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## Radiofrequency combined with immunomodulation for hepatocellular carcinoma: State of the art and innovations

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### Abstract

Hepatocellular carcinoma (HCC) is the most common primary liver tumor and has been considered a very immunogenic tumor. The treatment with radiofrequency ablation (RFA) has been established as the standard ablative therapy for early HCC, and is currently recognized as the main ablative tool for HCC tumors < 5 cm in size; however, progression and local recurrence remain the main disadvantages of this approach. To solve this clinical problem, recent efforts were concentrated on multimodal treatment, combining different strategies, including the combination of RFA and immunotherapy. This article reviewed the combination treatment of RFA with immunotherapy and found that this treatment strategy leads to an increased response of anti-tumor T cells, significantly reduces the risk of recurrence and improves survival rates compared to RFA alone. This review highlighted scientific evidence that supports the current recommendations for pre-clinical studies, and discuss the need for further research on this topic.

**Key words:** Hepatocellular carcinoma; Radiofrequency ablation; Immunotherapy; Liver cancer; Combined modality therapy; State-of-the-art review

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**Core tip:** Radiofrequency ablation (RFA) is a well-established surgical approach to treat hepatocellular carcinoma (HCC). However, it has the inconvenience of being related to tumor recurrence. The combination of RFA and immunotherapy has emerged as a promising approach to activate and potentialize local and systemic immune responses. It has potential to reinstate anti-tumor immunity in HCC through increase in antitumor T cell response. The approach seems quite pragmatic in limiting the recurrence and improving survival rates compared to RFA alone for HCC patients. Currently, there are

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only eight articles in the literature that studied the combination of RFA and immunotherapy.

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## INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary liver tumor<sup>[1]</sup>. It currently represents the sixth most common cancer worldwide and second major cause of cancer-related deaths<sup>[2]</sup>. The incidence of HCC varies widely according to geographic location, and death rates are increasing in many parts of the world, including North America, Latin America, and central Europe<sup>[3,4]</sup>. The most common risk factors for HCC include chronic hepatitis B and C, alcohol consumption, metabolic liver disease (particularly nonalcoholic fatty liver disease) and exposure to dietary toxins, such as aflatoxins and aristolochic acid, indicating that persistent inflammation is involved in its carcinogenesis<sup>[5]</sup>.

Radiofrequency ablation (RFA) is widely accepted as a first-line interventional oncology approach for HCC and has the advantages of high treatment efficacy and low risk of complications<sup>[6]</sup>. RFA causes destruction of the tumor through the induction of hyperthermia, and can be used to directly treat the liver tumors or to assist the liver resection<sup>[7,8]</sup>. The destruction of the tumor mediated by RFA may provide a way to the induction, *in vivo*, of the antitumoral immunity, through antigens presentation and maturation of the dendritic cells, having an action in resemblance to the vaccine<sup>[9]</sup>. The current evidence indicates that RFA leads to positive effects on the antitumoral immunity, not only at a local level, but also triggering systemic immune responses<sup>[9]</sup>. It has also been demonstrated an increase of CD4<sup>+</sup> and CD8<sup>+</sup> T cells in peritumoral area and on the peripheral blood<sup>[10]</sup>. Moreover, it is observed an increased number of pro-inflammatory agents, immunostimulators, such as IFN $\gamma$ , and expression of BDCA-3<sup>+</sup>/B7-H3<sup>-</sup> dendritic cells<sup>[11]</sup>. Although this immunologic response is not enough to avoid recurrence by its own, it has potential to bring enhanced and synergistic immune response in combination with other immunomodulators, such as checkpoint inhibitors<sup>[10]</sup>.

Recently, it has been observed that disease progression rates and local recurrence of HCC are high following RFA as monotherapy, particularly for larger tumors (> 3 cm)<sup>[6]</sup>. To solve this clinical problem, recent efforts have been made to improve the HCC multimodal treatment, combining different strategies, including the combination of RFA and immunotherapy. The intent of combination therapy is to achieve better outcomes in comparison to the RFA alone, in terms of improving survival rates and avoiding recurrence<sup>[6,12,13]</sup>. The association between RFA and immunomodulators induce a synergistic anticancer immune response as observed in pre-clinical studies, which seems quite promising to the future of oncological treatment<sup>[12]</sup>.

