Liver Research 7 (2023) 108–115

Contents lists available at ScienceDirect

Liver Research

journal homepage: http://www.keaipublishing.com/en/journals/liver-research

Review Article

Radiofrequency ablation of hepatocellular carcinoma: Current status, challenges, and prospects☆

Hongye Wang [a], Zhaorong Wu [a], Dan Cui [a], Yaoping Shi [a], Bo Zhai [a, b, *]

[a] Department of Interventional Oncology, Renji Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China
[b] State Key Laboratory of Oncogenes and Related Genes, Shanghai Cancer Institute, Renji Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

ARTICLE INFO

Article history:
Received 31 May 2022
Received in revised form
13 November 2022
Accepted 25 May 2023

Keywords:
Radiofrequency ablation (RFA)
Hepatocellular carcinoma (HCC)
Combined therapy
Immunotherapy
Transarterial chemoembolization (TACE)
Tyrosine kinase inhibitors (TKIs)

ABSTRACT

Local ablation technologies, such as radiofrequency ablation (RFA), microwave ablation (MWA) and cryoablation, have become a standard treatment option for hepatocellular carcinoma (HCC) less than 5 cm in size, particularly in individuals who are not candidates for hepatectomy. Except for equivalent prognosis and efficiency, RFA has various advantages over surgical excision, including a lower rate of complications, a cheaper cost, more normal tissue preservation, and a shorter hospital stay. However, the rate of tumor recurrence and/or distant metastasis after RFA therapy is still high. RFA has been widely employed in multiple cancers, large cancer, and lesion identified at "high-risk" sites in recent years, with the advancement of ablation types and operating techniques, particularly the combined use of many technologies. The real value of RFA technology has been more fully reflected. We will examine the status, progress, and problems of RFA in the treatment of HCC in this review.

1. Introduction

Hepatocellular carcinoma (HCC) is the sixth most prevalent cancer and ranked as the third cancer-related mortality globally. Morbidity has increased in recent years, with 630,000 new cases in males and 273,000 new cases in females per year.[1] In China, more than 50% of HCC cases were diagnosed at Barcelona Clinic Liver Cancer (BCLC) stage C or D and median tumor diameter ranged from 2.5 cm to 6.7 cm.[2,3]

Although surgical resection is still considered the first choice for the treatment of early-stage liver cancer, only 20%–25% of HCC patients are suitable for surgical resection due to the influence of patients' general physical condition, liver function status, and tumor characteristics (size, number, and location, etc).[4–6] In addition, because of the limited liver donors and high cost, the proportion of HCC patients suitable for liver transplantation is very low. Radiofrequency ablation (RFA) not only has no significant difference in long-term survival when compared to surgical resection and liver transplantation, but it also has other advantages, such as a lower risk of problems, lower cost, more normal tissue preservation, and a shorter hospital stay.[7] As a result, RFA has been regarded as the third local curative technique for HCC, while other therapies such as tyrosine kinase inhibitors (TKIs), immune checkpoint inhibitors, and transarterial chemoembolization (TACE) are usually considered palliative.

According to the BCLC prognosis and treatment strategy, RFA therapy is only suitable for HCC patients within BCLC stages 0–A.[4,8] Indeed, based on a large amount of current clinical research data, RFA has achieved considerable advances in the three dimensions of tumor size, number, and placement. Different from BCLC standard, the guidelines from China can reflect the application scope and value of RFA therapy from distinct perspectives. In the Chinese Guidelines for Diagnosis and Treatment of Primary Liver Cancer (2022 edition), surgical excision or local ablation alone is regarded as the first-line option for patients with stage Ia (single tumor $\leq$5 cm; or $\leq$ 3 nodules, the largest lesion is $\leq$ 3 cm in diameter), but for the patients with stages Ib–IIa (single tumor >5 cm; or $\leq$ 3 nodules, the largest lesion is > 3 cm in diameter), RFA is usually recommended to combine with TACE.[9,10] Actually, with the advancement of ablation technical types and operating approaches, particularly the combined strategy of many technologies, RFA has

☆ Edited by Yuxia Jiang and Peiling Zhu.

* Corresponding author. Department of Interventional Oncology, Renji Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China.
E-mail address: zhaiboshi@sina.com (B. Zhai).

https://doi.org/10.1016/j.livres.2023.05.002

become increasingly popular for multiple cancers, huge cancers, and lesions locating in "high-risk" areas. However, based on clinical practice and current research evaluations, including Chinese standards, present guidelines severely limit the population appropriate for RFA and underestimate the true value of RFA.

In this review, we will take RFA as a representative to briefly illustrate the status, progress, and challenges of local ablation in the treatment of HCC.

2. Status of RFA in the treatment of HCC

2.1. Indications for percutaneous RFA

Imagine-guided percutaneous RFA may result in a full response in 95% of patients with HCC smaller than 5 cm.[11–14] The rate of intrahepatic recurrence at 1-, 3-, and 5-year after RFA was 11.8%, 53.9%, and 75.8%, respectively, also frequently treated by repeated RFA sessions.[15,16] Many retrospective studies or randomized controlled trials have shown that RFA and surgical resection can achieve comparable overall survival (OS) in patients with early HCC, but the rate of local recurrence and intrahepatic neoplasia following RFA is generally higher (Table 1).[17–20]

Nevertheless, a few studies showed that surgical resection may provide better survival and lower recurrence rates than RFA for patients meeting Milan criteria.[21] Nanashima *et al.*[22] found no significant difference in OS between RFA and hepatectomy groups in individuals with isolated HCC. However, in patients with a tumor number of 2–3 and maximum diameter of <3 cm, the OS of surgical resection was better than that of local ablation. However, when surviving time is combined with the incidence of significant complications, operation efficiency, hospital stay, quality of life, economic expenses, and other metrics, RFA is undoubtedly more in line with the diverse expectations of HCC patients.

Compared with other treatment in HCC, RFA has unique advantages. To begin with, RFA outperforms solo TACE in terms of tumor control. For large HCCs sized 5–8 cm, despite comparable long-term survival and rates of complication, RFA achieved better initial tumor control.[23] In the case of HCC less than 3 cm in size, RFA had comparable OS and recurrence-free survival with TACE.[24,25] Notably, Yun *et al.*[26] found that the RFA group had a greater complete response and 5-year recurrence survival rate than the TACE group. Secondly, two thorough Meta-analyses showed that RFA outperforms stereotactic body radiation (SBRT) in terms of OS and disease control.[27,28] Kim *et al.*[29] included 2064 patients treated with RFA or SBRT, and while RFA and SBRT had comparable 1-year recurrence rates, RFA has a greater OS. However, despite RFA having better disease control than SBRT, SBRT was used for patients who are not amenable to RFA in practice. Taken together, RFA could have a wider range of indications in the future cancer treatment.

