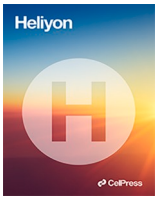
Heliyon 10 (2024) e36388

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Review article

Application of combined ablation and immunotherapy in NSCLC and liver cancer: Current status and future prospects

Jing-shun Zhang [a], Yuan-dong Sun [b,**], Yuan-min Li [c], Jian-jun Han [b,*]

[a] Department of Thoracic Surgery, Affiliated Hospital of Shandong University of Traditional Chinese Medicine, Ji'nan, Shandong, China
[b] Department of Interventional Radiology, Shandong Cancer Hospital and Institute Affiliated Shandong First Medical University and Shandong Academy of Medical Sciences, Ji'nan, Shandong, China
[c] Key Laboratory of Transplant Engineering and Immunology, NHC, Frontiers Science Center for Disease-Related Molecular Network, West China Hospital, Sichuan University, China

A B S T R A C T

This review examines combining tumor ablation therapy with immunotherapy for respiratory and digestive system tumors, particularly NSCLC and liver cancer. Despite advancements in traditional methods, they face limitations in advanced-stage tumors. Ablation techniques like RFA, MWA, and cryoablation offer minimally invasive options, while immune checkpoint inhibitors enhance the immune system's tumor-fighting ability. This review highlights their synergistic effects, clinical outcomes, and future research directions, including optimizing protocols, exploring new combinations, uncovering molecular mechanisms, advancing precision medicine, and improving accessibility. Combined therapy is expected to improve efficacy and patient outcomes significantly.

1. Introduction

The incidence and mortality rates of tumors affecting the respiratory and digestive systems have been rising steadily worldwide, posing a significant threat to global health. Based on the latest global cancer statistics, solid tumors in the respiratory system, such as non-small cell lung cancer (NSCLC) and small cell lung cancer, have some of the highest incidence and mortality rates. Similarly, solid tumors in the digestive system, including gastric cancer, liver cancer, and colorectal cancer, also rank among the highest in both incidence and mortality [1,2]. In the current field of medical research, liver cancer and lung cancer are particularly challenging malignancies and are among the leading causes of cancer-related deaths globally. Lung cancer, one of the most common and deadliest respiratory malignancies, accounts for millions of new cases and deaths each year [3,4]. NSCLC is the predominant type of lung cancer, comprising approximately 85 % of all lung cancer cases [5].

Similarly, within the realm of digestive system tumors, primary liver cancer, normally include hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma, and metastatic liver cancer cause numerous fatalities, making them significant contributors to mortality in both developed and developing countries [6,7]. The high incidence and mortality rates of NSCLC and liver cancer significantly add to the global health burden, highlighting the urgent need for enhanced cancer prevention and treatment strategies. Consequently, these cancers have become focal points in contemporary medical research, driving efforts to develop more effective diagnostic, therapeutic, and preventive measures.

* Corresponding author. Department of Interventional Radiology, Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, No. 440, Jiyan Road, Ji'nan, Shandong Province, CN, 250117, China.
** Corresponding author. Department of Interventional Radiology, Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, No. 440, Jiyan Road, Ji'nan, Shandong Province, CN, 250117, China.
E-mail addresses: 13176829692@163.com (Y.-d. Sun), jieruheweichuang@163.com, hanjianjun@sdfmu.edu.cn (J.-j. Han).

https://doi.org/10.1016/j.heliyon.2024.e36388
Received 1 June 2024; Received in revised form 13 August 2024; Accepted 14 August 2024
Available online 14 August 2024

Despite certain advancements in the treatment of solid tumors through surgery, chemotherapy, and radiotherapy, these methods still have significant limitations in treating advanced-stage respiratory and digestive system tumors [8,9]. Surgery remains the preferred option for early-stage solid tumors, but its efficacy diminishes for patients with late-stage tumors, and the risk of post-operative recurrence remains high [10–14]. Chemotherapy and radiotherapy can control tumor growth to some extent, but their severe side effects often lead to a decline in patients' quality of life, and achieving long-term tumor control is challenging [15–17]. Furthermore, the development of resistance to chemotherapeutic drugs by tumor cells further compromises the long-term efficacy of these treatments [18–21].

In this context, the exploration of new treatments for advanced solid tumors has gained unprecedented attention. There is a particular focus on research aimed at improving therapeutic outcomes and reducing side effects. Tumor ablation therapy is an innovative approach that has garnered significant attention. This method, commonly known as ablation, directly destroys tumor tissue using physical or chemical means [22,23]. This method offers several advantages, including being minimally invasive, highly effective, and promoting rapid recovery [24–26]. Ablation therapy can be used with multiple repetitions to achieve optimal results [27,28]. These characteristics make ablation a promising option for both palliative and curative treatment of solid tumors, demonstrating excellent clinical potential.

With the exploration and understanding of tumor immune mechanism and local microenvironment, cancer immunotherapy has rapidly made exciting progress and breakthroughs. Immune checkpoint inhibitors (ICIs) targeting programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) and Cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), which have become standard treatments, have significantly improved patient outcomes [29–31]. Additionally, emerging therapies such as CAR-T cell therapy and cancer vaccines are currently undergoing small-scale clinical trials and experimental studies, offering potential new treatment options for patients [32,33].

In this review, we examine the latest advancements in combining NSCLC and liver cancer treatments with ablation and immunotherapy, focusing on clinical studies and breakthroughs from the past three years. This review aims to highlight the synergistic potential of these therapies in improving patient outcomes and to provide insights for future research and clinical application directions.

2. Ablation therapy

2.1. Definition and principle

Ablation therapy is a localized treatment method for solid tumors that destroys tumor tissue through physical, chemical, or biological means. The basic principles of ablation include the use of high temperatures, low temperatures, radiofrequency, electromagnetic waves, lasers, or chemical agents to cause coagulative necrosis and apoptosis of tumor cells [34–37]. This rapidly kills a large number of tumor cells, effectively controlling tumor growth and potentially reducing or completely eliminating the tumor. The commonly used physical ablation include radiofrequency ablation (RFA), microwave ablation (MWA), cryoablation, laser ablation, high-intensity focused ultrasound (HIFU), and irreversible electroporation (IRE) [38–40].

