immune system. During this process, the proportion of cytotoxic subgroups ($CD3^+/CD8^+$, $CD8^+CD28^+$ and $CD3^+CD16^+CD56^+$ T cells) increased, whereas the proportion of regulatory or inhibitory subgroups ($CD4^+CD8^+$, $CD4^+$, $CD4^+CD25^+$) decreased. After an extended period of administration, the growth rates of dendritic cells and T lymphocytes in the bone marrow were significantly increased.

In the context of tumor immunity, the ultimate focus of the immune system is the T-cell-mediated killing of tumor cells. Zhang et al. [45] examined T-cell clusters and cytokines and found that after MWA, serum levels of $CD3^+$ cells, $CD4^+$ cells, and IL-12 in liver cancer patients was significantly increased, whereas IL-4 and IL-10 were significantly decreased. Thus, the immunosuppressive environment of the tumor tissue promoting the deviation of Th2/Th1 was alleviated as well as the immune dysfunction of liver cancer patients. Similarly, Zhou et al. [60] dynamically monitored T-cell clusters and found that Th17 was a risk factor for tumor recurrence after ablation. In addition, changes in cytokines occurred in the serum of liver cancer patients after MWA because of the activation of the immune system, including significant increases in IL-2, IL-1β, IL-6, IL-8, IL-10, and TNF-α levels [61]. Dendritic cells are the bridge between innate and adaptive immunity [62]. Zhong et al. [63] found that activating the innate immune system enhances the therapeutic effect of MWA and is a promising research direction. The combination of dendritic cell-derived extracellular vesicles with MWA treatment significantly inhibited tumor growth and improved the tumor-immune microenvironment. The immune checkpoint has always been an active area of investigation in immunotherapy. Chen et al. [64] used MWA treatment combined with granulocyte-macrophage colony-stimulating factor (GM-CSF) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) in a

mouse liver cancer model, which effectively resisted tumor re-attack and produced therapeutic effects on distant tumors. NK cells, $CD4^+$, and $CD8^+$ cells were significantly increased and played a major role in response. Similarly, Duan et al. [65] found that MWA significantly activated synergistic antitumor effects in a mouse model of Hepa1-6 HCC treated with PD-1/CTLA-4 combination therapy, increased Th1-type cytokines, and caused Th1 cell polarization. In addition, Li et al. [66] used MWA in combination with apatinib and camrelizumab to treat HCC patients, which significantly improved PFS and OS, and improved the antitumor-immune response. MWA also has a significant effect on the treatment of liver metastasis. MWA is an effective treatment strategy for liver metastasis in colorectal cancer [67], in which it can upregulate the expression of the immune inhibitory receptors, T-cell immunoglobulin and ITIM domain (TIGIT) as well as lymphocyte activation gene 3 (LAG3). TIGIT and LAG3 both participate in immune suppression and their blockade significantly increases the proliferation and function of $CD8^+$ T cells [68, 69].

The identification of the underlying mechanisms will lay the groundwork for potential clinical applications and several relevant studies are currently being conducted. In a Phase I clinical trial, MWA in combination with immunotherapy was assessed. Adoptive transfer was employed to treat 10 patients ($D \leq 5$ cm, fewer than 3 tumors) using a variety of immune cells, such as mature DCs, CTLs, cytokine-induced killer cells (CIKs), DC-CIK hybrids, and immature DCs. Effector cells were infused into resected tumors as well as the peritoneal cavity, mature dendritic cells were injected into the inguinal lymph nodes, and immature dendritic cells were injected into resected tumors. The results showed a significant reduction in $CD4^+CD25$ high Tregs, a marked increase in $CD8^+CD28^-$ effector cells, and notably, no Grade III/IV adverse events were observed; however, 6 months after therapy, there was no significant difference [55]. Another proof-of-concept clinical trial was performed on 50 patients to evaluate the feasibility and safety of tumor ablation in patients with advanced HCC, who had stable disease or an atypical response following single anti-PD-1 therapy after sorafenib failure. The results indicated that ablation increased the response rate from 10% to 24%, and the median time to progression, progression-free survival, and overall survival were 6.1 months (95% CI, 2.6-11.2), 5 months (95% CI, 2.9-7.1), and 16.9 months (95% CI, 7.7-26.1), respectively. This indicated that combination therapy elevated both the objective response rates and tolerance to drug resistance toxicity [70]. In a retrospective study, 87 patients were treated with hepatocellular carcinoma (HCC) after tyrosine kinase inhibitor (TKI) intolerance using MWA and synchronous carotid artery embolization chemotherapy (TACE) combined with PD-1 inhibitors. The combination group (n = 42) exhibited good PFS (median, 10.0 vs. 4.7 months, $P < 0.001$) and OS (median, 17.0 vs. 8.5 months, $P < 0001$) compared with patients treated without PD-1 inhibitors [71]. The positive results suggest a new treatment approach for TKI intolerant HCC. In a prospective study, Leuchte et al. [10] analyzed the relationship between the tumor-specific immune response in peripheral blood of patients before and after MWA and disease outcomes. Flow cytometry analysis revealed that MWA had only a moderate impact on the circulating immune subpopulations of 23 patients. Analysis of TAA-specific T-cell responses indicated that 30% (6/20) of the patients showed enhanced specific antitumor immunity and specific secretion of IFN-γ and/or IL-5, and a TAA-specific IL-5 and/or IFN-γ response was associated with longer DFS (27.5 months vs. 10 months, $P = 0.002$). In addition, patients with a high abundance of T cells exhibited a higher DFS (37.4 vs. 13.1 months, $P = 0.03$), which explains, in part, the clinical effects of MWA.