This review sought to analyze the current recommendations of combined therapies for HCC with RFA and immunomodulation, and discuss the need for further research on this topic.

## RADIOFREQUENCY ABLATION AND HCC

RFA technique involves application of high-frequency oscillating electrical currents to generate heat around the probe, which results in tissue hyperthermia (60-100 °C) and coagulative necrosis (Figure 1)<sup>[2]</sup>. RFA has been established as standard ablative therapy for early stage HCC, being currently recognized as the main ablative tool for HCC tumors < 5 cm in size<sup>[1,6,14]</sup>. However, the recurrence and local progression rates of HCC increases after treatment with RFA in instances of bigger lesions; this remains as the biggest challenge of RFA<sup>[6]</sup>. Hence, RFA is not recommended to ablate tumors bigger than 5 cm<sup>[6,14]</sup>. Furthermore, more aggressive ablative approaches are associated with an increased risk of injuries because of unwanted thermal damage to important

adjacent structures, such as the bile duct, gallbladder, diaphragm and intestinal tracts<sup>[15,16]</sup>.

Recently, a multicenter study including 18296 patients with primary HCC (8211 undergoing RFA, 10085 undergoing hepatic resection), compared the effectiveness of RFA with surgical resection and outlined superior post-treatment outcomes following RFA<sup>[17]</sup>. However, several other randomized controlled clinical trials have compared RFA to surgical resection with ambiguous results<sup>[18-20]</sup>. While some studies reported comparable effectiveness regarding overall and recurrence-free survival<sup>[18]</sup>, others have highlighted superior outcomes following surgical resection<sup>[19,20]</sup>.

## IMMUNOTHERAPY AND HCC

The natural immune system has potent antitumor action, which can be used to limit and treat hepatic tumors. The main purpose of immunotherapy is to enhance the expression of tumor-specific CD8<sup>+</sup> effector-/CD4<sup>-</sup> helper T cells and the reinvigoration of exhausted T cells at the site of the tumor nodules<sup>[21]</sup>.

The main modalities of cancer immunotherapy are immune checkpoint inhibitors, therapy with CAR-T cells and vaccines<sup>[22]</sup>. Common immune checkpoint proteins include cytotoxic T lymphocyte-associated antigen-4 (CTLA-4), programmed cell death protein-1 (PD-1), programmed cell death ligand 1 (PD-L1), VISTA, TIM-3, LAG-3, and OX40<sup>[23]</sup>. It is known that CTLA-4 and PD-1 inhibitors are negative regulators of T-cell immune function and they have the most important use in clinical research<sup>[24]</sup>. They have been well characterized and approved by the FDA for treating melanomas, and recent studies have outlined their role in management of HCC. CTLA-4 inhibitors, such as Tremelimumab and Ipilimumab, is predominantly expressed in activated T cells and natural killer (NK) cells<sup>[23]</sup>. CTLA-4 binds costimulatory B7 molecules (CD80/86) with a much higher affinity than CD28. Therefore, B7 binds CTLA-4 instead of CD28, what does not produce its usual stimulatory signal. When this protein is blocked, the inhibition on the immune system is released and the ability of T cells to kill cancer cells is increased<sup>[10]</sup>. Therefore, CTLA-4 functions to competitively inhibit T cell stimulation, and promote T cell anergy (Figure 2).

PD-1 is expressed in T cells, B cells, NK cells, mononuclear cells, and DCs. PD-1 inhibitors block the receptor binding of PD-L1 and PD-L2<sup>[25,26]</sup>. When PD-1 is activated by PD-L1, a ligand often found on tumor cells, it inhibits T cell functioning and induces apoptosis<sup>[24]</sup>. Some PD-1 inhibitors, such as Nivolumab, Pembrolizumab, and Pidilizumab, have been investigated for cancer treatment<sup>[27]</sup>. A phase I/II study has demonstrated the safety and antitumor effect of Nivolumab in patients with advanced HCC<sup>[28]</sup>.