RFA uses high-frequency current to heat tumor tissue, causing protein denaturation and cell death. It is effective for treating liver cancer and offers an alternative for patients who cannot undergo surgery [41]. MWA transmits microwave energy to the tumor, quickly raising its temperature and ablation speed, making it suitable for large or complex tumors without needing electrode pads [42]. Cryoablation uses extreme cooling with liquid nitrogen or argon gas to form ice crystals that disrupt cell structures, leading to cell death and microvascular occlusion [43]. It is effective for hard-to-reach tumors, providing precise control and pain relief [44]. Laser ablation employs specific wavelength lasers to heat tumor tissue, causing protein denaturation and cell necrosis, and is used for skin, liver, and prostate cancers. HIFU focuses ultrasound beams to heat tumor tissue, causing cell death through coagulative necrosis [45]. Its non-invasive nature and precision make it suitable for various cancers, including uterine, liver, pancreatic, and prostate [46]. IRE uses a high-voltage electric field to create nanopores in tumor cell membranes, disrupting cellular homeostasis and causing cell death without significant temperature increases, ideal for tumors near sensitive structures [47–49]. Table 1 concisely presents the principles, temperature changes, applicable ranges, and main advantages of each technology.

Compared to surgical treatment, ablation has its own unique advantages. Firstly, it is a minimally invasive treatment method, typically performed through skin puncture or laparoscopic guidance, resulting in minimal damage to the skin and surrounding normal tissues, quick postoperative recovery, and shorter hospital stays for patients. Secondly, ablation therapy can be precisely targeted and monitored under imaging guidance, ensuring both the efficacy and safety of the treatment. Thirdly, for patients who cannot undergo surgical resection or are unsuitable for surgery, ablation therapy provides an efficient alternative that can quickly control symptoms. Finally, ablation therapy can be combined with other treatments, such as surgery, radiotherapy, and chemotherapy, to enhance overall treatment efficacy.

Although there are many types of ablation therapies, they all share the characteristics of precision, minimal invasiveness, and significant effectiveness. They have broad indications for NSCLC and liver cancer and have shown excellent clinical outcomes.

3. Immunotherapy

3.1. Definition and principle

Tumor immunotherapy is a treatment method that against tumors by modulating and enhancing the body's immune system. The

Table 1
Comparative analysis of ablation techniques in tumor treatment.

Technique	Working Principle	Temperature Range	Effects	Applications	Advantages
Radiofrequency Ablation (RFA)	Uses high-frequency current (450–500 kHz) emitted by electrode needles to cause ion oscillation and friction within tumor tissue, generating heat	60 °C–80 °C or higher	Protein denaturation, tumor cell damage, and cell death	Treating all stages of HCC and metastatic liver cancer; alternative for patients unable to undergo surgery	Effective, potentially curative, applicable to various tumors
Microwave Ablation (MWA)	Transmits microwave energy to the tumor site through an antenna, converting to heat	60 °C–100 °C or higher	Rapid temperature rise, causing tumor cell death	Treating large tumors and tumors with complex anatomical structures	Wider heating range, faster ablation, no electrode pads required, suitable for patients with pacemakers
Cryoablation	Uses probes with liquid nitrogen or argon gas to adjust the local temperature to −40 °C to −80 °C	−40 °C to −80 °C	Ice crystal formation causing mechanical damage, microvascular occlusion, local immune response	Tumors difficult to treat with other techniques, cancer pain relief	Minimally invasive, precise control, preserves normal tissue, alleviates pain
Laser Ablation	Delivers laser beams of specific wavelengths through optical fibers, guided by imaging techniques	High temperatures generated by lasers	Protein denaturation, cell necrosis, coagulative necrosis	Skin cancer, liver cancer, prostate cancer	Minimal trauma, quick recovery, precise targeting of tumor tissue
High-Intensity Focused Ultrasound (HIFU)	Focuses ultrasound beams on the tumor site, causing rapid temperature rise and mechanical effects	55 °C–100 °C	Coagulative necrosis, disruption of tumor cells and structures	Uterine leiomyomas, liver cancer, pancreatic cancer, prostate cancer	Non-invasive, precise, minimal side effects, suitable for challenging tumor sites
Irreversible Electroporation (IRE)	Applies high-voltage electric field to create permanent nanopores in cell membranes	Non-thermal mechanism	Disruption of cell membrane integrity, uncontrolled ion movement, cell death	Tumors near sensitive structures like blood vessels, nerves, critical organs	Non-thermal, minimal collateral damage, preserves healthy tissues

basic principle is to use the body's immune system to recognize and destroy tumor cells, thereby controlling and eliminating them. Tumors use various methods to evade immune surveillance during growth and metastasis, making it difficult for the immune system to identify and attack these abnormal cells, leading to tumor development. For NSCLC, tumor cells often upregulate PD-L1 expression to inhibit T-cell function, while liver cancer cells exploit the liver's unique immune environment to further increase immune evasion [50–53].

Tumor immunotherapy aims to activate and enhance the immune system to recognize and attack tumor cells. Key treatment forms include ICIs, CAR-T therapy, tumor vaccines, cytokine therapy, and bispecific antibodies. ICIs, blocking inhibitory signals like PD-L1 and CTLA-4, restore T-cell function and are effective in cancers such as NSCLC and HCC [54,55]. CAR-T therapy engineers patient T-cells to target tumor cells, showing efficacy in hematologic malignancies. Tumor vaccines, preventive or therapeutic, are used in cancers like cervical cancer [56].

Additionally, Cytokine therapy enhances immune responses using interleukins and interferons, though its use is limited by potential side effects. Bispecific antibodies bind to T-cells and tumor cells, directing immune attacks. Immunotherapy's application in NSCLC and liver cancer is a clinical research focus.

