High-intensity focused ultrasound thermal ablation boosts the efficacy of immune checkpoint inhibitors in advanced cancers with liver metastases: A single-center retrospective cohort study

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Abstract. High-intensity focused ultrasound thermal ablation (HIFU) is a novel non-invasive technique in the treatment of liver metastases (LIM) that allows focal destruction and is not affected by dose limits. This retrospective study aimed to explore the efficacy of HIFU in improving survival and the safety of the method in newly diagnosed patients with cancer with LIM who received first-line immune checkpoint inhibitor (ICI) therapy. Between January 2018 and December 2023, data from 438 newly diagnosed patients with cancer and LIM who were treated at Mianyang Central Hospital (Mianyang, China) were reviewed. A total of 94 patients were enrolled in this study, of whom 28 were diagnosed with lung carcinoma, 36 with gastric carcinoma, 11 with esophageal carcinoma, 7 with cholangiocarcinoma and 12 with other malignancies. The patients were divided into groups depending on whether they underwent HIFU. Progression-free survival (PFS), overall survival (OS) and adverse events (AEs) were compared. Clinicopathological features were analyzed using the chi-squared test. Of the 94 patients, 28 received ICI + HIFU as first-line treatment. After a median follow-up of 13.8 months, the median PFS and OS in the HIFU group were 2.38 times [10.95 *vs*. 4.60 months, 95% confidence interval (CI): 1.087-3.106, P<0.0001] and 1.84 times (19.6 *vs*. 10.67 months, 95% CI: 1.087-3.106, P=0.0418), respectively, higher than in the group without HIFU. All-cause AEs and immune-mediated AEs were similar between the groups with and without HIFU. However, the incidence of grade 1-2 immune-mediated AEs, troponin elevation, hepatotoxicity and renal dysfunction were more common in the current patients with LIM than those reported previously for the entire population. No immune-mediated AEs of grade ≥3 occurred in either group. HIFU prolonged the PFS and OS of first-line ICI in newly diagnosed patients with advanced cancer with LIM, with manageable safety and tolerability. The efficacy of HIFU in patients with LIM who plan to undergo ICI treatment warrants further prospective clinical investigation.

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Abbreviations: HIFU, high-intensity focused ultrasound thermal ablation; LIM, liver metastasis; ICI, immune checkpoint inhibitor; AEs, adverse events; PFS, progression-free survival; OS, overall survival; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HR, hazard ratio; CI, confidence interval

Key words: high-intensity focused ultrasound thermal ablation, liver metastases, immune checkpoint inhibitors

Introduction

The liver is a common site for malignant tumor metastasis and patients with liver metastases (LIM) have poor survival rates (1,2). Currently, immune checkpoint inhibitors (ICIs) are the standard treatment for various solid tumors (3). However, clinical studies on lung cancer, melanoma, breast cancer and gastric cancer have shown that patients with LIM benefit less from ICI therapy compared to those with metastases at other

sites (4-8). For instance, a sub-analysis of two Phase III clinical trials on metastatic non-small cell lung cancer reported that the 3-year survival rate and median survival time for the LIM subgroup were considerably worse than those for the non-LIM subgroup (8 vs. 17% and 6.8 vs. 11.1 months, respectively) (9). Similarly, a meta-analysis of various cancer types demonstrated that the efficacy of ICI therapy is greatly reduced when LIM is present (10).

This diminished efficacy of ICI therapy is likely due to the unique anatomical structure and physiological functions of the liver (11). The liver features a dual venous system with an abundant blood supply, which offers optimal conditions for tumor cell colonization. By absorbing blood from the digestive tract, the liver is constantly exposed to food and intestinal flora antigens, maintaining an immune-tolerant state (12,13). Yu *et al* (14) reported that ICI therapy was less beneficial for patients with LIM than for those with lung, bone or brain metastases. In addition, the authors confirmed in mouse models that LIM alters the systemic immune microenvironment by attracting peripheral T cells to the liver, where they are subsequently eliminated by macrophages (14).