2.2. Extension of newly developed devices

Some innovative ablation devices have recently been developed to improve the safety of ablation focus, including microwave ablation (MWA), cryoablation, laser ablation, irreversible electroporation (IRE), multi-tined RFA, and no-touch RFA using bipolar electrodes.[30–35] MWA, in particular, can induce a higher ablation volume than traditional RFA, making it more appropriate for the treatment of large liver tumors (>5 cm).[36] Hocquelet *et al.*[35] proved that no-touch multipolar RFA has a lower recurrence rate than other ablation devices. Furthermore, unlike monopolar RFA, which causes heat centrifugal diffusion, no-touch multipolar RFA causes heat centripetal diffusion by two or more separate electrodes, allowing for better control of the shape and range of the ablation focus and, as a result, a higher complete necrosis rate of the tumor during pathological examination.[33] Although there are still many defects, it is obvious that RFA or other ablation techniques have great potential to successfully treat large or multiple liver cancers.

2.3. Advances in ablation-assisted technology

According to the image-guided percutaneous ablation technique, "high-risk location" liver cancer is classified into two types, superficial lesion (on the surface of the liver) and central lesion (near the vena cava). The former mainly includes the diaphragm, gallbladder, and gastrointestinal tract. Thermal ablation of a liver tumor can easily result in lung injury, broncho biliary fistula, gastrointestinal perforation, and other complications. The latter mainly refers to the confluence of hepatic veins, hilar and caudate lobes. Ablation in this location is prone to causing biliary tract and vascular damage. Because image-guided percutaneous puncture was nearly the only ablation strategy available at the start of local ablation for tumor treatment, "high-risk location" HCC is currently considered a contraindication to ablation treatment. Nowadays, with the application of various auxiliary technologies, thermal ablation of "high-risk site" HCCs has been able to obtain safe and effective outcomes.

2.3.1. Artificial ascites and pleural effusion

In recent years, some researchers have attempted to use artificial pleural effusion or artificial ascites technology to aid ablation to increase the safety and thoroughness of image-guided

Table 1
Comparison of LR with RFA for HCC.

Variable	Conticchio *et al.*[17]			Feng *et al.*[18]			Hsiao *et al.*[19]			Wang *et al.*[20]		
	LR	RFA	*P*-value	LR	RFA	*P*-value	LR	RFA	*P*-value	LR	RFA	*P*-value
Publishing year	2021			2020			2020			2012		
Study design	RCT			Retrospective study			RCT			RCT		
Tumor diameter	<5 cm			<5 cm			<2 cm			<5 cm		
Number (*n*)	136	136		91	199		156	231		52	91	
DFS or PFS (%)												
1-year	84.0	63.0	0.001	50.2	56.5	0.800	94.6	87.7	<0.001	89.8	68.8	0.006
3-year	60.0	36.0		21.9	27.9		84.1	62.1		62.1	39.8	
5-year	44.0	25.0		19.2	14.6		78.3	46.8		40.7	29.3	
Overall survival (%)												
1-year	91.0	97.0	0.001	87.7	90.7	0.110	100.0	100.0	<0.001	98.0	96.7	0.073
3-year	80.0	67.0		62.9	69.0		97.2	88.6		98.0	80.3	
5-year	76.0	41.0		38.1	55.6		93.4	73.5		91.5	72.0	

Abbreviations: DFS, disease free survival; HCC, hepatocellular carcinoma; LR, liver resection; PFS, progression-free survival; RCT, randomized controlled trials; RFA, radiofrequency ablation.

percutaneous RFA for malignancies on the liver surface. Rhim *et al.*[37] found that visibility was achieved in 93.4% of patients with HCC abutting the diaphragm. Kitchin *et al.*[38] found that performance success rates were considerably greater in groups with fake ascites than in the control group. With the assistance of artificial ascites, the danger of organ perforation caused by percutaneous RFA is greatly reduced in HCC near the stomach, colon, or gallbladder, or abutting the diaphragm.[39] Also, in a study that enrolled 44 patients with HCC abutting the diaphragm, artificial ascites-assisted RFA have low risks of right shoulder pain and lung injury.[40] As can be seen, RFA is entirely capable of successfully treating some "high-risk" tumors on the surface of the liver with the use of artificial ascites technology.

2.3.2. RFA assisted by laparoscopy or laparotomy

RFA under laparoscope and laparotomy is another choice for HCC located on the liver surface, which reflects the classic combination of minimally invasive surgery and interventional therapy. Laparotomy approach ablation with more severe harm has been seldom used in recent years, with the combined use of brachytherapy or percutaneous ethanol injection with RFA, whereas laparoscopic RFA is increasingly performed.[41–43] Due to imprecise positioning and limited ablation range, percutaneous RFA of high-risk liver cancer is typically difficult to acquire a reasonable complete ablation rate. Some studies indicated that laparoscopic RFA is safe and could achieve comparable outcomes compared with percutaneous RFA or surgery.[44,45] Laparoscopic RFA is also regarded as a first-line treatment choice for HCC near the diaphragm, gallbladder, and gastrointestinal system, as it reduces the risk of tumoral seeding and enhances overall complete response (Fig. 1).[46]

2.4. Other neglected important values of thermal ablation

Local ablation provides several advantages over surgical resection, in addition to its similar efficacy, which mainly includes: (i) Fewer severe complications and extremely low mortality; (ii) Preservation of more healthy liver tissue; (iii) Quick and simple ablation process; (iv) Quick recovery and short hospital stay; (v) Rare long-term sequelae and higher quality of life after ablation; (vi) Repeated application; and (vii) Lower treatment costs. Because of the benefits listed above, local ablation may enable more HCC patients to achieve curative outcomes and longer-term survival with a higher quality of life.

3. Combinational strategy of RFA with other therapies for HCC

Some research demonstrated that RFA alone is associated with a higher risk of tumor recurrence at 5 years compared with surgery for small HCC.[32,47] Furthermore, for advanced HCC, RFA alone is difficult to achieve adequate long-term survival, and the adaptable population is small. Therefore, the combination of RFA and other treatment technologies is particularly important, which is also another way to maximize the real value of local ablation. Three combination therapy options will be thoroughly examined in this section (Fig. 2).