Lung cancer

MWA can destroy tumor tissue and cause the release of immunogenic substances. Animal models have revealed [52] that MWA reshapes the tumor microenvironment in the lung, reverses immune suppression, enhances the effect of CAR-T cell therapy, and promotes the activation, infiltration, and persistence of CAR-T cells in tumors. It also increases the mitochondrial oxidative metabolism of CAR-T cells infiltrating the tumor, resulting in significant tumor suppression without toxicity in humanized immunocompetent mice. MWA combined with adoptive transfer of Th9 cells can also reshape the tumor immune microenvironment, activate

$CD8^+$ T effector memory cells, and enhance the anti-tumor efficacy of T-helper type 9 (Th9) cells by upregulating interleukin (IL)-1β and subsequently activating the downstream STAT1/IRF1 pathway [72]. These studies provide a new paradigm and method for the treatment of NSCLC. Zhang et al. [73] conducted a prospective study on the immunogenic changes induced by MWA. They enrolled 22 patients with malignant tumors who received MWA treatment and found that $CD8^+$ T cells were increased following ablation, whereas negatively regulated Tregs were decreased and independently associated with PFS. IL-2 concentration was also decreased. T-cell subsets are indicative of the strength of antitumor-immune response. Takaki et al. [74] reported that MWA significantly increased the population of peripheral blood CTL and the CTL/Treg ratio, whereas the Th1/Th2 ratio remained unchanged following treatment. Ablation therapy changed the T-cell balance by increasing the overall CTL/Treg ratio.

Many clinical studies have focused on the combination of MWA and immune checkpoint inhibitors, which have shown therapeutic efficacy and safety. Wei et al. [75] prospectively enrolled 21 patients with advanced NSCLC and administered camrelizumab after MWA. The technical success rate was 100% and the ORR was 33.3%, with two patients achieving a complete response and five patients achieving a partial response. The median PFS was 5.1 months and OS was not reached. This indicates that the combination of camrelizumab and MWA was superior to PD-1 antibody alone. Further prospective studies with a larger cohort are needed to confirm the superiority of combination therapy. Huang et al. [76] retrospectively enrolled 77 patients with epidermal growth factor receptor/anaplastic lymphoma kinase-wild-type NSCLC. Based on a technical efficacy rate of 97.4%, the ORR was 29.9%. The PFS was 11.8 months (95% confidence interval, 9.5-14.1) and the OS were not reached. Complications were observed in 33 patients (42.9%), but remained within effective control. MWA combined with camrelizumab monotherapy is effective and safe for the treatment of NSCLC. Another retrospective study evaluated the changes in cytokine levels after MWA and found that one month after ablation, IL-2 and IFN-γ levels were increased [77]. In addition to a high response rate, Wei et al. [78] also rechallenge two patients with camrelizumab who were previously treated with MWA and camrelizumab. Although objective responses were achieved, camrelizumab therapy was discontinued because of the development of immune-related pneumonia. This compensated for the challenge of ICB treatment for advanced NSCLC. Shao et al. [79] performed local ablation on advanced squamous cell lung cancer patients who were resistant to acquired immunotherapy. They found that MWA had a long-lasting abscopal effect, which further supports the superior immunotherapeutic effects of MWA. Similarly, Xu et al. [80] also documented a patient with bilateral lung metastasis in endometrial cancer. After MWA was performed on the right side, the left lesion gradually subsided, which indicates an abscopal effect of MWA.