Owing to its non-invasive and reproducible nature and efficiency, high-intensity focused ultrasound (HIFU) is increasingly being employed to treat LIM. Zhou *et al* (15) presented a clinical study on the efficacy of HIFU in patients with gastric cancer with LIM who were contraindicated for either hepatectomy or radiofrequency ablation. The results showed that HIFU improved long-term prognosis without any considerable increase in the occurrence of adverse events (AEs) (15). Similar findings were reported in colorectal cancer with LIM (16). HIFU, delivered via a specialized transducer, can concentrate ultrasound energy at a focal point, generating transient high temperatures (65-100˚C) that induce coagulative necrosis in tumor tissues (17,18). Concurrently, the cavitation effect induces the rupture of the cell and nuclear membranes, rendering the cells incapable of proliferation (19-21). Numerous preclinical studies have confirmed that HIFU can enhance the efficacy of ICI therapy (22-25). The potential mechanisms for the enhanced antitumor response to ICI therapy after HIFU treatment include the release of large amounts of tumor antigens or antigen fragments, damage-associated molecular patterns, inflammatory chemokines, cytokines and increased expression of interferon-stimulating genes. These factors promote the activation of innate immune cells, facilitate antigen presentation to adaptive immune cells and attenuate the immunosuppressive tumor microenvironment by reducing the activity of regulatory T cells and myeloid-derived suppressor cells (23-25).

In recent years, emerging clinical data on prostate and breast cancers have highlighted the potential of HIFU to modulate the immune system (26,27). However, limited clinical reports have focused on the effects of this technology on other cancers in real-world settings. Considering that HIFU is already being used to treat LIM in numerous types of solid malignancies, the question arises of whether the combination of HIFU with ICI therapy can lead to improved efficacy in patients with LIM. In the present study, a retrospective cohort study was conducted using data from newly diagnosed patients with solid malignancies and LIM who received first-line ICI therapy to explore the efficacy of HIFU in this subgroup.

Materials and methods

Patient selection and data collection. The medical records of 94 patients with advanced metastatic solid malignant LIM who were treated at Mianyang Central Hospital (Mianyang, China) between January 2018 and December 2023 were retrospectively reviewed. The study protocol was approved by the Ethics Committee of Mianyang Central Hospital (Mianyang, China; file no. S20240390-01) and the study was conducted in accordance with the principles of the Declaration of Helsinki. The Ethics Committee granted an exemption from informed consent due to the retrospective nature of the study and no specimens were collected from the patients.

The inclusion criteria were as follows: i) Newly clinically and pathologically diagnosed advanced metastatic solid malignancy; ii) concurrent LIM confirmed in at least two types of imaging or pathology tests, iii) Eastern Cooperative Oncology Group scores ≥1; iv) completion of at least two courses of a first-line regimen of ICI-based therapy with subsequent therapeutic effect evaluation using imaging; and v) availability of comprehensive medical records, imaging data and follow-up information.

The exclusion criteria were as follows: i) Patients with a history of cancer but with relapse confined to the liver without pathological confirmation; ii) patients diagnosed with advanced cancer who received small-molecule tyrosine kinase inhibitors based on gene mutations during first-line ICI-based therapy; iii) patients with unknown metastatic sites or survival status; iv) patients with a history of ICI administration; or v) lack of target lesions that could be used for evaluating the efficacy of systemic therapy. A flowchart of the participant selection process is shown in Fig. 1.

The collected data included sex, age, primary tumor pathology, first-line and subsequent treatment regimens, HIFU plan details, time of diagnosis of the advanced solid malignancies with LIM, time of disease progression and time of death. The immunotherapy and chemotherapy regimens for the patients included in the study followed the guidelines of the Chinese Society of Clinical Oncology for the specific cancer type (28-31).

Oligometastasis was defined as the involvement of no more than five metastatic nodules and a maximum of three organs (32).

HIFU lesions selection and ablations methods. Patients were divided into a HIFU group and non-HIFU group based on whether they received HIFU treatment during first-line treatment.