The basis of CAR-T cell therapy is to generate an immune-mediated antitumor response through gene transfer of a chimeric antigen receptor into T-cells<sup>[29]</sup>. Its benefits has been largely reported for hematological malignancies; however, for solid tumors, it is still incipient, with some challenges ahead, including the tumor microenvironment, which is more immunosuppressive, and the “on-target off-tumor” toxicity, since these lesions are generally expressed in other sites<sup>[29,30]</sup>.

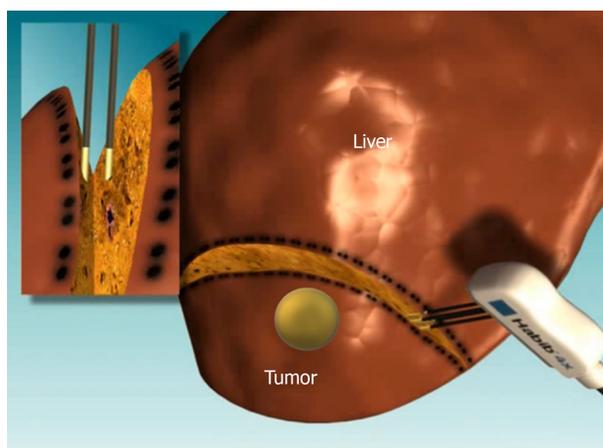
For vaccines, it consists of the generation of endogenous cancer-specific cytotoxic CD8<sup>+</sup> T cells (CTLs), which present a paramount feature to kill cancer cells upon specific recognition through the T cell receptor of CTLs<sup>[31]</sup>. Therefore, it leads to cancer cell death through different mechanisms, including upregulation of FasL or TRAIL, leading to apoptosis, or through the induction of degranulation, releasing perforin and granzyme B<sup>[31,32]</sup>.

## RFA COMBINED WITH IMMUNOTHERAPY FOR HCC

A total of 37 articles were identified from the literature research for this review. However, only seven articles studied the combined therapy of RFA and immunotherapy<sup>[12,13,33-37]</sup>. Of these, 3 articles consisted of animal studies, and 4 consisted of human studies (Table 1).

In a noncomparative clinical trial involving patients with advanced HCC, a combination therapy with Tremelimumab and RFA increased the number of intratumoral CD8<sup>+</sup> T cells infiltration<sup>[38]</sup>. However, this study included a substantial number of patients treated with not only RFA, but also cryoablation and/or TACE.

A comparative study involving patients with middle-advanced stage HCC has investigated the effectiveness of monoclonal antibody (131I-*chTNT*) and RFA as a combination therapy<sup>[13]</sup>. This study showed that the survival time of patients who received combination therapy was significantly longer than that of the RFA alone



**Figure 1** Radiofrequency ablation device used to treat hepatocellular carcinoma.

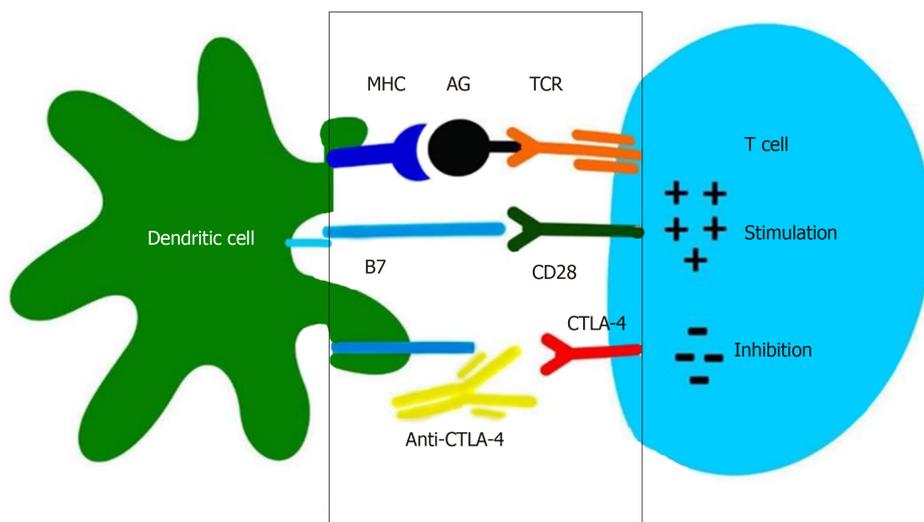
group ( $P = 0.052$ ). The number of white blood cells was significantly increased in the group that use monoclonal antibody treatment. In middle-advanced stage HCC patients, the combination of  $^{131}\text{I}$ - chTNT and RFA therapy was found to be significantly more effective than the RFA treatment alone for primary HCC<sup>[13]</sup>.