3.1. RFA with TACE

TACE is the primary therapy option for patients with BCLC stages B–C who are not candidates for surgical resection, according to current guidelines.[4] TACE utilized a microcatheter for local chemotherapy followed by catheterization of a targeted branch of the liver tumor. TACE aimed to transport chemical medications into tumors while avoiding systemic harm to normal liver and other tissues. Furthermore, tumor embolization generated tumor hypoxia, which may increase the sensitivity of liver cancers to local chemotherapy.[48,49] In clinical settings, doxorubicin, cisplatin, and mitomycin are commonly used. However, because TACE alone results in a lower rate of tumor total necrosis, combining TACE with

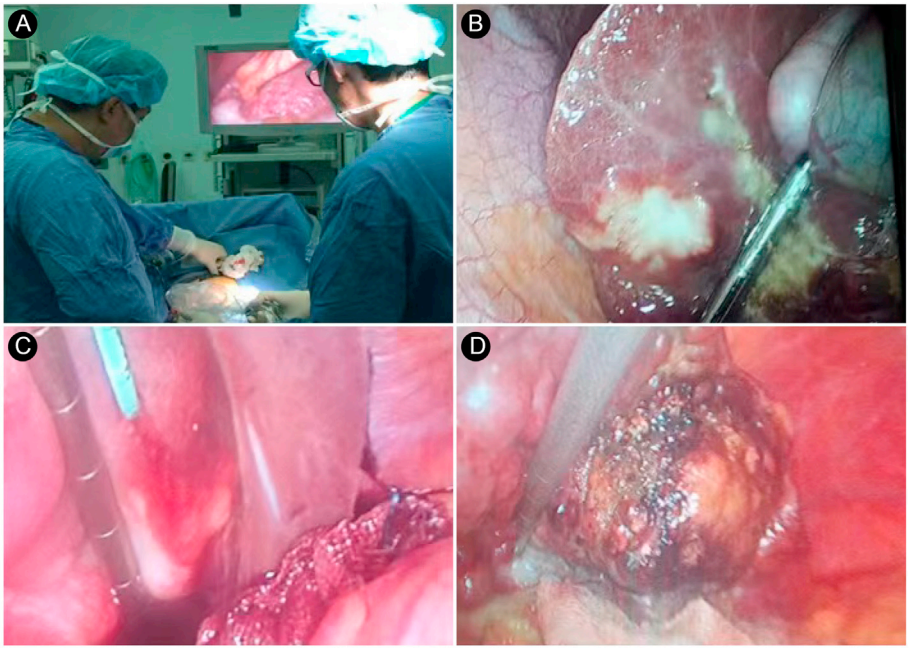

Fig. 1. Laparoscopic direct-vision microwave ablation of hepatocellular carcinoma close to the gastrointestinal tract. (A) Tumor imaging before laparoscopic ablation, gallbladder-tumor adhesion. **(B)** Preparing for laparoscopic-assisted tumor ablation. **(C)** Following gallbladder protection, a microwave electrode was introduced into the tumor under direct laparoscopic visualization to begin the multiple tracts, location, and angle ablation process. **(D)** The shape of the ablation focus after treatment. It showed complete coagulation necrosis of the tumor.

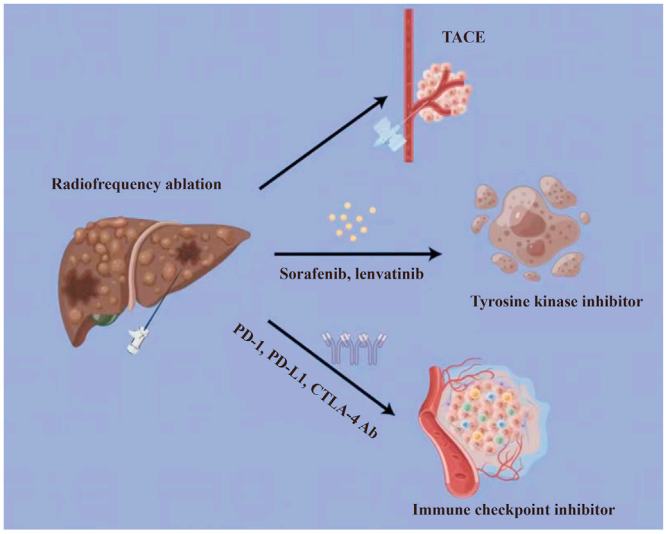

Fig. 2. RFA in combination with TACE, TKIs, and ICIs. A combination of RFA with TACE could enhance tumor hypoxia and sensitivity to heat, thus improving RFA efficiency. TKIs may also reduce remaining tumors when used in conjunction with TKIs, and heat stimulation may make tumor cells more responsive to this. RFA could enhance the immunogenicity of the tumor, provoking an intrinsic anti-tumor response. This combinational technique, when combined with PD-1, CTLA-4, and PD-L1 antibodies, has the potential to significantly improve immune response. Abbreviations: Ab, antibody; CTLA-4, cytotoxic T lymphocyte-associated antigen 4; ICI, immune checkpoint inhibitor; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; RFA, radiofrequency ablation; TACE, transarterial chemoembolization; TKIs, tyrosine kinase inhibitors.

other technologies or systemic medication therapy has become the standard therapeutic method for advanced liver cancer. Large or numerous liver tumors with abundant blood supply can generally have partial necrosis after one or more TACE treatments, laying the groundwork for further surgical resection or local ablation to eradicate the leftover active tumor tissue.

Several retrospective types of research proved that this combination is feasible and safe.[50–52] Wang *et al.*[53] revealed that when compared to surgery in HCC, RFA plus TACE achieved equivalent overall survival and recurrence in 5 years. According to Kim *et al.*,[54] TACE combined with RFA appears to result in a longer hospital stay, more frequent patient discomfort, and more problems than RFA or TACE alone. Furthermore, in large HCC, certain randomized controlled trials found that RFA plus TACE improved overall survival and recurrence-free survival compared to RFA alone. However, as for small HCCs less than 3 cm, combination therapy seems ineffective.[55–57] When combined, RFA and TACE could be useful treatments for advanced HCC that is not amenable to surgical resection (Table 2).[58–63]

3.2. RFA with TKIs

TKIs were a type of oral small-molecule multi-kinase inhibitor that inhibited tumor angiogenesis and cell proliferation by inhibiting the phosphorylation of vascular endothelial growth factor (VEGR), epidermal growth factor receptor (EGFR) and platelet-derived growth factor receptor (PDGFR).[64] The USA Food and Drug Administration has approved five TKIs (sorafenib, lenvatinib, cabozantinib, ramucirumab, and regorafenib) for the treatment of unresectable HCC. Sorafenib and lenvatinib, two of the five approved TKIs, were recommended as the first-line therapy for patients with advanced-stage HCC.[4,65] In comparison with the placebo, sorafenib significantly extended median overall survival (sorafenib: 10.7 months *vs.* placebo: 7.9 months).[66] In the case of lenvatinib, despite the lack of data demonstrating an advantage over sorafenib in terms of overall survival, progression-free survival was enhanced from 3.7 months to 7.4 months.[67] TKI monotherapy had a low overall response rate for advanced HCC, however, combining TKIs with other therapeutic methods may assist patients in clinical practice. In this section, we will describe recent advances in the combinational strategy of RFA and TKIs in the treatment of liver cancer.