The selection of HIFU lesions requires comprehensive evaluation of multiple factors, including tumor staging, clinical symptoms, skin condition in the treatment area, lesion size, lesion location and compression to adjacent tissue or organ. A few basic conditions were required to be met before application: i) The targeted lesions must be located within the focus of the ultrasound transducer; ii) the ultrasound path should not be obstructed by bony structures or gas-containing tissues; and iii) the presence of substantially calcified arterial walls in the channel of ultrasound therapy is contraindicated for HIFU treatment. Lesions that were more likely to alleviate discomfort symptoms or reduce the compression of tumors on adjacent blood vessels or bile

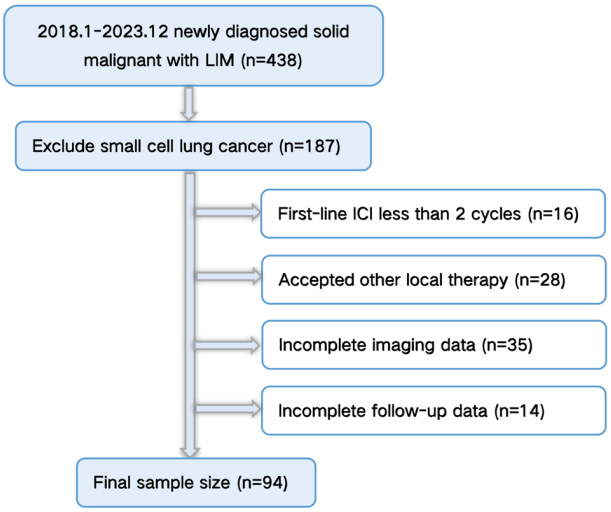

Figure 1. Flowchart of participant selection. LIM, liver metastases; ICI, immune-checkpoint inhibitor.

ducts were prioritized. Thus, the largest lesions are usually selected for HIFU following the selection criteria. HIFU surgeries were commonly completed within 5 h under general anesthesia, with a total HIFU duration of usually <3,000 sec.

HIFU ablations were scheduled in advance. A sagittal or axial orientation, which facilitates real-time monitoring of the lesion and adjacent tissue structures, was chosen as the scanning direction for guided imaging. The treatment protocol for each layer was formulated with a spacing of 3 or 5 mm, determined by the left and right or upper and lower diameters of the target tumor. Typically, treatment commenced at the maximum level of the lesion and the deeper side of the lesion was treated before the superficial side. The doses were evaluated during the initial treatment session or whenever a new high dose was proposed, with adjustments made based on the ultrasound imaging and patient status.

HIFU was performed using the model-JC200 Focused Ultrasound Tumor Therapeutic System integrated therapy machine from Chongqing Haifu Medical Technology Co., Ltd. Transducers with focal lengths of 115 and 165 mm were often used based on the depth of tumor treatment. All patients underwent HIFU under intravenous anesthesia, with real-time evaluation of ablation efficacy based on intraoperative monitoring of ultrasound grayscale changes.

Treatment efficacy evaluation. Treatment efficacy in each patient was assessed by two experienced radiologists using computed tomography or magnetic resonance images, following the Response Evaluation Criteria In Solid Tumours (version 1.1) (33). If their evaluations differed, the images were reviewed until a consensus was reached. If other lesions could be evaluated for treatment efficacy, those treated with HIFU were not considered target lesions. However, in the absence of other assessable lesions, those treated using HIFU were designated as target lesions. AEs, including those related to ICI and chemotherapy within 30 days after the last treatment with first-line ICI therapy were graded according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (version 4.0) (34).

In the current study, progression-free survival (PFS) refers to the time from the beginning of first-line treatment to the observation of disease progression in patients; overall survival (OS) refers to the time from the confirmation of diagnosis as cancer with liver metastases to death caused by any reason.

Statistical analysis. Demographic information and clinicopathological characteristics were summarized and presented using counts and percentages. Differences between qualitative variables and continuous variables were analyzed using χ^2 statistics and analysis of variance, respectively. Survival probabilities were calculated using the Kaplan-Meier method with GraphPad 10.0 and survival curves were compared using the log-rank test. The follow-up duration was estimated with the reverse Kaplan-Meier method. Statistical significance was set at a P-value of <0.05.