Breast cancer

Breast cancer surgery has evolved from classic radical mastectomy to modified radical mastectomy and to breast-conserving surgery, which has become minimally invasive and precise, resulting in improved cosmetic outcomes for breast appearance. MWA is well-suited for breast cancer surgery; however, it has a poor response to immunotherapy thus far [81]. MWA serves as an immunomodulatory option as it not only kills tumors, but enhances the response of breast tumors to immunotherapy. In animal models, NK cells were activated and showed increased cytotoxic activity following MWA of primary tumors through the macrophage/IL-15/NK-cell axis, whereas they lung metastasis of breast cancer was inhibited and survival was increased [42]. Zhou et al. [82] analyzed the immune response induced by MWA in 35 breast cancer patients and found that MWA induced significant increases in $ICOS^+$ $CD4^+$ T cells and interferon-γ levels, which indicates a shift in the Th1/Th2 balance toward Th1. The activated ICOS pathway is involved in the MWA-induced adaptive immune response. MWA induces a $CD4^+$ effector memory T-cell response, which can produce an immune response following tumor removal. Further analysis by Zhou et al. [83] of PBMCs in six patients before and after ablation using single-cell RNA sequencing revealed changes in gene expression associated with the systemic antitumor-immune response. NK and $CD8^+$ T cells were activated by MWA in breast cancer,

$CD8^+$ T-cell inhibitory function was enhanced, but not impaired, $CD4^+$ T-cell co-stimulatory signals were increased, and the interaction between B cells and $CD4^+$ T cells was enhanced. This suggests that B cells are important antigen-presenting cells in the microwave ablation-induced immune response to activate $CD4^+$ T cells. TCR sequencing results indicated TCR clone expansion, which provides a global characterization of the immune system response induced by MWA. Moreover, when combined with OK-432 treatment, MWA activated the T-cell immune response, induced a Th1-type response, and triggered specific antitumor immunity, significantly prolonging the survival of mice and effectively preventing tumor recurrence [84]. Combinations with immune checkpoint blockade therapy can synergistically enhance the antitumor effect and specific immune responses [85].

Kidney cancer

Malignant tumors of the kidney are mostly renal cell carcinoma and the main treatment is surgical resection, while preserving the renal unit as much as possible. RFA and cryoablation have been successfully applied for the treatment of renal tumors, especially cryoablation, which exhibits a good immunostimulatory effect. For tumors around the kidney, however, MWA is significantly superior compared with other ablation methods in terms of faster speed and a larger range of ablation [86, 87]. Guo et al. [56] treated mice with renal cell carcinoma using anti-PD-1/CTLA-4 combination therapy and found that the combination therapy group exhibited an increased number of $CD8^+$ T cells, a decreased number of regulatory T cells, and the highest level of interferon-γ. In addition, the combination group also had a superior ability to withstand tumor rechallenge. With respect to clinical treatment, Pandolfo SD et al. [88] compared the efficacy of IGTA with surgery for the treatment of renal masses and the results confirmed that IGTA is an effective treatment method. Similarly, Pandolfo SD et al. [89] conducted a retrospective study to analyze the efficacy of various IGTA energy sources for the treatment of renal tumors. MWA had a therapeutic advantage compared with cryoablation and RFA, with a reduction in complications, shorter surgical time, and similar surgical results.

Other cancers

Osteosarcoma is the most common primary malignant bone tumor and bone is the preferred site for metastases. Yu et al. [90] used three osteosarcoma cell lines derived from mice, rats, and humans as ablation models to examine in vitro and in situ tumor ablation. The results indicated that tumor cell death caused by MWA resulted from immunogenic cell death and induced an increase in $CD8^+$ T-cell expression as a vaccine. Furthermore, Fas-FasL binding-induced ICD plays a central role in $CD8^+$ T-cell killing of osteosarcoma cells induced by the vaccine. Ma et al. [91] utilized the thermal therapy characteristics of microwaves combined with 3D printing technology to design an ICB-loaded therapy for osteosarcoma. The results indicated that microwave hyperthermia induced ICD, significantly enhanced the adaptive immune response, and generated significant antitumor effects. The detection rate of papillary thyroid microcarcinoma has increased annually. MWA has flourished as a treatment in this field. Wu et al. [92] evaluated the effect of MWA on patient immune function by observing changes in T-cell subpopulations and cytokine levels before and after MWA treatment. The results indicated that $CD4^+$, $CD4^+/CD8^+$ T cells, IL-2, and IFN-γ levels in the peripheral blood of patients 1 day and 2 weeks after MWA treatment were increased; however, $CD8^+$ changes were insignificant. The patient's immune function was mobilized by MWA in the short-term and exerted antitumor effects. This further confirms from another perspective that MWA alone exhibits antitumor-immune effects through NK cells, rather than $CD8^+$ T cells [42]. Specific applications were summarized in **Tables 1** and **2**.