Updated, several clinical data of sorafenib combined with RFA have been disclosed. Much research is being conducted to evaluate the synergistic role of sorafenib in conjunction with RFA. Some Meta-analyses has proven combination therapy with RFA plus sorafenib has a better response than each treatment alone.[68,69] A retrospective study discovered that plus sorafenib significantly enhanced OS in HCC patients with BCLC stage C but no vascular invasion or extrahepatic dissemination, with 1-, 3-, 5-year survival rates of 84.0%, 43.1%, and 22.8%, respectively, compared to 55.6%, 29.6%, and 4.8%, respectively.[70] For the treatment of medium-sized HCC, Kan *et al.*[71] reported that RFA combined with sorafenib efficiently prolonged survival time and decreased recurrence rate. One study found that RFA plus sorafenib significantly improved overall survival compared to sorafenib alone, in patients with unresectable large HCC (diameter 5 cm), with 1-, 2-, and 3-year survival rates of 56.9%, 34.3%, 11.7% *vs.* 42.5%, 22.0%, and 5.5%, respectively.[72] Pre-clinical studies in HCC mice indicated that sorafenib might reduce hypoxia inducible factor 1a (HIF-1a) and vascular endothelial growth factor A (VEGFA) expression after RFA therapy.[73]

For other TKIs, one pre-clinical study observed that sunitinib together with RFA greatly ignited intrinsic anti-tumor immune response in the murine HCC model. Mechanically, sunitinib suppressed hepatocyte growth factor (HGF) and vascular endothelial growth factor (VEGF) signaling pathways upon heat stimulation, allowing RFA-released *in situ* tumor-specific antigen to elicit an effective anti-tumor immune response.[74] However, at present, this pre-clinical finding lacks clinical evidence in HCC patients. Also, one case report also indicated the potential combinational strategy for EGFR kinase inhibitor and RFA for the treatment of EGFR mutant advanced lung cancer.[75] Through follow-up observation, these two patients showed tumor remission after combinational therapy.

In conclusion, RFA combined with sorafenib had a greater clinical response than either treatment alone and should be considered as an alternative therapy option. Also, many other combinational strategies with newly developed TKIs ought to be tried in the future.

3.3. RFA with immunotherapy

Cancer immunotherapy has achieved remarkable advances in recent years. Patients treated with checkpoint blockade therapy have shown remarkable clinical responses in a variety of solid malignancies (*e.g.*, non-small cell lung cancer, melanoma, bladder cancer, and HCC). HCC and other tumor cells exploited different mechanisms evading immunosurveillance and anti-tumor immune response by T cells. Many co-inhibitory receptors, such as programmed death-1 (PD-1), cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), Tim-3, and lymphocyte-activation gene 3 (LAG-3), are upregulated in activated T cells, limiting effector actions in the tumor microenvironment (TME).[76,77] As the major ligand of PD-1, PD-L1 was mainly expressed by tumor cells and immunosuppressive cells including regulatory T (Treg) cells, myeloid-derived suppressor cells (MDSCs), and stromal cells. The combination of PD-1 and PD-L1 could significantly inhibit T cell function and lead to T cell exhaustion in TME. Also, NK cells and dendritic cells in TME may upregulate PD-1 in TME, thus impairing anti-tumor response. Blocking these immunological checkpoints mechanically could

Table 2
Comparison of RFA + TACE with LR for HCC.

Variable	Peng *et al.*[58]			Takuma *et al.*[59]			Li *et al.*[60]			Bholee *et al.*[61]			Kagawa *et al.*[62]			Kim *et al.*[63]		
	LR	R + T	*P*-value	LR	R + T	*P*-value	LR	R + T	*P*-value	LR	R + T	*P*-value	LR	R + T	*P*-value	LR	R + T	*P*-value
Publishing year	2018			2013			2015			2017			2010			2013		
Study design	RCT			Retrospective study			RCT			Retrospective study			Retrospective study			Retrospective study		
Tumor diameter	<5 cm			<5 cm			<2 cm			3–5 cm			<3 cm			2–5 cm		
Number (*n*)	79	107		176	154		148	137		148	74		55	62		49	37	
Disease free survival (%)																		
1-year	64.8	58.2	0.258	84.0	85.0	0.048	75.0	92.0	0.001	68.9	87.8	0.619	75.6	64.5	0.010	81.8	89.2	NA
3-year	41.6	35.2		56.0	37.0		58.0	69.0		49.2	48.3		41.1	40.1		68.5	69.4	
5-year	38.3	29.6		40.0	15.0		44.0	61.0		40.9	33.5		36.4	18.0		NA	NA	
Overall survival (%)																		
1-year	84.8	84.6	0.871	95.0	99.0	0.393	88.0	95.0	0.004	91.2	94.6	0.488	92.5	100.0	0.788	95.7	97.3	NA
3-year	60.2	66.9		87.0	88.0		66.0	74.0		64.4	75.1		82.7	94.8		84.3	78.4	
5-year	51.9	49.1		75.0	70.0		47.0	67.0		47.7	55.3		76.9	64.6		NA	NA	

Abbreviations: HCC, hepatocellular carcinoma; LR, liver resection; NA, not applicable; R + T, radiofrequency ablation plus transarterial chemoembolization; RCT, randomized controlled trials; RFA, radiofrequency ablation; TACE, transarterial chemoembolization.

restore the function of T cells, NK cells, and dendritic cells.[78] Among different checkpoint blockade inhibitors, anti-PD-1, PD-L1 and CTLA-4 antibodies were mostly used in the clinic.

RFA has been proven in numerous *in vivo* and *in vitro* studies to greatly increase tumor-associated antigen release and T cell activation *in situ* and at distant tumor sites.[79,80] Theoretically, RFA combined with immunotherapy can greatly improve tumor antigen-specific T-cell responses and enhance the effect of immunotherapy.

RFA therapy reduced the proportions of immunosuppressive cells such as tumor-associated macrophages, Treg cells, and tumor-associated neutrophils while increasing the numbers of effect T cells in distant metastatic tumors.[81,82] However, the initially powerful immune response elicited by RFA was transient and did not induce a long-lasting anti-tumor response, as evidenced by the upregulation of PD-1/PD-L1 axis and a shift to a higher Treg cell to effector T cell ratio in tumor cells after RFA.[83] Also, immunosuppression function in macrophages was enhanced after RFA. Mechanically, heat-treated cells are engulfed by macrophages by autophagy-associated phagocytosis, increasing IL-4 production and macrophage programming via the PI3Kgamma/AKT pathway.[84]

According to several research data, Wang *et al.*[85] deduced a schematic representation of ablation-induced immunological effects on HCC. Local and systemic anticancer responses could be improved by ablation by boosting anti-tumor immunity and decreasing immunosuppressive effects. On the one hand, non-specific tumor killing is achieved by activating or increasing innate immune cells and cytokines that destroy tumor cells. The activation of or increase in adaptive immune cells and the release of tumor-associated or tumor-specific antigens mediates specific anti-tumor immunity. However, the immunological responses of local ablation are generally weak and may not be sufficient to sustain anti-tumor actions and avoid recurrence.