Results

Patient characteristics. Demographic data and clinicopathological characteristics were well-balanced between the treatment groups (Table I). A total of 94 eligible patients diagnosed with LIM who received first-line ICI between February 2018 and December 2023 were included. The mean age of the 94 patients was 60.98 years (range, 36.0-81.0 years). Of these, 75 (79.79%) were between 50 and 75 years of age and 71.28% were men. Gastric carcinoma was the most common primary tumor, followed by non-small cell lung cancer and esophageal carcinoma. Among the patients, 97.87% (n=92) had metastases in organs other than the liver and 65.96% (n=62) had metastases in at least three organs (including the liver). The lungs and bones were the most common sites of metastases, at 52.13% (n=49) and 41.49% (n=39), respectively. Adenocarcinoma was the most common histological subtype, accounting for 67.02% (n=63) of the cases. There were no differences between the HIFU group and non-HIFU group in terms of sex, age, primary disease, metastasis organs, histology, oligometastasis and systemic therapy regimens (P=0.309, 0.713, 0.053, 0.406, 0.404, 0.941 and 0.844, respectively). However, there was a significant difference in the distribution of organ metastases between the two groups (P=0.033). There was no case of single organ metastasis in the HIFU group but 3.03% (n=2) in the non-HIFU group. Furthermore, the incidence of metastasis to 2, 3, and 4 organs was significantly higher in the HIFU group compared to the non-HIFU group. A total of 88 patients received combination therapy that included ICI, whereas six patients received ICI monotherapy (two patients in the HIFU group). Metastatic sites and liver metastasis details of 94 patients with LIM who accepted first-line systemic therapy including ICI are presented in Table SI.

Of the 94 patients, seven were classified as having oligometastases (five men and two women). Of these patients, two received HIFU as first-line treatment. Of the seven patients with oligometastases, four had gastric carcinoma and all experienced recurrence after radical surgery, in accordance with the guidelines for gastric cancer LIM (35,36). Of the seven patients, two had esophageal carcinoma and one had non-small cell lung cancer. The clinicopathological characteristics of the seven patients with oligometastases are presented in Table SII.

Table I. Clinicopathological variables of 94 patients with liver metastases who accepted first-line systemic therapy including ICI.

Variable	Total (n=94)	With HIFU (n=28)	Systemic therapy only (n=66)	P-value
Sex				0.309
Male	67 (71.28)	22 (78.57)	45 (68.18)	
Female	27 (28.72)	6 (21.43)	21 (31.81)	
Age, years (mean, 60.98; range, 36.0-81.0)				0.713
≤50	12 (12.77)	4 (14.28)	8 (12.12)	
51-65	45 (47.87)	11 (39.29)	34 (51.51)	
65-75	30 (31.91)	11 (39.29)	19 (28.79)	
>75	7 (7.45)	2 (7.14)	5 (7.58)	
Primary disease				0.053
Lung carcinoma	28 (29.79)	10 (35.71)	18 (27.27)	
Gastric carcinoma	36 (38.29)	9 (32.14)	27 (40.91)	
Esophageal carcinoma	11 (11.70)	4 (14.29)	7 (10.60)	
Gallbladder carcinoma	2 (2.13)	0 (0)	2 (3.03)	
Cholangiocarcinoma	7 (7.45)	3 (10.72)	4 (6.06)	
Pancreatic carcinoma	4 (4.26)	1 (3.57)	3 (4.55)	
Nasopharyngeal carcinoma	2 (2.13)	0 (0)	2 (3.03)	
Other carcinoma	4 (4.26)	1 (3.57)	3 (4.55)	
Metastasis to other sites				0.406
LUM	49 (52.13)	18 (64.29)	31 (46.97)	
BOM	39 (41.49)	13 (46.43)	26 (39.39)	
BRM	9 (9.57)	1 (3.57)	8 (12.12)	
Others	86 (91.49)	24 (85.71)	62 (93.94)	
Number of organs with metastases				0.033
1	2 (2.13)	0 (0)	2 (3.03)	
2	30 (31.91)	9 (32.14)	21 (31.82)	
3	35 (37.23)	11 (39.29)	24 (36.36)	
4	23 (24.47)	7 (25.00)	16 (24.24)	
5	4 (4.26)	1 (3.57)	3 (4.55)	
Histology				0.404
AC	63 (67.02)	20 (71.43)	43 (65.15)	
SCC	27 (28.72)	8 (28.57)	19 (28.79)	
Other	4 (4.26)	0 (0)	4 (6.06)	
Oligometastasis				0.941
Yes	7 (7.45)	2 (7.14)	5 (7.58)	
No	87 (92.55)	26 (92.86)	61 (92.42)	
Systemic therapy regimens				0.844
Chemotherapy + ICI	88 (93.62)	26 (92.86)	62 (93.94)	
ICI only	6 (6.38)	2 (7.14)	4 (6.06)	

Values are expressed as n (%). AC, adenocarcinoma; BOM, bone metastases; BRM, brain metastases; HIFU, high-intensity ultrasonic focusing; LUM, lung metastases; SCC, squamous cell carcinoma; ICI, immune-checkpoint inhibitor.