Future perspectives

Immunotherapy has emerged as a game-changer for cancer treatment, opening a new era of hope and progress. Over the past half-century, this field has experienced a rapid and transformative development, which has revolutionized our approach to combating tumors. One of the major breakthroughs has been the discovery and development of immune checkpoint inhibitors (ICIs) [93]. These drugs inhibit the molecules that act as "checkpoints" on immune cells, such as CTLs [94], to prevent

Table 1. The immunomodulatory effects of MWA therapy on tumors in different organs

Species	Cancer type	Combination/non combination immunotherapy	Immunomodulation effect	Outcome	Ref
Human	HCC	--	NK cells, T cells, Macrophages ↑	Reduced recurrence rate Improved survival	[58]
Human	HCC	DC-CIK	T cells ↑ Treg ↓	Reduced recurrence rate	[59]
Human	HCC	--	$CD3^+$, $CD4^+$ T cell, IL-12 ↑ IL-4, IL-10 ↓	Improved immune dysfunction	[45]
Human	HCC	--	Th17 ↑	Evoked a transitional immune response	[60]
Human	HCC	--	IL-2, IL-1β, IL-6, IL-8, IL-10, and TNF-α ↑	Improved circulating cytokine levels	[61]
Human	HCC	Anti-PD-1 antibody	Tumor-specific immune responses ↑	Improved PFS and OS	[66]
Human	HCC	Idc, CTL, mDC	$CD8^+$ T cells ↑ Treg ↓	Improved survival	[55]
Human	HCC	Anti-PD-1 antibody	Tumor-specific immune responses ↑	Enhanced drug response rate Improved median survival	[70]
Human	HCC	Anti-PD-1 antibody	Tumor-specific immune responses ↑	Improved PFS and OS	[71]
Human	HCC	--	Tumor-specific T cell responses ↑ TTAs ↑	Improved PFS and DFS	[10]
Human	Pulmonary malignancies	--	Treg ↓	Improved survival	[73]
Human	Pulmonary malignancies	--	The systemic CTL/Treg ↑	Enhanced systemic antitumor immunity	[74]
Human	NSCLC	Anti-PD-1 antibody	Tumor-specific immune responses ↑	Improved ORR	[75]
Human	NSCLC	Anti-PD-1 antibody	Tumor-specific immune responses ↑	Enhanced drug response rate	[76]
Human	NSCLC	--	IL-2 and IFN-γ ↑	Improved survival	[77]
Human	NSCLC	Anti-PD-1 antibody	Abscopal effect	Improved survival	[79]
Human	Endometrial cancer with lung metastasis	--	Abscopal effect	Improved survival	[80]
Human	Breast cancer	--	$ICOS^+$ $CD4^+$ T cells and IFN-γ ↑ Th1 cells polarization ↑ $CD4^+$ effector memory T cell response ↑	Improved immune microenvironment	[82]
Human	Breast cancer	--	NK and $CD8^+$ T cells ↑ Inhibitory signature of $CD8^+$ T cells ↑ Interactions between B cells and $CD4^+$ T cells ↑	Improved immune microenvironment	[83]
Human	RENCA	Anti-PD-1/Anti-CTLA-4 antibody	Treg ↓ $CD8^+$ T cells ↑	Reduced tumor and metastasis growth	[56]
Human	PTMC	--	$CD3^+$, $CD4^+$, $CD8^+$ T cells ↑ IL-2 and IFN-γ ↑	Improved immune function	[92]

Table 2. The immunomodulatory effects of MWA therapy on tumors in different animal studies