All these results suggested a shift from an immune activation to an immune suppression environment after RFA therapy. In clinical settings, it is uncertain if combination therapy with checkpoint blockade inhibitors and RFA is superior to RFA monotherapy due to a paucity of randomized controlled trials. A propensity score matching analysis revealed that anti-PD-1 antibody plus RFA improved survival in patients with recurrent HCC more than RFA alone.[86] In another clinical trial,[87] tried to assess whether ablation could be combined safely and feasibly with anti-CTLA-4 antibody. The result demonstrated that RFA in conjunction with tremelimumab cause intra-tumoral $CD8^{+}$T cell accumulation, good clinical activity, and a putative surrogate reduction in HCV viral load. As a result, it could be a promising new therapy option for individuals with advanced HCC. Although some studies have shown that patients can benefit from the combination of RFA and checkpoint blockade inhibitors, more clinical evidence is needed.

4. Challenges and prospects for thermal ablation

Local ablation has made significant progress worldwide over the last 30 years, but there has been no qualitative leap in terms of popularization or indication expansion. In comparison to surgical resection, which has a history of more than 100 years, local ablation, which has a history of barely 30 years, is relatively immature, as evidenced by: (i) The ablation equipment and operation means in most hospitals are still relatively single, which cannot meet the needs for ablation of complex tumors. (ii) The ablation clinicians originate from many disciplines, and there is a clear gap in their overall medical management and operation skill. Thus, standardized training should be carried out concerning surgery. (iii) Ablation practitioners are primarily concerned with how to improve their ablation skills and are opposed to high-quality clinical trials. (iv) There are still significant gaps in basic and translational research linked to tumor ablation.

Overall, the indications of thermal ablation are limited, and its real therapeutic value has not been fully demonstrated. Improving various ablation technologies, selecting suitable operational techniques, and establishing an ideal holistic treatment system are the fundamental tenets for HCC patients to attain long-term survival with a great quality of life. It is gratifying that the current therapies of HCC have been unprecedentedly rich, but no therapy can independently obtain a perfect treatment outcome. Long-term survival of HCC patients is the consequence of multi-disciplinary and multi-technology collaboration. However, surgical resection and ablation technology are undoubtedly the leaders in the local treatment of HCC.

5. Conclusions

Because of the limitations of surgical resection, it will be required in the future to construct two comprehensive treatment systems centered on surgical resection or local ablation. They are not only relatively independent but also combined. More importantly, to improve the treatment system, local ablation must learn from surgical training and the complete process management model. In this way, local ablation technology can benefit more HCC patients, and show its real value to the greatest extent.

Authors' contributions

H. Wang: writing-original draft preparation. B. Zhai: conceptualization, writing reviewing and editing. Z. Wu, D. Cui and Y. Shi helped revised the paper. All authors read and approved the final manuscript.

Declaration of competing interest

The authors declare that they have no conflict of interest.