A total of 28 patients received HIFU during first-line ICI treatment, while 66 patients received systemic therapy with ICI only. As of the data cutoff date of June 11, 2024, the median follow-up duration was 13.8 months. Details on the application of HIFU to the 28 patients, including treatment site and time, total energy, energy and time at different output powers, are presented in Table II. During first-line treatment, the 28 patients underwent 36 HIFU treatments. A total of 26 patients received HIFU after the start of ICI therapy; two patients with newly diagnosed lung cancer underwent liver HIFU within one week before immunotherapy while waiting for genetic testing. Among the 28 patients, six underwent HIFU ablation twice and one underwent three HIFU sessions.

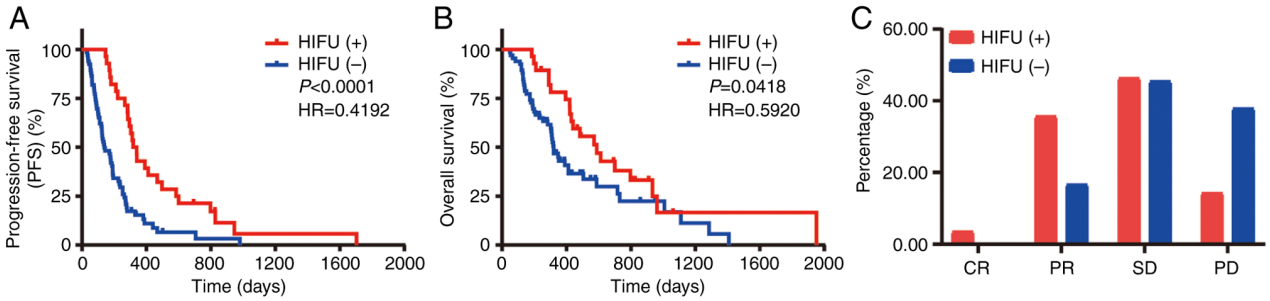

Figure 2. Kaplan-Meier curves and risk tables of (A) progression free survival and (B) overall survival for patients with and without HIFU-t during first-line therapy. (C) Response rate comparison between patients with versus without HIFU during first-line treatment. HR, hazard ratio; HIFU, high-intensity ultrasonic focusing; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Survival analyses. The Kaplan-Meier plots in Fig. 2 show the survival data for all patients. Fig. 2A shows that the patients who received HIFU had longer PFS [hazard ratio (HR)=0.4192, 95% confidence interval (CI): 0.2747-0.6398, P<0.001] than those who did not receive HIFU, with a 6-month PFS rate of 85.71 vs. 42.42% and 1-year PFS rates of 46.43 and 12.12%, respectively. The median PFS for the patients who received HIFU was 2.38 times that of those who did not (95% CI: 1.502-3.772), at 10.95 and 4.60 months, respectively. Fig. 2B shows that OS was better for the patients who received HIFU (HR=0.5920, 95% CI: 0.3633-0.9646, P=0.0418) than in those who did not, with a 6-month OS rate of 100 vs. 74.24%, respectively. The 1-year OS rates were 78.57 and 34.85%, respectively. The median OS in the HIFU group was 1.84 times that in the non-HIFU group (95% CI: 1.087-3.106), at 19.6 and 10.67 months, respectively. The disease control rate (defined as the ratio of the sum of complete response, partial response and stable disease to the total number of subgroups) in the HIFU group was 82.14% (23/28), higher than that in the systemic therapy group with ICI only, which was 66.67% (44/66) (Fig. 2C).