Behm *et al*<sup>[33]</sup> studied the addition of CpG B oligonucleotides, toll like receptor (TLR) 9 agonists, to radiofrequency ablation in a VX-2 rabbit model of liver cancer, and observed that the combination significantly increased mean survival, cytolytic activity, and tumor-specific T cell activation compared to RFA alone. Additionally, the combined therapy demonstrated increased protection against pulmonary metastasis and peritoneum subjected to a re-challenge to injected malignant cells. Animals treated with combination RFA/CpG B survived longer than average in contrast to those treated with RFA or CpG B alone. In addition, they also observed that a smaller number of animals subjected to the combination therapy group showed residual malignant tissue after 120 days in comparison to monotherapy groups ( $P < 0.05$ ), justifying the need for further exploration of the combination of RFA and TLR9 agonists in liver cancer.

Ma *et al*<sup>[34]</sup> reported the combination of RFA and autologous RetroNectin activated killer (RAK) cells in the treatment of HCC with a tumor size less than 4 cm. Recently, T lymphocytes were found to be efficiently expanded by stimulation with a combination of immobilized RetroNectin and anti-CD3mAb in HCC. It was observed that the percentage of  $\text{CD3}^+\text{CD8}^+$  cells displayed a trend of continuous increase during the study, with no severe adverse events along the follow-up period, with no recurrence nor deaths reported. These preliminary results suggest the feasibility and safety of the combined therapeutic regimen for HCC, and that the RAK cell adoptive immunotherapy might be helpful in preventing recurrence and metastasis rates in HCC patients after RFA<sup>[34]</sup>.

Nakagawa *et al*<sup>[35]</sup> demonstrated that the administration of dendritic cells stimulated by OK-432 (a clinical bacterial product, which can induce DC maturation) after RFA conferred a significant decrease in mean tumor volume compared to RFA alone or RFA in combination with immature dendritic cells ( $P < 0.001$ ). Additionally, they showed that combination therapy significantly increased the number of  $\text{CD8}^+$  T cells infiltrating untreated secondary tumors as compared to RFA alone ( $P < 0.001$ ). On the basis of these findings, they believe that combination therapy for liver cancer consisting of OK-432-stimulated DCs combined with RFA can proceed to clinical trials, and it is anticipated to be markedly superior to RFA single therapy.

Cui *et al*<sup>[12]</sup> studied the efficiency and safety of the combined treatment, with radiofrequency ablation (RFA) with cellular immunotherapy (CIT), for HCC patients. In this study, 62 patients with HCC who were treated with radical RFA were divided into two groups: RFA alone (32 patients) and RFA + CIT (30 patients). Autologous mononuclear cells were collected from the peripheral blood and separated by apheresis, and then induced into NK cells,  $\gamma\delta\text{T}$  cells and cytokine-induced killer (CIK) cells. The tumor recurrent status of these patients was evaluated with computed tomography or magnetic resonance imaging every 3 mo after RFA. Progression free survival (PFS), liver function, HCV viral load and adverse effects were examined. The results implied that PFS was higher in the RFA + CIT group than in the RFA alone group. In the RFA + CIT group, six courses had better survival prognosis than three courses. Viral load of hepatitis C was decreased in patients without antiviral therapy in the RFA + CIT group, but was increased in the RFA alone group. No significant



**Figure 2** Cytotoxic T lymphocyte- associated antigen 4 up regulated on T-cell surfaces. MHC: major histocompatibility complex; AG: Antigen, TCR: T-cell receptor; CTLA-4: Cytotoxic T-lymphocyte antigen-4.

adverse reaction was found in the patients to whom CIT was administered. In summary, these preliminary results suggest that the combination of sequential CIT with RFA for HCC is efficient and safe, and may be helpful in the prevention of recurrence. However, a multicenter, randomized controlled clinical trial is still needed to further verify its efficacy.