ICIs in NSCLC, including anti-PD-1, anti-PD-L1, and anti-CTLA-4 antibodies, have improved survival rates, with drugs like nivolumab and pembrolizumab approved for various treatment lines [57–59]. Combining immunotherapy with targeted therapy may enhance outcomes for patients with specific genetic mutations, despite challenges like resistance and immune-related adverse events (irAEs).

In HCC, ICIs such as nivolumab, pembrolizumab, and atezolizumab (combined with bevacizumab) show promise, but risks of irAEs and complications necessitate close monitoring. Challenges in immunotherapy include partial or non-responses in many patients, irAEs affecting quality of life, and the complex tumor microenvironment which employs mechanisms to inhibit immune attacks.

Firstly, not all tumor patients respond to immunotherapy; some may show no response or only partial response, leading to suboptimal treatment outcomes. Studies have found that nearly half of NSCLC patients are not sensitive to these drugs [60,61]. Similarly, the proportion of liver cancer patients showing significant effects from common immunotherapies is not high.

Secondly, common irAEs not only affect patients' quality of life but may also lead to treatment interruption or discontinuation. Additional complications arise from concomitant liver diseases and the liver's immune tolerance, leading to treatment resistance in HCC patients. Predicting and managing these effects and improving efficacy are critical research areas in tumor immunotherapy. Table 2 summarizes the characteristics and indications of various antitumor immunotherapies.

Despite its promising potential, not all NSCLC patients exhibit positive benefits and antitumor responses to immunotherapy due to various factors. One key factor is the expression rate of PD-1/PD-L1. High PD-L1 expression on tumor cells is often associated with a better response to PD-1/PD-L1 inhibitors, as these therapies block the interaction between PD-1 on T-cells and PD-L1 on tumor cells, restoring T-cell activity. However, tumors with low or absent PD-L1 expression may not respond as effectively. Additionally, tumor mutational burden (TMB) plays a significant role; tumors with a high TMB are more likely to produce neoantigens that the immune system can recognize, making them more susceptible to immunotherapy.

The tumor microenvironment significantly influences the response to immunotherapy. An environment rich in immunosuppressive cells can inhibit effective immune responses. These cells include regulatory T-cells and myeloid-derived suppressor cells. Genetic mutations and alterations in immune evasion pathways can also lead to resistance. These include mutations in the STK11/LKB1 or EGFR genes. Such mutations may alter the immune landscape. They can make the tumor less recognizable or less responsive to immune attack. Patient-specific factors can also affect immunotherapy effectiveness. These factors include overall health, comorbidities, and prior treatments. Therefore, understanding and improving immunotherapy responses in NSCLC requires a multifaceted approach. This approach must consider PD-1/PD-L1 expression, TMB, the tumor microenvironment, genetic factors, and patient-specific conditions.

To improve the effectiveness of tumor immunotherapy, researchers are exploring various combination therapy strategies. Likely, the combined use of ICIs with chemotherapy, radiotherapy, or targeted therapy has shown potential for enhanced efficacy [62–65].

Table 2
Summary of key characteristics of tumor immunotherapy techniques.

Immunotherapy Technique	Mechanism	Applications	Advantages	Challenges
ICIs	Block immune checkpoint molecules like PD-L1 and CTLA-4, restoring T-cell function.	Various cancers including NSCLC and HCC.	Significant clinical efficacy in various cancers.	Non-response in some patients, irAEs.
CAR-T Cell Therapy	Genetically engineer T-cells to express chimeric antigen receptors that target tumor cells.	Hematologic malignancies such as leukemia and lymphoma.	Significant efficacy in blood cancers.	Limited success in solid tumors, high cost.
Tumor Vaccines	Preventive and therapeutic vaccines to stimulate an immune response against tumors.	Preventive: cervical cancer; Therapeutic: ongoing research.	Potential to prevent and treat cancers.	Limited success in therapeutic vaccines.
Cytokine Therapy	Inject or induce cytokines to enhance immune response.	Various cancers.	Promotes activation and proliferation of immune cells.	Potential adverse reactions and limited efficacy.
Bispecific Antibodies	Bind to two different antigens simultaneously, directing T-cells to attack tumor cells.	Various cancers, commonly using CD3 and tumor-specific antigens.	Activates T-cells to directly target tumors.	Development of resistance and immune-related side effects.

Studies have also indicated that certain factors within the tumor microenvironment, such as tumor-associated macrophages and stromal cells, may influence the effectiveness of immunotherapy, making the modulation of the tumor microenvironment another important research direction.

Overall, while immunotherapy has shown unprecedented potential in the treatment of NSCLC and liver cancer, it still faces multiple challenges and limitations. Further research and clinical trials are needed to continuously optimize treatment strategies, improve efficacy, reduce side effects, and promote the development of personalized treatment, providing patients with safer and more effective therapeutic options.

4. The theoretical basis of combination therapy

4.1. Collaborative mechanism

Tumor ablation therapy is emerging as a crucial component in combination treatment strategies, enhancing outcomes and alleviating symptoms such as shortness of breath, compression, or cachexia when combined with chemotherapy, radiotherapy, or immunotherapy. The synergistic mechanisms of ablation therapy and immunotherapy in NSCLC and liver cancer have garnered significant attention. Ablation therapy destroys tumor tissue through physical, chemical, or thermal means, causing tumor cell necrosis and releasing antigens. These antigens are processed by antigen-presenting cells, activating T-cells and initiating an antitumor immune response. This "antigen release effect" enhances antigen presentation and T-cell activation, promoting a robust antitumor immune response. Combined immunotherapy not only eliminates tumor cells but also establishes long-lasting immune memory, reducing recurrence risk.

ICIs enhance local T-cell activity. They relieve immune suppression within the tumor microenvironment. Combining these inhibitors with ablation therapy enhances T-cell activation and infiltration. This synergy significantly improves tumor control. In NSCLC, this combination induces a systemic immune response. It effectively controls primary and metastatic lesions. In liver cancer, ablation disrupts tumor tissue. The local inflammatory response that follows enhances immune recognition and response to tumor antigens. This improves progression-free and overall survival rates. Ablation therapy can reduce immune suppression and promote the recognition and killing of tumor cells by the immune system. This method greatly enhances the efficacy of immunotherapy.