AEs. The all-cause and immune-mediated AEs in the two groups are presented in Table III. All-cause AEs occurred in 96.42% (n=27) of the patients in the HIFU group and in 95.45% (n=63) in the non-HIFU group. Myelosuppression was the most frequent AE and the most common AE of grade ≥3 in both groups, followed by elevated levels of alanine aminotransferase (ALT)/aspartate aminotransferase (AST), fatigue and decreased appetite. Both groups had one case of treatment suspension due to ALT/AST elevation, with treatment resumed after recovery. Diarrhea was more common in the HIFU than in the non-HIFU group (10.71 and 0%, respectively). However, this difference is unlikely to be meaningful, as intake of laxatives was necessary for bowel preparation before abdominal HIFU. The most frequent immune-mediated AEs were troponin elevation, skin reactions and thyroid dysfunction. There was no significant difference in immune-mediated AEs between the two groups and no immune-mediated AEs of grade ≥3 in either group.

Discussion

Although the widely used ICIs have markedly improved efficacy in the clinical treatment of various histologically advanced cancers, their benefits for patients with LIM are limited (4-10). Local treatment strategies for LIM, such as radiotherapy and radiofrequency ablation, have been shown to enhance the efficacy of ICI (37-40), but the disadvantages of these local treatment methods cannot be overlooked. For instance, radiotherapy is constrained by long treatment duration and normal-tissue dose limitations, while radiofrequency ablation is invasive and less reliable for tumors close to the gallbladder, main biliary tract and major blood vessels. HIFU, a recent technology for local treatment, has gained traction in cancer therapy, particularly when LIM has occurred, due to its non-invasive nature, efficiency, limited side effects and reproducibility, regardless of dose limits (41). In the present retrospective cohort study, the clinicopathological characteristics, survival and AEs of 94 patients diagnosed with LIM who received first-line ICI treatment were analyzed. The findings indicate that HIFU prolonged PFS and OS in newly diagnosed patients with LIM, with similar AEs across the study groups.

Both preclinical and clinical studies have demonstrated that HIFU enhances anti-tumor immunity. Preclinical studies have shown that HIFU ablation can generate *in situ* antigens, increase the activity of antigen-presenting cells such as dendritic cells and promote innate immune cell activity (23-26). Zhou *et al* (41) observed decreased serum levels of immunosuppressive cytokines, including VEGF, TGF-β1 and TGF-β2, in 15 solid tumors after HIFU treatment. This suggests that HIFU not only directly destroys tumors but also reduces the production of immunosuppressive cytokines secreted by cancer cells. In addition, a prospective randomized clinical trial by Zhu *et al* (42) revealed that HIFU ablation induces marked infiltration of CD3, CD4, CD8, B lymphocytes and natural killer (NK) cells in treated breast lesions, with notable increases in the numbers of FasL(+), granzyme(+) and perforin(+) tumor-infiltrating lymphocytes post-HIFU treatment. These findings suggest that HIFU can restore anti-tumor immunity, and the increased infiltration of T lymphocytes provides mechanistic support for the efficacy of ICI. Eranki *et al* (43) found that HIFU can effectively induce immune sensitization in a previously unresponsive murine neuroblastoma model and is a promising novel and efficacious immuno-adjuvant modality to overcome therapeutic resistance. HIFU alone causes upregulation of the expression of splenic and lymph node NK cells and circulating IL-2, IFN-γ and damage-associated molecular patterns, whereas the levels of immune regulators such as CD4+forkhead box p3+, IL-10 and VEGF-A are reduced considerably. Combining HIFU with α-cytotoxic T lymphocyte antigen-4 and α-programmed

Table II. Key parameters of 36 HIFU ablation programs.