Sodergren *et al*<sup>[36]</sup> in a recent study to investigate any synergistic effect of MTL-CEBPA (enhancer-binding protein alpha) with RFA and immune checkpoint inhibition, initiated a reverse translation experiment, where syngeneic BNL hepatocellular carcinoma tumor cells were injected in the two opposite flanks of immunocompetent BALB/c mice ( $n = 8$  in each group). Treatments for hepatoma bearing mice included: (1) RFA on one flank; (2) Anti-PD-1 inhibition immunotherapy; and (3) MTL-CEBPA as well as combinations of all 3 interventions. They found that tumor control on the opposite flank was increased by addition of RFA, and it more prominent in the triple combination group (RFA + anti-PD1 + MTL-CEBPA), in which 2/8 of the animals showed a complete response and 5/8 a partial response. This was also the only group that showed a statistically significant increase in CD8<sup>+</sup> (Cytotoxic) as well as CD49b<sup>+</sup>/CD45<sup>+</sup> (Natural Killer) tumor infiltrating lymphocytes. These data suggest a clinical role for combination treatment with checkpoint blockade, RFA and MTL-CEBPA through the synergistic priming of the immune response, enabling RFA to have a pronounced anti-tumor abscopal effect.

A single-center randomized controlled trial of radioimmunoconjugate <sup>131</sup>I metuximab in treatment of HCC after percutaneous RFA compared with RFA alone was conducted<sup>[37]</sup>. In this study, 127 patients received either RFA followed by <sup>131</sup>I metuximab ( $n = 62$ ) or RFA alone ( $n = 65$ ), and the primary outcome assessed was overall tumor recurrence. The one- and two-year recurrence rates in the combination group were 31.8% and 58.5%, whereas those in the RFA alone group were 56.3% and 70.9%, respectively. The median time to overall tumor recurrence was 17 mo in the combination group and 10 mo in the RFA alone group ( $P = 0.03$ ). The RFA-<sup>131</sup>I metuximab treatment showed a greater anti-recurrence benefit than RFA alone ( $P = 0.007$ ). The <sup>131</sup>I metuximab may yielded prevention of tumor recurrence after RFA<sup>[37]</sup>.

The table below illustrates all the studies published so far in the literature and summarizes the findings regarding the combination of RFA and immunotherapy for the treatment of HCC (Table 1).

## DISCUSSION

Immunotherapy is a relatively new strategy of treatment for HCC. It aims to improve the body's immune system against tumor associated antigens and induces tumor cell death<sup>[6]</sup>. Immunotherapy has the benefit of eliminating residual microscopic lesions of the tumor and preventing recurrences after RFA, being clear that the combination of immunotherapy and RFA improves oncological outcomes in patients with HCC<sup>[34]</sup>.

Immunosuppression in patients with HCC is an important factor leading to its

**Table 1 Radiofrequency ablation and immunotherapy combined in hepatocellular carcinoma**

Ref.	Tumor	Intervention	Results	Level of evidence
Cui <i>et al</i> <sup>[12]</sup> , 2014	HCC from 2 to 8 cm	RFA with cellular immunotherapy	Avoid HCC recurrence	III
Tu <i>et al</i> <sup>[13]</sup> , 2015	Middle-advanced HCC	RFA and monoclonal antibody ( <sup>131</sup> I-chTNT)	Increased circulating white blood cells; Increased overall survival; Improved progress-free survival	IV
Behm <i>et al</i> <sup>[33]</sup> , 2016	VX2 rabbit HCC	RFA and CpG B	Increased antitumor T cell response; prevented tumor spread; Improved survival	II
Ma <i>et al</i> <sup>[34]</sup> , 2010	HCC < 4 cm	RFA and autologous RAK cells	Increased intratumoral percentage of CD3 <sup>+</sup> CD8 <sup>+</sup> cells; avoided HCC recurrence	IV
Nakagawa <i>et al</i> <sup>[35]</sup> , 2014	C57B1/6 mice	RFA and OK-432 stimulated DCs	Decreased tumor volume; increased intratumoral CD8 <sup>+</sup> T cells	IV
Sodergren <i>et al</i> <sup>[36]</sup> , 2019	BALB/c mice	RFA, checkpoint blockade and MTL-CEBPA	Increase in CD8 <sup>+</sup> and CD49b <sup>+</sup> /CD45 <sup>+</sup> immune tumor response; abscopal effect	III
Bian <i>et al</i> <sup>[37]</sup> , 2014	Tumors < 3 cm <i>vs</i> > 3 cm	RFA and <sup>131</sup> I metuximab	Prevention of tumor recurrence	II