This dual approach combines direct tumor cell elimination and immune microenvironment reshaping. It creates a powerful antitumor synergy. Ablation quickly reduces tumor size and symptoms, providing immediate clinical benefits. It induces antigen release and activates immune responses. This mitigates the immunosuppressive microenvironment and amplifies immunotherapy effects. The local inflammatory response attracts immune cells and releases cytokines. This mechanism enhances immune recognition and elimination of tumor antigens.

Fig. 1 illustrates the synergistic mechanism between tumor ablation and immunotherapy. It shows how ablation induces coagulation necrosis, releases tumor-associated antigens, and activates antigen-presenting cells. This enhances T-cell mediated cytotoxicity, leading to effective tumor cell lysis.

Combined immunotherapy further activates T-cells and other immune cells, strengthening the antitumor immune response and establishing long-term immune memory, preventing recurrence. This strategy embodies precision medicine principles, utilizing multiple approaches for comprehensive tumor eradication. Safety and side effect management are also anticipated advantages, with optimized treatment plans and personalized strategies minimizing damage to normal tissues and improving patient tolerability and quality of life. In summary, combining tumor ablation therapy and immunotherapy in NSCLC and liver cancer offers significant advantages, including direct tumor cell elimination, enhanced immune responses, improved treatment durability, and optimized side effect management.

4.2. Existing research and clinical trials

In preclinical studies, ablation therapy has demonstrated a potent immune activation effect. This therapy directly kills tumor cells,

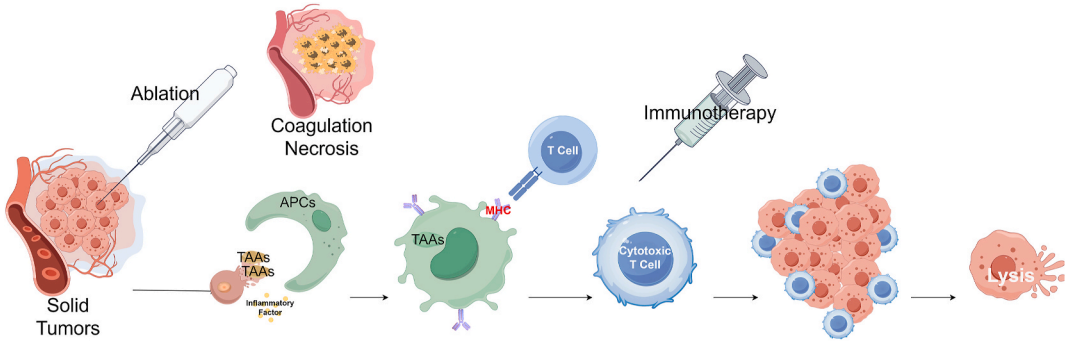


Fig. 1. Mechanism of Synergy between Tumor Ablation and Immunotherapy.

releases antigens, induces a local inflammatory response, and attracts immune cells. When combined with PD-1/PD-L1 or CTLA-4 inhibitors, ablation therapy can enhance the immune response, inhibiting tumor growth and metastasis. Animal experiments have shown that this combined therapy significantly suppresses the growth of primary and metastatic liver cancer lesions, prolongs survival time, improves chronic inflammation and liver fibrosis, and promotes liver function recovery.

Clinical trials have also shown promising results for the combined use of tumor ablation therapy and immunotherapy in treating NSCLC and liver cancer. In NSCLC clinical trials, combination therapy has demonstrated enhanced antitumor effects and improved patient outcomes. One review evaluated the efficacy of combining RFA with the PD-1 inhibitor pembrolizumab [66].

Patients receiving the combination therapy exhibited a significantly higher tumor regression rate compared to those receiving immunotherapy alone. These patients not only experienced effective local tumor control but also showed a significant reduction in distant metastases. Another trial assessed the combination of cryoablation with the PD-L1 inhibitor atezolizumab, revealing that the combination therapy group had significantly extended progression-free survival and overall survival [67]. A study supports cryoablation induces higher PD-L1 expression and T cell infiltration, but fewer PD-L1highCD11b + myeloid cells than MWA. CRA combined with anti-PD-L1 therapy shows superior curative effects in mice by enhancing CTL/NK cell responses and reducing the immunosuppressive microenvironment.

The anti-PD-L1 antibody avelumab (Bavencio) outperforms atezolizumab (Tecentriq) in inducing ADCC effects against PD-L1highCD11b + myeloid cells [68]. These findings indicate that tumor ablation therapy can release large amounts of tumor antigens and alter the tumor microenvironment, making it more conducive to immune cell infiltration and activation, thereby enhancing the efficacy of immunotherapy.

In clinical studies of liver cancer, the combination of tumor ablation therapy and immunotherapy has also shown significant efficacy. Liver cancer patients often face limitations with traditional surgical treatments due to impaired liver function or the tumor's location, making ablation therapy a minimally invasive alternative [69]. One study evaluated the combination of RFA with the PD-1 inhibitor nivolumab, finding that the combination therapy significantly improved overall survival and reduced tumor recurrence rates [70].

After drastic heat changes, necrotic tumor cells led to a significant increase in antigen release and activated specific T cell responses. The PD-1 inhibitor further lifted immune suppression, enhancing the antitumor immune effect. Another study evaluated the combination of MWA with the CTLA-4 inhibitor ipilimumab, showing that the combination therapy significantly inhibited tumor growth and metastasis, and was well-tolerated with a favorable safety profile [71].

These clinical trials and studies suggest that the combined use of tumor ablation therapy and immunotherapy can produce synergistic effects, effectively improving therapeutic outcomes. Tumor ablation therapy directly destroys tumor tissue, induces immunogenic cell death, releases tumor antigens, and triggers a local inflammatory response, thereby attracting and activating immune cells. Immunotherapy, by blocking immune checkpoint molecules, relieves immune suppression and enhances T-cell antitumor activity, further amplifying the immune effects of ablation therapy. This combination not only effectively controls primary tumors but also prevents tumor recurrence and distant metastasis through immune memory effects.