No.	Ablation site	Total energy, J	Average power, W	Actual power	Ablation volume, cm^3	Ablation time, sec	Gray scale change
1	LL	114,500	183	100 W, 20 sec, 3.2%; 150 W, 170 sec, 27.2%; 200 W, 435 sec, 69.6%	3.12	625	MGC
2	RL	213,600	368	300 W, 76 sec, 13.74%; 400 W, 477 sec, 86.26%	5.85	553	MGC
	LAG	182,950	314	300 W, 422 sec, 72.38%; 350 W, 161 sec, 27.62%	6.22	583	MGC
3	RL	836,000	400	400 W, 2,090 sec, 100%	266.40	2,090	OGC
	HGS	291,100	386	300 W, 105 sec, 3.93%; 400 W, 649 sec, 86.07%	26.88	754	MGC
4	RL	195,250	250	250 W, 781 sec, 100%	9.72	781	MGC
	RAG	318,600	389	300 W, 90 sec, 10.99%; 400 W, 729 sec, 89.01%	26.77	819	OGC
5	RL	365,200	400	400 W, 913 sec, 100%	57.58	913	OGC
6	RL	328,400	364	300 W, 151 sec, 16.74%; 350 W, 346 sec, 38.36%; 400 W, 405 sec, 44.90%	98.26	902	MGC
7	LL, RL	337,350	366	250 W, 83 sec, 9.00%; 300 W, 190 sec, 0.61%; 400 W, 649 sec, 70.39%	112.08	922	MGC
8	LL	232,960	299	80 W, 147 sec, 18.87%; 350 W, 632 sec, 81.13%	24.63	779	MGC
	LL	126,300	300	300 W; 421 sec; 100%	24.32	421	OGC
9	RL	523,750	365	365 W, 1436 sec, 100%	82.50	1,436	OGC
10	RL	130,200	350	350 W, 174 sec, 75.65%	21.60	479	OGC
11	RL	1,042,000	400	400 W, 2,605 sec, 100%	27.90	2,605	OGC
	LL	542,600	379	300 W, 171 sec, 11.96%; 350 W, 246 sec, 17.2%; 400 W, 1,013 sec, 70.84%	112.02	1,430	MGC
12	LL	405,300	399	300 W, 15 sec, 1.47%; 400 W, 1,002 sec, 98.53%	8.1	1,017	MGC
	LL	592,800	384	300 W, 240 sec, 15.56%; 400 W, 1,302 sec, 84.44%	132.8	1,542	MGC
13	LL, RL	141,800	392	350 W, 60 sec, 16.57%; 400 W, 302 sec, 83.43%	153.9	362	MGC
14	LL	324,400	400	400 W, 811 sec, 100%	122.55	811	OGC
15	HGS	527,150	391	250 W, 53 sec, 3.93%; 300 W, 41 sec, 3.04%; 400 W, 1,254 sec, 93.03%	35.5	1,348	MGC
16	RL, PALN	165,000	267	200 W, 174 sec, 28.16%; 250 W, 153 sec, 24.76%; 300 W, 198 sec, 32.04%; 350 W, 93 sec, 15.5%	8.16	618	MGC
17	LL, RL	250,200	333	200 W, 56 sec, 7.46%; 300 W, 85 sec, 11.32%; 350 W, 610 sec, 81.22%	21.32	751	MGC
18	LL	417,800	397	350 W, 60 sec, 5.7%; 400 W, 992 sec, 94.3%	30.9	1,052	OGC
19	HOP	113,250	238	150 W, 20 sec, 4.21%; 200 W, 206 sec, 43.37%; 250 W, 113 sec, 23.79%; 300 W, 136 sec, 28.63%	63.2	475	OGC

Table II. Continued.

No.	Ablation site	Total energy, J	Average power, W	Actual power	Ablation volume, cm^3	Ablation time, sec	Gray scale change
20	CL	745,550	349	300 W, 255 sec, 11.93%; 350 W, 1,683 sec, 78.72%; 400 W, 200 sec, 9.35%	204.7	2,138	OGC
21	HGS	278,400	332	200 W, 66 sec, 7.88%; 300 W, 100 sec, 11.93%; 350 W, 672 sec, 80.19%	36.72	838	OGC
22	LL	60,000	200	200 W, 300 sec, 100%	1.2	300	MGC
23	RL	1,210,000	400	400 W, 3,025 sec, 100%	318.5	3,025	OGC
	RL	1,161,600	400	400 W, 2,904 sec, 100%	1,080	2,904	MGC
	RL	956,360	399	310 W, 36 sec, 1.5%; 400 W, 2,363 sec, 98.50%	154.0	2,399	MGC
24	LL	476,800	400	400 W, 1,192 sec, 100%	30.9	1,192	OGC
25	RL	826,400	400	400 W, 2,066 sec, 100%	429.7	2,066	OGC
26	LL	187,500	300	300 W, 625 sec, 100%	12.1	625	MGC
27	RL	874,800	400	400 W, 2,187 sec, 100%	283.5	2,187	MGC
28	RL	735,700	391	300 W, 105 sec, 5.58%; 350 W, 140 sec, 7.43%; 400 W, 1,638 sec, 86.99%	37.2	1,883	OGC