Species	Cell type	Combination/non combination immunotherapy	Immunomodulation effect	Outcome	Ref
Mouse	Hepa1-6	DC-derived exosomes/DC	$CD8^+$ T cells ↑ Treg ↓		[63]
Mouse	Hepa1-6	GM-CSF/Anti-CTLA-4 antibody	NK cells, $CD4^+$ and $CD8^+$ T cells ↑	Improved survival Inhibit tumor rechallenge	[64]
Mouse	Hepa1-6	Anti-PD-1/Anti-CTLA-4 antibodies	$CD4^+$ and $CD8^+$ T cell ↑ Th1 cells polarization ↑	Improved survival Reduced recurrence rate	[65]
Mouse	MC38	Anti-TIGIT antibody/Anti-LAG3 antibody	$CD8^+$ T cells ↑ Reshaped myeloid cells	Improved survival	[68, 69]
Mouse	A549, HCC827	CAR-T cell	Tumor-specific-CAR T cells ↑	Improved survival Reshaped the immune microenvironment	[52]
Mouse	LLC	Adoptive Th9 cell	$CD8^+$ T effector memory cells ↑ IL-1β ↑, STAT1/IRF1 pathway ↑	Improved survival	[72]
Mouse	4T1	--	The macrophage/IL-15/NK-cell axis	Inhibited tumor metastasis	[42]
Mouse	4T1	OK-432	Local and systemic T-cell responses ↑ Th1-type cytokines ↑ Th1 cells polarization ↑	Resistant to tumor rechallenge	[84]
Mouse	4T1	Anti-PD-1/Anti-CTLA-4 antibody	Plasma IFN-γ ↑ Local and systemic $CD8^+$ T-cell responses ↑	Resistant to tumor rechallenge	[85]
Rat/Mouse	UMR106/K7M2	--	Immunogenic cell death ↑ DAMPs ↑	Improved survival	[89]

them from attacking normal cells. By blocking these checkpoints, ICIs unleash the immune system's full potential, allowing it to mount a robust and sustained attack. Another promising approach is adoptive cell transfer, including CAR-T [95], CIK, DC therapy [55]. Cancer vaccines also can stimulate the immune system to recognize and target cancer cells, whereas immune system modulators enhance the immune response against tumors. These approaches hold great promise in further advancing the field of immunotherapy and expanding its application across various cancer types. However, challenges still remain in the field of immunotherapy. Not all patients respond equally to immunotherapy and resistance mechanisms can develop over time [96].

With the development of modern image-guided devices and advances in minimally invasive techniques, MWA has gradually become another therapeutic option for treating tumors, particularly for patients who are not suitable for surgery because of intolerance. MWA offers significant survival benefits for such patients; however, current indications for MWA treatment remain limited, with risks of recurrence, metastasis, and inadequate immune activation following ablation. In clinical practice, MWA may be combined with immunotherapy to not only reduce tumor burden, but also enhance the body's immune response. Studies have indicated that MWA acts as an "immunomodulator" when used in combination with immunotherapy by releasing tumor antigens in situ, creating an inflammatory environment to recruit immune cells, and activating the innate and adaptive immune response. However, most studies thus far are based on measuring immune modulating factors in the circulation and there is little information regarding immune changes in situ after tumor ablation. Although the immune effects induced by MWA are similar to those induced by RFA, the complete denaturation and coagulative necrosis of tumor antigens during MWA can prevent the activation of antitumor-immune effects, resulting in a weaker immune response compared with that induced by RFA [97, 98]. Therefore, it is important to control output power, ablation time, ablation range, and other MWA parameters. Moreover, a single MWA is not sufficient to prevent tumor recurrence. To achieve the maximum effect in combination with immunotherapy, it is necessary to completely ablate the tumor, while maximizing the activation of the body's antitumor-immune response. In addition, because of the clinical heterogeneity of the operation, incomplete tumor ablation may occur, resulting in residual tumor cells that may metastasize or accelerate tumor progression [99], which undoubtedly limits the use of MWA. Although the research data is still limited, the prospects of MWA combined with immunotherapy are very promising. Both animal and human clinical studies need to explore the specific mechanisms of MWA in the activation of the host immune response, examine the feasibility of MWA combined with other treatments, promote the standardization of treatment methods in clinical practice, and provide new strategies and ideas for tumor treatment.

In conclusions, MWA represents an effective treatment for malignant tumors because it is minimally invasive, repeatable, low cost, and effective. It has matured as a treatment system for organs such as the liver, lungs, and thyroid, and is gradually being applied to other organs. MWA can also induce antitumor immunity. Unfortunately, the immune response is generally weak and lasts for a short time. Therefore, combining MWA with immunotherapy has emerged as a promising new direction in cancer treatment. Multiple prospective and retrospective studies have confirmed the effectiveness of the combination, with varying degrees of improvement in patient PFS, OS, DPF and ORR. However, the underlying mechanism of the synergistic effect of MWA combined with immunotherapy remains unclear and requires further study.

Disclosure of conflict of interest

None.

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