4.3. Future research directions

Future research directions for the combined use of tumor ablation therapy and immunotherapy in treating NSCLC and liver cancer will focus on optimizing treatment strategies, exploring new therapeutic combinations, uncovering molecular mechanisms, and developing precision medicine and personalized treatment methods. These research directions aim to further enhance the efficacy and safety of combined treatments, improving patient prognosis and quality of life.

Firstly, optimizing treatment strategies is a crucial area of future research. This includes determining the best ablation techniques and immunotherapy combinations, as well as optimizing treatment timing and dosage. Different ablation techniques may exhibit varying effectiveness in different types and stages of tumors [72,73]. Research should compare these techniques in combination with immunotherapy to identify the optimal protocols. Additionally, the types and dosages of immunotherapies, including ICIs like PD-1/PD-L1 inhibitors, CTLA-4 inhibitors, tumor vaccines, and adoptive T-cell therapies, need further optimization through clinical trials.

Secondly, exploring new therapeutic combinations is another key research direction. Beyond the existing ICIs, future research could investigate other types of immunotherapies such as oncolytic virus therapy, cytokine therapy, and novel immunomodulators. These new therapies, when used in conjunction with ablation therapy, could further enhance antitumor immune responses. Moreover, targeted therapies and anti-angiogenic drugs could be combined with ablation and immunotherapy to form multi-faceted treatment strategies that inhibit tumor growth and metastasis from multiple angles.

Uncovering the molecular mechanisms of combined therapy is essential for a deeper understanding and improvement of treatment outcomes. Ablation therapy induces immunogenic cell death, releases a large number of tumor antigens, and alters the tumor microenvironment [74]. The specific processes by which these changes enhance the effectiveness of immunotherapy require thorough investigation. Multi-omics approaches, including genomics, transcriptomics, and proteomics, can systematically analyze changes in the tumor and its microenvironment before and after combined treatment, revealing key molecular pathways and immune response mechanisms. These studies will not only help to understand the mechanisms of action but also identify new therapeutic targets and biomarkers, laying the foundation for precision therapy.

Precision medicine and personalized treatment are important future directions for combined therapy. Patients exhibit significant variability in their responses to treatment, and personalized treatment plans can improve efficacy and safety. Through gene sequencing and biomarker analysis, researchers can identify patient populations suitable for combined therapy, predict treatment outcomes and

adverse reaction risks, and develop individualized treatment plans. Biomarkers such as tumor mutation burden, microsatellite instability, and specific immune gene expression levels may serve as predictive indicators for combined therapy. Future research should establish and validate the clinical utility of these biomarkers, advancing personalized treatment.

Moreover, future research should focus on the long-term efficacy and safety of combined therapy. Existing clinical trials primarily assess short-term efficacy, while long-term outcomes and safety require further validation. This includes long-term follow-up of patients to evaluate tumor recurrence, metastasis, and survival, as well as documenting and managing long-term adverse reactions. Large-scale, multicenter clinical trials can provide comprehensive efficacy and safety data, supporting clinical application.

Future research should consider the economic feasibility and accessibility of combined therapy. The high cost of tumor ablation therapy and immunotherapy can pose a financial burden on patients and healthcare systems. Research should assess the cost-effectiveness of combined therapy, explore methods to reduce treatment costs, and improve accessibility so that more patients can benefit. This includes developing more efficient, low-cost ablation devices and immunotherapy drugs, simplifying treatment protocols, and reducing hospitalization time and treatment frequency.

The future research directions for the combined use of tumor ablation therapy and immunotherapy in treating NSCLC and liver cancer encompass optimizing treatment strategies, exploring new combinations, uncovering molecular mechanisms, advancing precision medicine, evaluating long-term efficacy and safety, and improving economic feasibility and accessibility. These studies will provide important theoretical and practical foundations for further enhancing the efficacy and safety of combined therapy, improving patient prognosis and quality of life. Through continuous innovation and exploration, the combined application of tumor ablation therapy and immunotherapy is expected to play a more significant role in future cancer treatment, bringing more hope and benefits to patients.

In conclusion, combining tumor ablation therapy and immunotherapy for NSCLC and liver cancer enhances tumor control, survival rates, and quality of life. Ablation therapy's direct tumor destruction and immunogenic cell death complement checkpoint inhibitors, targeting primary tumors and stimulating systemic antitumor responses to reduce recurrence and metastasis. Future research should optimize protocols, techniques, and schedules, understand molecular mechanisms, and address economic aspects for better accessibility. Overall, this integration offers new hope and improved outcomes for solid cancer patients.

Data availability statement

This article synthesizes existing published data on combined ablation and immunotherapy for NSCLC and liver cancer, with no new data generated or collected, thus no need for data disclosure. The illustration was created by Figdraw (www.figdraw.com).

Ethics declarations

Review and/or approval by an ethics committee was not needed for this study because it is a review article.

CRediT authorship contribution statement

Jing-shun Zhang: Writing – original draft, Supervision. **Yuan-dong Sun:** Writing – original draft, Software, Project administration. **Yuan-min Li:** Writing – original draft, Supervision. **Jian-jun Han:** Supervision, Funding acquisition.

Declaration of AI and AI-assisted technologies in the writing process

Only use these technologies to improve readability and language, not to replace key researcher tasks such as interpreting data or drawing scientific conclusions Only use these technologies to improve readability and language, not to replace key researcher tasks such as interpreting data or drawing scientific conclusions.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Jian-jun Han reports article publishing charges was provided by the National Key Research and Development Program. Jian-jun Han reports was provided by the National Natural Science Foundation of China. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] L.S. Rebecca, N.G. Angela, J. Ahmedin, Cancer statistics, 2024, CA Cancer J Clin 74 (1) (2024).
[2] B. Freddie, L. Mathieu, S. Hyuna, et al., Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA Cancer J Clin 74 (3) (2024).
[3] Q. Bin, G. Wei, Z. Fan, et al., Dynamic recurrence risk and adjuvant chemotherapy benefit prediction by ctDNA in resected NSCLC, Nat. Commun. 12 (1) (2021).
[4] L. Yinshan, Y. Mengmeng, G. Xiaoling, et al., "Two birds with one stone" strategy for the lung cancer therapy with bioinspired AIE aggregates, J. Nanobiotechnol. 21 (1) (2023).