Acknowledgements

This work was supported by the National Key R&D Program of China (2020YFC0122300) and the General programs of the National Natural Science Foundation of China (82070619) to B. Zhai.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71:209–249. https://doi.org/10.3322/caac.21660.
2. Park JW, Chen M, Colombo M, et al. Global patterns of hepatocellular carcinoma management from diagnosis to death: the BRIDGE Study. *Liver Int*. 2015;35:2155–2166. https://doi.org/10.1111/liv.12818.
3. Xu XF, Xing H, Han J, et al. Risk factors, patterns, and outcomes of late recurrence after liver resection for hepatocellular carcinoma: a multicenter study from China. *JAMA Surg*. 2019;154:209–217. https://doi.org/10.1001/jamasurg.2018.4334.
4. Reig M, Forner A, Rimola J, et al. BCLC strategy for prognosis prediction and treatment recommendation: the 2022 update. *J Hepatol*. 2022;76:681–693. https://doi.org/10.1016/j.jhep.2021.11.018.
5. Forner A, Reig ME, de Lope CR, Bruix J. Current strategy for staging and treatment: the BCLC update and future prospects. *Semin Liver Dis*. 2010;30:61–74. https://doi.org/10.1055/s-0030-1247133.
6. Wee IJY, Moe FNN, Sultana R, et al. Extending surgical resection for hepatocellular carcinoma beyond barcelona clinic for liver cancer (BCLC) stage A: a novel application of the modified BCLC staging system. *J Hepatocell Carcinoma*. 2022;9:839–851. https://doi.org/10.2147/JHC.S370212.
7. Chu KF, Dupuy DE. Thermal ablation of tumours: biological mechanisms and advances in therapy. *Nat Rev Cancer*. 2014;14:199–208. https://doi.org/10.1038/nrc3672.
8. Wang F, Numata K, Takeda A, et al. Safety and efficacy study: short-term application of radiofrequency ablation and stereotactic body radiotherapy for Barcelona Clinical Liver Cancer stage 0-B1 hepatocellular carcinoma. *PLoS One*. 2021;16, e0245076. https://doi.org/10.1371/journal.pone.0245076.
9. Gao J, Fan RF, Yang JY, et al. Radiofrequency ablation for hepatic hemangiomas: a consensus from a Chinese panel of experts. *World J Gastroenterol*. 2017;23:7077–7086. https://doi.org/10.3748/wjg.v23.i39.7077.
10. Wu MC, Tang ZY, Ye SL, et al. Expert consensus on local ablation therapies for primary liver cancer. *Chin Clin Oncol*. 2012;1:11. https://doi.org/10.3978/j.issn.2304-3865.2012.06.01.
11. Lin SM, Lin CJ, Lin CC, Hsu CW, Chen YC. Randomised controlled trial comparing percutaneous radiofrequency thermal ablation, percutaneous ethanol injection, and percutaneous acetic acid injection to treat hepatocellular carcinoma of 3 cm or less. *Gut*. 2005;54:1151–1156. https://doi.org/10.1136/gut.2004.045203.
12. Lencioni RA, Allgaier HP, Cioni D, et al. Small hepatocellular carcinoma in cirrhosis: randomized comparison of radio-frequency thermal ablation versus percutaneous ethanol injection. *Radiology*. 2003;228:235–240. https://doi.org/10.1148/radiol.2281020718.
13. Brunello F, Veltri A, Carucci P, et al. Radiofrequency ablation versus ethanol injection for early hepatocellular carcinoma: a randomized controlled trial. *Scand J Gastroenterol*. 2008;43:727–735. https://doi.org/10.1080/00365520701885481.
14. Gaia S, Ciruolo M, Ribaldone DG, et al. Higher efficiency of percutaneous microwave (MWA) than radiofrequency ablation (RFA) in achieving complete response in cirrhotic patients with early hepatocellular varcinoma. *Curr Oncol*. 2021;28:1034–1044. https://doi.org/10.3390/curroncol28020101.
15. Okuwaki Y, Nakazawa T, Kokubu S, et al. Repeat radiofrequency ablation provides survival benefit in patients with intrahepatic distant recurrence of hepatocellular carcinoma. *Am J Gastroenterol*. 2009;104:2747–2753. https://doi.org/10.1038/ajg.2009.414.
16. Wei M, Lin M, Zhong X, et al. Role of preoperational imaging traits for guiding treatment in single ≤ 5 cm hepatocellular carcinoma. *Ann Surg Oncol*. 2022;29:5144–5153. https://doi.org/10.1245/s10434-022-11344-3.
17. Conticchio M, Inchingolo R, Delvecchio A, et al. Radiofrequency ablation vs surgical resection in elderly patients with hepatocellular carcinoma in Milan criteria. *World J Gastroenterol*. 2021;27:2205–2218. https://doi.org/10.3748/wjg.v27.i18.2205.
18. Feng Y, Wu H, Huang DQ, et al. Radiofrequency ablation versus repeat resection for recurrent hepatocellular carcinoma (≤ 5 cm) after initial curative resection. *Eur Radiol*. 2020;30:6357–6368. https://doi.org/10.1007/s00330-020-06990-8.
19. Hsiao CY, Hu RH, Ho CM, Wu YM, Lee PH, Ho MC. Surgical resection versus radiofrequency ablation for Barcelona Clinic Liver Cancer very early stage hepatocellular carcinoma: long-term results of a single-center study. *Am J Surg*. 2020;220:958–964. https://doi.org/10.1016/j.amjsurg.2020.03.017.
20. Wang JH, Wang CC, Hung CH, Chen CL, Lu SN. Survival comparison between surgical resection and radiofrequency ablation for patients in BCLC very early/early stage hepatocellular carcinoma. *J Hepatol*. 2012;56:412–418. https://doi.org/10.1016/j.jhep.2011.05.020.
21. Huang J, Yan L, Cheng Z, et al. A randomized trial comparing radiofrequency ablation and surgical resection for HCC conforming to the Milan criteria. *Ann Surg*. 2010;252:903–912. https://doi.org/10.1097/SLA.0b013e3181efc656.
22. Nanashima A, Tobinaga S, Masuda J, et al. Selecting treatment for hepatocellular carcinoma based on the results of hepatic resection and local ablation therapy. *J Surg Oncol*. 2010;101:481–485. https://doi.org/10.1002/jso.21523.
23. Dai WC, Cheung TT, Chok KS, et al. Radiofrequency ablation versus transarterial chemoembolization for unresectable solitary hepatocellular carcinomas sized 5-8 cm. *HPB (Oxford)*. 2015;17:226–231. https://doi.org/10.1111/hpb.12324.
24. Martin AN, Wilkins LR, Das D, et al. Efficacy of radiofrequency ablation versus transarterial chemoembolization for patients with solitary hepatocellular carcinoma ≤ 3 cm. *Am Surg*. 2019;85:150–155.
25. Song MJ, Bae SH, Lee JS, et al. Combination transarterial chemoembolization and radiofrequency ablation therapy for early hepatocellular carcinoma. *Korean J Intern Med*. 2016;31:242–252. https://doi.org/10.3904/kjim.2015.112.
26. Yun BY, Lee HW, Min IK, et al. Prognosis of early-stage hepatocellular carcinoma: comparison between trans-arterial chemoembolization and radiofrequency ablation. *Cancers (Basel)*. 2020;12:2527. https://doi.org/10.3390/cancers12092527.
27. Lee J, Shin IS, Yoon WS, Koom WS, Rim CH. Comparisons between radiofrequency ablation and stereotactic body radiotherapy for liver malignancies: meta-analyses and a systematic review. *Radiother Oncol*. 2020;145:63–70. https://doi.org/10.1016/j.radonc.2019.12.004.
28. Sanuki N, Takeda A. Are head-to-head comparisons between radiofrequency ablation and stereotactic body radiotherapy really necessary for localized hepatocellular carcinoma? *J Clin Oncol*. 2018;36:2563–2564. https://doi.org/10.1200/JCO.2018.78.2805.
29. Kim N, Cheng J, Jung I, et al. Stereotactic body radiation therapy vs. radiofrequency ablation in Asian patients with hepatocellular carcinoma. *J Hepatol*. 2020;73:121–129. https://doi.org/10.1016/j.jhep.2020.03.005.
30. Cho YK, Rhim H, Ahn YS, Kim MY, Lim HK. Percutaneous radiofrequency ablation therapy of hepatocellular carcinoma using multitined expandable electrodes: comparison of subcapsular and nonsubcapsular tumors. *AJR Am J Roentgenol*. 2006;186:S269–S274. https://doi.org/10.2214/AJR.04.1346.
31. Yap S, Ooi EH, Foo JJ, Ooi ET. Bipolar radiofrequency ablation treatment of liver cancer employing monopolar needles: a comprehensive investigation on the efficacy of time-based switching. *Comput Biol Med*. 2021;131, 104273. https://doi.org/10.1016/j.compbiomed.2021.104273.
32. Tanaka T, Takata K, Kunimoto H, et al. The efficacy and therapeutic outcome of bipolar radiofrequency ablation for the treatment for hepatocellular carcinoma in the real-world setting, compared with monopolar radiofrequency ablation conducted during the same period. *Oncology*. 2020;98:859–868. https://doi.org/10.1159/000508921.
33. Seror O, N'Kontchou G, Van Nhieu JT, et al. Histopathologic comparison of monopolar versus no-touch multipolar radiofrequency ablation to treat hepatocellular carcinoma within Milan criteria. *J Vasc Interv Radiol*. 2014;25:599–607. https://doi.org/10.1016/j.jvir.2013.11.025.
34. Seror O, N'Kontchou G, Tin-Tin-Htar M, et al. Radiofrequency ablation with internally cooled versus perfused electrodes for the treatment of small hepatocellular carcinoma in patients with cirrhosis. *J Vasc Interv Radiol*. 2008;19:718–724. https://doi.org/10.1016/j.jvir.2008.01.007.
35. Hocquelet A, Aube C, Rode A, et al. Comparison of no-touch multi-bipolar vs. monopolar radiofrequency ablation for small HCC. *J Hepatol*. 2017;66:67–74. https://doi.org/10.1016/j.jhep.2016.07.010.
36. Abdelaziz AO, Nabeel MM, Elbaz TM, et al. Microwave ablation versus transarterial chemoembolization in large hepatocellular carcinoma: prospective analysis. *Scand J Gastroenterol*. 2015;50:479–484. https://doi.org/10.3109/00365521.2014.1003397.
37. Rhim H, Lim HK, Kim YS, Choi D. Percutaneous radiofrequency ablation with artificial ascites for hepatocellular carcinoma in the hepatic dome: initial experience. *AJR Am J Roentgenol*. 2008;190:91–98. https://doi.org/10.2214/AJR.07.2384.
38. Kitchin D, Lubner M, Ziemlewicz T, et al. Microwave ablation of malignant hepatic tumours: intraperitoneal fluid instillation prevents collateral damage and allows more aggressive case selection. *Int J Hyperthermia*. 2014;30:299–305. https://doi.org/10.3109/02656736.2014.936050.
39. Wu CC, Chen WS, Ho MC, et al. Minimizing abdominal wall damage during high-intensity focused ultrasound ablation by inducing artificial ascites. *J Acoust Soc Am*. 2008;124:674–679. https://doi.org/10.1121/1.2839907.
40. Kang TW, Rhim H, Lee MW, et al. Radiofrequency ablation for hepatocellular carcinoma abutting the diaphragm: comparison of effects of thermal