HCC: Hepatocellular carcinoma; RFA: Radiofrequency ablation; RAK: RetroNectin activated killer.

recurrence and metastasis, justifying the need of improving the immune system with immunomodulatory drugs<sup>[12]</sup>. Cui and colleagues<sup>[12]</sup> demonstrated in their study that the progression-free survival curve in the group aged  $\leq 60$  years was significantly better than the group aged  $> 60$  years ( $P > 0.05$ ). This difference can be explained by the fact that the immune system changes with age progression, with a decrease in the performance of immune cells in the elderly, and a better immune function in young patients.

Kaseb *et al*<sup>[39]</sup> in a randomized, open-label, perioperative phase II study, assessed the efficacy and safety of anti-PD-1 and anti-CTLA-4 antibodies, evaluating nivolumab alone versus nivolumab plus ipilimumab in patients with resectable HCC. They reported that 37.5% of patients treated with perioperative immunotherapy had complete response, and this response was correlated with an increase in intratumoral infiltration of CD8<sup>+</sup> T cells, making it clear that HCC is a very immunogenic tumor, and immunotherapy can be a useful tool as an effective neoadjuvant or adjuvant therapy. Based on this study, we can propose neoadjuvant treatment with PD1 and CTLA4 in order to reduce the size of the tumor, and then perform RFA in the residual lesion. Therefore, neoadjuvant immunotherapy reduces tumor size, making RFA more efficient, as well as having the benefit of preventing tumor recurrence and progression.

RFA treatment is increasingly being used for local ablation of solitary liver tumors up to 5 cm in size<sup>[1,6,14]</sup>. Unfortunately, many of these patients still experience recurrence and multiple metastases, suggesting that adding relevant systemic therapy with immunomodulators would be highly valuable<sup>[34]</sup>.

The immune responses induced by ablation monotherapy are well documented, but independently they tend to be incapable of evoking a clinically significant antitumor response. By adding immunomodulators to traditional ablative techniques, several researchers have sought to amplify the induced immune response and trigger systemic antitumor activity<sup>[10]</sup>. Besides that, RFA is responsible for its ability to trigger a systemic antitumor immune response where surgical resection would not<sup>[40]</sup>.

Tu *et al*<sup>[13]</sup> by analyzing the data from two groups, showed that in the RFA alone group, the lesion diameter of  $> 5$  cm was significantly associated with poor prognosis, indicating that unless combined with immunotherapy, this model of treatment is insufficient to eliminate larger tumors. This study suggested that RFA combined with immunotherapy is superior to RFA alone in treating the primary HCC with diameter  $> 3$  cm. However, for lesions with  $> 5$  cm diameter, the doses of both therapies used in this study were relatively insufficient to control the local recurrence.

The combination of RFA and immunotherapy shows better results than isolated therapies on patients with HCC, suggesting that the combination is more beneficial

than RFA alone. Furthermore, we observed that this treatment strategy leads to an increase in the response of antitumor T cells, significantly reduces the risk of recurrence and improves overall survival compared to RFA isolated. However, a limiting factor was the relatively small number of studies and the short follow-up periods<sup>[12,13,33-37]</sup>. Therefore, the long-term effects of these studies have yet to be validated. In addition, a multicenter randomized controlled clinical trial is utterly needed to further verify its effectiveness.

## CONCLUSION

RFA is a safe and efficient treatment for HCC, however therapeutic outcomes are limited by recurrence and metastasis. In our review, we observed only seven articles that studied the combination of RFA and Immunotherapy. The combined treatment with RFA and immunotherapy has emerged as a promising approach to activate immune response. Here, the authors investigated the applicability of combined RFA and Immunotherapy and observed that this strategy has potential to reinstate anti-tumor immunity in HCC through increase in antitumor T cell response. The approach seems quite pragmatic in limiting the recurrence and improving survival compared to RFA alone for HCC patients. However further studies are of paramount importance to elucidate its true potential.

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