[5] T. Xingyu, L. Yang, F. Songqing, et al., Downregulation of Linc00173 increases BCL2 mRNA stability via the miR-1275/PROCA1/ZFP36L2 axis and induces acquired cisplatin resistance of lung adenocarcinoma, J. Exp. Clin. Cancer Res. 42 (1) (2023).
[6] P. Nikos, M. Georgios, K. Afroditi, et al., An umbrella review of the evidence associating diet and cancer risk at 11 anatomical sites, Nat. Commun. 12 (1) (2021).
[7] L. Longfei, Y. Lei, L. Yuling, Q. Changhai, N. Jian, L. Hui, The burden and trends of primary liver cancer caused by specific etiologies from 1990 to 2017 at the global, regional, national, age, and sex level results from the global burden of disease study 2017, Liver Cancer 9 (5) (2020).
[8] H. Wei, X. Tingting, L. Du, et al., Intelligent molybdenum disulfide complexes as a platform for cooperative imaging-guided tri-mode chemo-photothermo-immunotherapy, Adv. Sci. 8 (14) (2021).
[9] W. Biyuan, F. Jintao, Z. Yixian, et al., Tailored core–shell dual metal-organic frameworks as a versatile nanomotor for effective synergistic antitumor therapy, Acta Pharm. Sin. B 10 (11) (2020).
[10] J.C. Erika, C.H. Amy, N. Donna, et al., Long-term survival of patients with stage III colon cancer treated with VRP-CEA(6D), an alphavirus vector that increases the CD8+ effector memory T cell to Treg ratio, J Immunother Cancer. 8 (2) (2020).
[11] W. Peng-Xiang, S. Yun-Fan, Z. Kai-Qian, et al., Circulating tumor cells are an indicator for the administration of adjuvant transarterial chemoembolization in hepatocellular carcinoma: a single-center, retrospective, propensity-matched study, Clin. Transl. Med. 10 (3) (2020).
[12] C. Zhixiong, S. Xiaoping, Q. Liman, et al., Personalized neoantigen vaccine prevents postoperative recurrence in hepatocellular carcinoma patients with vascular invasion, Mol. Cancer 20 (1) (2021).
[13] T. Hiroyuki, G. Ryousuke, O. Yoshinao, et al., Clinical features and diagnostic imaging of cholangiolocellular carcinoma compared with other primary liver cancers: a surgical perspective, Technol. Cancer Res. Treat. 19 (0) (2020).
[14] W. Chengdi, W. Yuxuan, S. Jun, L. Dan, L. Weimin, Clinicopathological variables influencing overall survival, recurrence and post-recurrence survival in resected stage I non-small-cell lung cancer, BMC Cancer 20 (1) (2020).
[15] L. Joo-Leng, L. Dawn Pingxi, Z. Xiaoqian, et al., A chemical genetic screen identifies Aurora kinases as a therapeutic target in EGFR T790M negative, gefitinib-resistant head and neck squamous cell carcinoma (HNSCC), EBioMedicine 64 (0) (2021).
[16] Ean T. Sing, A.S. Nur Fadhlina, Abdul M. Hazreen, Effects of immunonutrition in head and neck cancer patients undergoing cancer treatment - a systematic review, Front. Nutr. 9 (0) (2022).
[17] J. vdK. Henrieke, M. Marthe Te, J.G.S. Karlijn, et al., Impact of lung cancer treatment on cognitive functioning, Clin. Lung Cancer 21 (2) (2019).
[18] L. Delong, M. Debin, N. Rungui, Exosome-reversed chemoresistance to cisplatin in non-small lung cancer through transferring miR-613, Cancer Manag. Res. 12 (0) (2020).
[19] N. Jennifer, S. Ravi, W. Howard, et al., Ablative radiotherapy as a strategy to overcome TKI resistance in EGFR-mutated NSCLC, Cancers 14 (16) (2022).
[20] M. Ying, W. Jun, W. Jing, et al., Asiaticoside antagonizes proliferation and chemotherapeutic drug resistance in hepatocellular carcinoma (HCC) cells, Med Sci Monit 26 (0) (2020).
[21] L. Xiaoliang, W. Quanlin, M. Fujun, Z. Xinxin, C. Lei, Y. Xuekang, Mitochondrial fission factor promotes cisplatin resistancein hepatocellular carcinoma, Acta Biochim. Biophys. Sin. 54 (3) (2022).
[22] R.C. Matthew, A.W. David, C.N. Francis, et al., Multicenter study of metastatic lung tumors targeted by interventional cryoablation evaluation (SOLSTICE), J. Thorac. Oncol. 15 (7) (2020).
[23] M. Zezhong, C. Yiling, Z. Zheyu, et al., Cryoablation inhibits the recurrence and progression of bladder cancer by enhancing tumour-specific immunity, Clin. Transl. Med. 13 (5) (2023).
[24] L. Xiaodi, Z. Wenyue, X. Yanni, et al., Targeting PI3Kγ/AKT pathway remodels LC3-associated phagocytosis induced immunosuppression after radiofrequency ablation, Adv. Sci. 9 (7) (2022).
[25] Y. Zhijuan, Z. Yujie, D. Ziliang, et al., Tumor-killing nanoreactors fueled by tumor debris can enhance radiofrequency ablation therapy and boost antitumor immune responses, Nat. Commun. 12 (1) (2021).