protection and therapeutic efficacy. *AJR Am J Roentgenol*. 2011;196:907–913. https://doi.org/10.2214/AJR.10.4584.
41. Liu LX, Jiang HC, Piao DX. Radiofrequence ablation of liver cancers. *World J Gastroenterol*. 2002;8:393–399. https://doi.org/10.3748/wjg.v8.i3.393.
42. Ushijima H, Hida JI, Yane Y, Kato H, Ueda K, Kawamura J. Laparoscopic repair of diaphragmatic hernia after radiofrequency ablation for hepatocellular carcinoma: case report. *Int J Surg Case Rep*. 2021;81, 105728. https://doi.org/10.1016/j.ijscr.2021.105728.
43. Ko SE, Lee MW, Min JH, et al. Laparoscopic radiofrequency ablation of subcapsular hepatocellular carcinomas: risk factors related to a technical failure. *Surg Endosc*. 2022;36:504–514. https://doi.org/10.1007/s00464-021-08310-7.
44. Jiang K, Zhang W, Su M, et al. Laparoscopic radiofrequency ablation of solitary small hepatocellular carcinoma in the caudate lobe. *Eur J Surg Oncol*. 2013;39:1236–1242. https://doi.org/10.1016/j.ejso.2013.08.002.
45. Reccia I, Kumar J, Kusano T, et al. A systematic review on radiofrequency assisted laparoscopic liver resection: challenges and window to excel. *Surg Oncol*. 2017;26:296–304. https://doi.org/10.1016/j.suronc.2017.06.003.
46. de la Serna S, Vilana R, Sanchez-Cabus S, et al. Results of laparoscopic radiofrequency ablation for HCC. Could the location of the tumour influence a complete response to treatment? A single European centre experience. *HPB (Oxford)*. 2015;17:387–393. https://doi.org/10.1111/hpb.12379.
47. Li YC, Chen PH, Yeh JH, et al. Clinical outcomes of surgical resection versus radiofrequency ablation in very-early-stage hepatocellular carcinoma: a propensity score matching analysis. *BMC Gastroenterol*. 2021;21:418. https://doi.org/10.1186/s12876-021-01995-z.
48. Garg T, Shrigiriwar A, Habibollahi P, et al. Intraarterial therapies for the management of hepatocellular carcinoma. *Cancers (Basel)*. 2022;14:3351. https://doi.org/10.3390/cancers14143351.
49. Tsochatzis EA, Fatourou E, O'Beirne J, Meyer T, Burroughs AK. Transarterial chemoembolization and bland embolization for hepatocellular carcinoma. *World J Gastroenterol*. 2014;20:3069–3077. https://doi.org/10.3748/wjg.v20.i12.3069.
50. Yan L, Ren Y, Qian K, et al. Sequential transarterial chemoembolization and early radiofrequency ablation improves clinical outcomes for early-intermediate hepatocellular carcinoma in a 10-year single-center comparative study. *BMC Gastroenterol*. 2021;21:182. https://doi.org/10.1186/s12876-021-01765-x.
51. Ren Y, Cao Y, Ma H, et al. Improved clinical outcome using transarterial chemoembolization combined with radiofrequency ablation for patients in Barcelona clinic liver cancer stage A or B hepatocellular carcinoma regardless of tumor size: results of a single-center retrospective case control study. *BMC Cancer*. 2019;19:983. https://doi.org/10.1186/s12885-019-6237-5.
52. El Dorry AK, Shaker MK, El-Fouly NF, et al. Effectiveness of combined therapy radiofrequency ablation/transarterial chemoembolization versus transarterial chemoembolization/radiofrequency ablation on management of hepatocellular carcinoma. *Eur J Gastroenterol Hepatol*. 2021;33:1573–1577. https://doi.org/10.1097/MEG.0000000000001878.
53. Wang H, Liu Y, Shen K, et al. A comparison between radiofrequency ablation combined with transarterial chemoembolization and surgical resection in hepatic carcinoma: a meta-analysis. *J Cancer Res Therapeut*. 2019;15:1617–1623. https://doi.org/10.4103/jcrt.JCRT_503_19.
54. Kim W, Cho SK, Shin SW, Hyun D, Lee MW, Rhim H. Combination therapy of transarterial chemoembolization (TACE) and radiofrequency ablation (RFA) for small hepatocellular carcinoma: comparison with TACE or RFA monotherapy. *Abdom Radiol (NY)*. 2019;44:2283–2292. https://doi.org/10.1007/s00261-019-01952-1.
55. Wang W, Shi J, Xie WF. Transarterial chemoembolization in combination with percutaneous ablation therapy in unresectable hepatocellular carcinoma: a meta-analysis. *Liver Int*. 2010;30:741–749. https://doi.org/10.1111/j.1478-3231.2010.02221.x.
56. Peng ZW, Zhang YJ, Liang HH, Lin XJ, Guo RP, Chen MS. Recurrent hepatocellular carcinoma treated with sequential transcatheter arterial chemoembolization and RF ablation versus RF ablation alone: a prospective randomized trial. *Radiology*. 2012;262:689–700. https://doi.org/10.1148/radiol.11110637.
57. Cao S, Zou Y, Lyu T, et al. Long-term outcomes of combined transarterial chemoembolization and radiofrequency ablation versus RFA monotherapy for single hepatocellular carcinoma $\leq$ 3 cm: emphasis on local tumor progression. *Int J Hyperthermia*. 2022;39:1–7. https://doi.org/10.1080/02656736.2021.1998660.
58. Peng Z, Wei M, Chen S, et al. Combined transcatheter arterial chemoembolization and radiofrequency ablation versus hepatectomy for recurrent hepatocellular carcinoma after initial surgery: a propensity score matching study. *Eur Radiol*. 2018;28:3522–3531. https://doi.org/10.1007/s00330-017-5166-4.
59. Takuma Y, Takabatake H, Morimoto Y, et al. Comparison of combined transcatheter arterial chemoembolization and radiofrequency ablation with surgical resection by using propensity score matching in patients with hepatocellular carcinoma within Milan criteria. *Radiology*. 2013;269:927–937. https://doi.org/10.1148/radiol.13130387.
60. Li S, Zhang L, Huang ZM, Wu PH. Transcatheter arterial chemoembolization combined with CT-guided percutaneous thermal ablation versus hepatectomy in the treatment of hepatocellular carcinoma. *Chin J Cancer*. 2015;34:254–263. https://doi.org/10.1186/s40880-015-0023-9.
61. Bholee AK, Peng K, Zhou Z, et al. Radiofrequency ablation combined with transarterial chemoembolization versus hepatectomy for patients with hepatocellular carcinoma within Milan criteria: a retrospective case-control study. *Clin Transl Oncol*. 2017;19:844–852. https://doi.org/10.1007/s12094-016-1611-0.
62. Kagawa T, Koizumi J, Kojima S, et al. Transcatheter arterial chemoembolization plus radiofrequency ablation therapy for early stage hepatocellular carcinoma: comparison with surgical resection. *Cancer*. 2010;116:3638–3644. https://doi.org/10.1002/cncr.25142.
63. Kim JW, Shin SS, Kim JK, et al. Radiofrequency ablation combined with transcatheter arterial chemoembolization for the treatment of single hepatocellular carcinoma of 2 to 5 cm in diameter: comparison with surgical resection. *Korean J Radiol*. 2013;14:626–635. https://doi.org/10.3348/kjr.2013.14.4.626.
64. Tian Y, Lei Y, Fu Y, Sun H, Wang J, Xia F. Molecular mechanisms of resistance to tyrosine kinase inhibitors associated with hepatocellular carcinoma. *Curr Cancer Drug Targets*. 2022;22:454–462. https://doi.org/10.2174/1568009622666220330151725.
65. Galle PR, Dufour JF, Peck-Radosavljevic M, Trojan J, Vogel A. Systemic therapy of advanced hepatocellular carcinoma. *Future Oncol*. 2021;17:1237–1251. https://doi.org/10.2217/fon-2020-0758.
66. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med*. 2008;359:378–390. https://doi.org/10.1056/NEJMoa0708857.
67. Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. *Lancet*. 2018;391:1163–1173. https://doi.org/10.1016/S0140-6736(18)30207-1.
68. Jin M, Yu Q, Liu Y, Xu W, Fu X, Ji B. Safety and efficacy of physical thermal ablation combined sorafenib for hepatocellular carcinoma: a meta-analysis. *J Clin Transl Hepatol*. 2021;9:149–159. https://doi.org/10.14218/JCTH.2020.00125.
69. Chen L, Ma X, Liu X, Cui X. Sorafenib combined with radiofrequency ablation as treatment for patients with hepatocellular carcinoma: a systematic review and meta-analysis. *J BUON*. 2017;22:1525–1532.
70. Liu L, Zhang Q, Geng J, et al. Comparison of radiofrequency ablation combined with sorafenib or sorafenib alone in patients with ECOG performance score 1: identifying optimal candidates. *Ann Transl Med*. 2020;8:583. https://doi.org/10.21037/atm.2020.03.71.
71. Kan X, Jing Y, Wan QY, et al. Sorafenib combined with percutaneous radiofrequency ablation for the treatment of medium-sized hepatocellular carcinoma. *Eur Rev Med Pharmacol Sci*. 2015;19:247–255.
72. Yuan H, Lan Y, Li X, Tang J, Liu F. Large hepatocellular carcinoma with local remnants after transarterial chemoembolization: treatment by sorafenib combined with radiofrequency ablation or sorafenib alone. *Am J Cancer Res*. 2019;9:791–799.
73. Xu M, Xie XH, Xie XY, et al. Sorafenib suppresses the rapid progress of hepatocellular carcinoma after insufficient radiofrequency ablation therapy: an experiment in vivo. *Acta Radiol*. 2013;54:199–204. https://doi.org/10.1258/ar.2012.120249.
74. Qi X, Yang M, Ma L, et al. Synergizing sunitinib and radiofrequency ablation to treat hepatocellular cancer by triggering the antitumor immune response. *J Immunother Cancer*. 2020;8, e001038. https://doi.org/10.1136/jitc-2020-001038.
75. Shi X, Zhou J, Qian C, Gao L, Wang B, Feng X. Radiofrequency ablation with continued EGFR tyrosine kinase inhibitor therapy prolongs disease control in EGFR-mutant advanced lung cancers with acquired resistance to EGFR tyrosine kinase inhibitors: two case reports. *OncoTargets Ther*. 2020;13:6789–6793. https://doi.org/10.2147/OTT.S257431.
76. Sangro B, Sarobe P, Hervas-Stubbs S, Melero I. Advances in immunotherapy for hepatocellular carcinoma. *Nat Rev Gastroenterol Hepatol*. 2021;18:525–543. https://doi.org/10.1038/s41575-021-00438-0.
77. Foerster F, Gairing SJ, Ilyas SI, Galle PR. Emerging immunotherapy for HCC: a guide for hepatologists. *Hepatology*. 2022;75:1604–1626. https://doi.org/10.1002/hep.32447.
78. Liu Z, Liu X, Liang J, et al. Immunotherapy for hepatocellular carcinoma: current status and future prospects. *Front Immunol*. 2021;12, 765101. https://doi.org/10.3389/fimmu.2021.765101.
79. Schneider T, Hoffmann H, Dienemann H, et al. Immune response after radiofrequency ablation and surgical resection in nonsmall cell lung cancer. *Semin Thorac Cardiovasc Surg*. 2016;28:585–592. https://doi.org/10.1053/j.semtcvs.2016.02.008.
80. Mauda-Havakuk M, Hawken NM, Owen JW, et al. Comparative analysis of the immune response to RFA and cryoablation in a colon cancer mouse model. *Sci Rep*. 2022;12, 18229. https://doi.org/10.1038/s41598-022-22279-w.
81. Fei Q, Pan Y, Lin W, et al. High-dimensional single-cell analysis delineates radiofrequency ablation induced immune microenvironmental remodeling in pancreatic cancer. *Cell Death Dis*. 2020;11:589. https://doi.org/10.1038/s41419-020-02787-1.
82. Lemdani K, Mignet N, Boudy V, et al. Local immunomodulation combined to radiofrequency ablation results in a complete cure of local and distant colorectal carcinoma. *OncoImmunology*. 2019;8, 1550342. https://doi.org/10.1080/2162402X.2018.1550342.
83. Shi L, Chen L, Wu C, et al. PD-1 blockade boosts radiofrequency ablation-elicited adaptive immune responses against tumor. *Clin Cancer Res*. 2016;22:1173–1184. https://doi.org/10.1158/1078-0432.CCR-15-1352.

84. Liu X, Zhang W, Xu Y, et al. Targeting PI3Kgamma/AKT pathway remodels LC3-associated phagocytosis induced immunosuppression after radiofrequency ablation. *Adv Sci (Weinh)*. 2022;9, e2102182. https://doi.org/10.1002/advs.202102182.
85. Wang K, Wang C, Jiang H, et al. Combination of ablation and immunotherapy for hepatocellular carcinoma: where we are and where to go. *Front Immunol*. 2021;12, 792781. https://doi.org/10.3389/fimmu.2021.792781.
86. Wang X, Liu G, Chen S, et al. Combination therapy with PD-1 blockade and radiofrequency ablation for recurrent hepatocellular carcinoma: a propensity score matching analysis. *Int J Hyperthermia*. 2021;38:1519–1528. https://doi.org/10.1080/02656736.2021.1991011.
87. Duffy AG, Ulahannan SV, Makorova-Rusher O, et al. Tremelimumab in combination with ablation in patients with advanced hepatocellular carcinoma. *J Hepatol*. 2017;66:545–551. https://doi.org/10.1016/j.jhep.2016.10.029.