[26] T. Shuilian, Y. Xiaoling, C. Zhigang, et al., Cause analysis and diagnosis and treatment of intestinal fistulas after ultrasound-guided microwave ablation of abdominopelvic lesions, Front Surg 8 (0) (2021).
[27] X. Han, C. Ze-Bin, J. Hui-Lin, et al., Treatment selection of recurrent hepatocellular carcinoma with microvascular invasion at the initial hepatectomy, Am J Transl Res 11 (3) (2019).
[28] D. Zhong-Shan, L. Jing, Chemothermal therapy for localized heating and ablation of tumor, J Healthc Eng 4 (3) (2013).
[29] D.G. Andrea, D.F. Alessandro, N. Giacomo, D. Chiara, G. Francesco, The landscape of immunotherapy in advanced NSCLC: driving beyond PD-1/PD-L1 inhibitors (CTLA-4, LAG3, IDO, OX40, TIGIT, vaccines), Curr. Oncol. Rep. 23 (11) (2021).
[30] F. Yuqian, J. Huimin, G. Kaibo, et al., Results from a meta-analysis of combination of PD-1/PD-L1 and CTLA-4 inhibitors in malignant cancer patients: does PD-L1 matter? Front. Pharmacol. 12 (0) (2021).
[31] K. Masatoshi, Scientific rationale for combination immunotherapy of hepatocellular carcinoma with anti-PD-1/PD-L1 and anti-CTLA-4 antibodies, Liver Cancer 8 (6) (2020).
[32] M.C. Gregory, M. Jan Joseph, T. Kai, B cell targeting in CAR T cell therapy: side effect or driver of CAR T cell function? Sci. Transl. Med. 14 (650) (2022).
[33] J. Jesper, H. Eve, K. Panos, Outcomes-based reimbursement for gene therapies in practice: the experience of recently launched CAR-T cell therapies in major European countries, J Mark Access Health Policy 8 (1) (2020).
[34] B. Guiu, MWA versus RFA in HCC: superior? Equivalent? Will we ever know? Cardiovasc. Intervent. Radiol. 43 (11) (2020) 1619–1620.
[35] F. Ziglioli, M. Baciarello, G. Maspero, et al., Oncologic outcome, side effects and comorbidity of high-intensity focused ultrasound (HIFU) for localized prostate cancer. A review, Annals of medicine and surgery 56 (2020) (2012) 110–115.
[36] Z. Chen, L. Meng, J. Zhang, X. Zhang, Progress in the cryoablation and cryoimmunotherapy for tumor, Front. Immunol. 14 (2023) 1094009.
[37] T. Li, W. Huang, Z. Wu, et al., Percutaneous ablation of hepatic tumors at the hepatocaval confluence using irreversible electroporation: a preliminary study, Curr. Oncol. 29 (6) (2022) 3950–3961.
[38] J. Hinshaw, M. Lubner, T. Ziemlewicz, F. Lee, C. Brace, Percutaneous tumor ablation tools: microwave, radiofrequency, or cryoablation–what should you use and why? Radiographics : a review publication of the Radiological Society of North America, Inc. 34 (5) (2014) 1344–1362.
[39] Z. Ashikbayeva, A. Aitkulov, T. Atabaev, W. Blanc, V. Inglezakis, D. Tosi, Green-synthesized silver nanoparticle-assisted radiofrequency ablation for improved thermal treatment distribution, Nanomaterials 12 (3) (2022).
[40] A. Blazevski, W. Gondoputro, M. Scheltema, et al., Salvage robot-assisted radical prostatectomy following focal ablation with irreversible electroporation: feasibility, oncological and functional outcomes, BMC Urol. 22 (1) (2022) 28.
[41] I. Yusuke, H. Masahiro, K. Masaki, et al., Dynamic tumor-tracking stereotactic body radiotherapy with real-time monitoring of liver tumors using a gimbal-mounted linac: a multi-institutional phase II study, Clin Transl Radiat Oncol 39 (0) (2023).
[42] J. Kushalee Poornima, T.M. Dimuthu, K. Chithranga, P. Lalitha, A.A. Buddhi, A rare case of insulinoma presenting with deep vein thrombosis, successfully treated with minimally invasive procedures including microwave ablation, Endocrinol Diabetes Metab Case Rep 2022 (0) (2022).
[43] T. Yulong, Q. Xingshun, J. Xin, S. Liqi, X. Ke, S. Haibo, Cryoablation and immune synergistic effect for lung cancer: a review, Front. Immunol. 13 (0) (2022).
[44] K. Shaghayegh, N. Alireza, Y. Mir Saeed, R. Nima, Cryoablation for the palliation of painful bone metastasis: a systematic review, Cardiovasc. Intervent. Radiol. 46 (11) (2023).
[45] G. Xue, Z. Xinyue, L. Dang, et al., Evaluation of physician experience in achieving non-perfused volume ratio of high-intensity focused ultrasound ablation for uterine fibroids: a multicentre study, J. Int. Med. Res. 50 (5) (2022).
[46] K.C.N. Kelvin, T.P.P. Ronnie, Ching C. See, et al., High-intensity focused ultrasound for hepatocellular carcinoma: a single-center experience, Ann. Surg. 253 (5) (2011).
[47] K. Oliwia, H. Stanisław, P. Joanna, S. Michał, Benefitial role of electrochemotherapy in locally advanced pancreatic cancer - radiological perspective, Pol. J. Radiol. 87 (0) (2022).

[48] N. Govindarajan, M.B. Malcolm, J.H. Peter, S. Zhaohui, M.M. Kathleen, C.G. 2nd M. Robert, Multicenter randomized controlled trial and registry study to assess the safety and efficacy of the NanoKnife® system for the ablation of stage 3 pancreatic adenocarcinoma: overview of study protocols, BMC Cancer 21 (1) (2021).
[49] M. René Michael, T. Parham, dF. Ricardo Daniel, et al., Impact of needle positioning on ablation success of irreversible electroporation: a unicentric retrospective analysis, Sci. Rep. 10 (1) (2020).
[50] H. Min, H. Lee, Mechanisms of resistance to chemotherapy in non-small cell lung cancer, Arch Pharm. Res. (Seoul) 44 (2) (2021) 146–164.
[51] B. Duchemann, J. Remon, M. Naigeon, et al., Current and future biomarkers for outcomes with immunotherapy in non-small cell lung cancer, Transl. Lung Cancer Res. 10 (6) (2021) 2937–2954.
[52] B. Zhou, J. Yan, L. Guo, et al., Hepatoma cell-intrinsic TLR9 activation induces immune escape through PD-L1 upregulation in hepatocellular carcinoma, Theranostics 10 (14) (2020) 6530–6543.
[53] D. Rong, Y. Wang, L. Liu, et al., GLIS1 intervention enhances anti-PD1 therapy for hepatocellular carcinoma by targeting SGK1-STAT3-PD1 pathway, Journal for immunotherapy of cancer 11 (2) (2023).
[54] P. Liping, L. Yang, L. Lin, et al., Roles of cancer-associated fibroblasts (CAFs) in anti- PD-1/PD-L1 immunotherapy for solid cancers, Mol. Cancer 22 (1) (2023).
[55] I. Ariel, K.L. Natalie, P.S. Jonathan, Biomaterials to enhance antigen-specific T cell expansion for cancer immunotherapy, Biomaterials 268 (0) (2020).
[56] S. Jiawei, M. Fan, Z. Shanshan, et al., Combination treatment of radiofrequency ablation and peptide neoantigen vaccination: promising modality for future cancer immunotherapy, Front. Immunol. 13 (0) (2022).
[57] Z. Yixin, Z. Yaqiong, G. Guifang, et al., Nivolumab plus ipilimumab versus pembrolizumab as chemotherapy-free, first-line treatment for PD-L1-positive non-small cell lung cancer, Clin. Transl. Med. 10 (1) (2020).
[58] M.G. Aaron, C. Andrea, P. Rachel Marty, et al., MHC-I genotype and tumor mutational burden predict response to immunotherapy, Genome Med. 12 (1) (2020).
[59] G.L. Etienne, H.-R. Zofia, T.K. Paul, et al., Sequential ctDNA whole-exome sequencing in advanced lung adenocarcinoma with initial durable tumor response on immune checkpoint inhibitor and late progression, J Immunother Cancer 8 (1) (2020).
[60] X. Wendi, H. Huayan, Y. Yongfeng, S. Lan, L. Ziming, L. Shun, Treatment strategies based on different oligoprogressive patterns after immunotherapy failure in metastatic NSCLC, Ther Adv Med Oncol 15 (0) (2023).
[61] T. Tian, Y. Min, Y. Yang, et al., Immune checkpoint inhibitor (ICI)-based treatment beyond progression with prior immunotherapy in patients with stage IV non-small cell lung cancer: a retrospective study, Transl. Lung Cancer Res. 11 (6) (2022).
[62] W. Liu, L. Zhang, Z. Xiu, et al., Combination of immune checkpoint inhibitors with chemotherapy in lung cancer, OncoTargets Ther. 13 (2020) 7229–7241.
[63] N. Ngamphaiboon, S. Ithimakin, T. Siripoon, N. Sintawichai, V. Sriuranpong, Patterns and outcomes of immune-related adverse events in solid tumor patients treated with immune checkpoint inhibitors in Thailand: a multicenter analysis, BMC Cancer 21 (1) (2021) 1275.
[64] L. Ma, From photon beam to accelerated particle beam: antimetastasis effect of combining radiotherapy with immunotherapy, Front. Public Health 10 (2022) 847119.
[65] Y. Guo, N. Liu, Systematic analysis and identification of molecular subtypes of TRP-related genes and prognosis prediction in lung adenocarcinoma, Journal of oncology 2022 (2022) 5388283.
[66] B. Bonnet, L. Tournier, F. Deschamps, et al., Thermal ablation combined with immune checkpoint blockers: a 10-year monocentric experience, Cancers 16 (5) (2024).
[67] T. Jizhou, L. Ting, F. Wenzhe, et al., Anti-PD-L1 antibody enhances curative effect of cryoablation via antibody-dependent cell-mediated cytotoxicity mediating PD-L1(high)CD11b(+) cells elimination in hepatocellular carcinoma, Acta Pharm. Sin. B 13 (2) (2023).
[68] J. Tan, T. Liu, W. Fan, et al., viaAnti-PD-L1 antibody enhances curative effect of cryoablation antibody-dependent cell-mediated cytotoxicity mediating PD-L1CD11b cells elimination in hepatocellular carcinoma, Acta Pharm. Sin. B 13 (2) (2023) 632–647.
[69] Y. Xiyue, L. Yao, F. Lingli, et al., High-intensity focused ultrasound ablation combined with immunotherapy for treating liver metastases: a prospective non-randomized trial, PLoS One 19 (7) (2024).
[70] D. Kim, Combination of interventional oncology local therapies and immunotherapy for the treatment of hepatocellular carcinoma, Journal of liver cancer 22 (2) (2022) 93–102.
[71] L. Yin, X. Li, L. Zhu, et al., Clinical application status and prospect of the combined anti-tumor strategy of ablation and immunotherapy, Front. Immunol. 13 (2022) 965120.
[72] B. Wolf, Philipp B. Lukas, L. Lukas, et al., Detection of incomplete irreversible electroporation (IRE) and microwave ablation (MWA) of hepatocellular carcinoma (HCC) using iodine quantification in dual energy computed tomography (DECT), Diagnostics 12 (4) (2022).
[73] W. Jun, W. Wei, H. Yunlong, G. Wei, L. Shandong, Incomplete radiofrequency ablation accelerates proliferation and angiogenesis of residual lung carcinomas via HSP70/HIF-1α, Oncol. Rep. 36 (2) (2016).
[74] S. Zheng-Rong, D. Yu-Xin, C. Fang, et al., Integrated proteogenomic characterization reveals an imbalanced hepatocellular carcinoma microenvironment after incomplete radiofrequency ablation, J. Exp. Clin. Cancer Res. 42 (1) (2023).