LL, left lobe; RL, right lobe; CL, caudate lobe; HGS, hepato-gastric space; LAG, left adrenal gland; RAG, right adrenal gland; HOP, head of pancreas; PALN, para-aortic lymph node; MGC, massive grayscale changes; OGC, overall grayscale change.

death ligand 1 markedly enhanced the anti-tumor response, improving survival from 0 to 62.5%, and, importantly, led to abscopal effects (43). However, these studies did not explore the combination of HIFU and ICI in real-world patients with advanced cancer. To our knowledge, only one article, published by our team in 2024, has focused on this novel combination therapy in patients with LIM, confirming the feasibility and safety of the method in clinical settings, although survival data were not presented (44). In the present study, it was reported that HIFU with ICI prolonged PFS in patients with advanced cancers and LIM. Based on these results, it may be speculated that HIFU may reverse the unfavorable immune microenvironment caused by LIM. In our opinion, this longer PFS may be caused by HIFU's inferences to the micro-immune environment. However, the effect was temporary, as resistance to ICI developed and the condition progressed after approximately six months. Thus, the method could not completely alter the deterioration of the immune microenvironment caused by multiple LIM and multiple organ metastases.

HIFU combined with ICI represents a new therapeutic model for patients with LIM; however, numerous issues, such as safety, treatment sequence and timing, require further exploration. Dupré *et al* (45,46) confirmed the safety of HIFU ablation before surgical resection of liver tumors and its effectiveness in reducing intraoperative bleeding in patients with LIM.

Although these results support the safety of HIFU therapy, surgical candidates often have a limited tumor burden in the liver and the entire body, whereas patients in the present study had multiple LIM. Furthermore, the proportion of patients with elevated ALT, AST and bilirubin levels was much higher among the 94 patients in the present cohort. Previous meta-analyses and studies reported liver toxicity incidences of 16-37.8% with immunotherapy (47,48), whereas in the present study, the incidence in both the HIFU and non-HIFU groups exceeded 60%. This result may be due to the damage caused by the occurrence of multiple LIM, chemotherapy drugs and ICIs rather than HIFU itself. Zhou *et al* (15) reported that HIFU treatment improved the long-term prognosis of patients with gastric cancer without any notable increase in AEs in patients with LIM without extrahepatic metastasis who could not undergo surgery or radiofrequency ablation. This study supports the safety and survival benefits of HIFU, but it included patients without extrahepatic metastases. LIM are frequently accompanied by metastases to other organs, which also explains the higher incidence of grade 1-2 AEs, such as troponin elevation, hepatotoxicity and renal dysfunction, in both groups compared to previous results. These observations suggest the necessity of closer monitoring of relevant indicators in patients with advanced cancer with LIM undergoing ICI therapy. Importantly, no immune-mediated AEs of grade ≥3 were observed in either group.

The present study has certain limitations. First, it was a retrospective clinical study from a single institution that included only 94 patients across eight cancer types. Therefore, the possibility of incomplete or inaccurate records inherent in retrospective research or the influence of specific environments and populations in a single institution center cannot be excluded. Second, it was not possible to provide the size and quantity of the LIM lesions. There were too many patients with multiple liver metastases and numerous small lesions, even diffuse small

Table III. Summary of AEs.

A, Common AEs of chemotherapy

	With HIFU therapy (N=28)		Systemic therapy with ICI only (N=66)	
Event	Any grade	Grade ≥3	Any grade	Grade ≥3
Myelosuppression	27 (96.42)	11 (39.29)	60 (90.90)	19 (28.79)
Vomiting	4 (14.29)	1 (3.57)	7 (10.61)	2 (3.03)
Fatigue	12 (42.86)	2 (7.14)	27 (40.91)	2 (4.55)
Nausea	7 (25.00)	0	18 (27.27)	2 (3.03)
Diarrhea	3 (10.71)	0	2 (3.03)	0
Decreased appetite	10 (35.71)	0	23 (34.85)	0
Hepatotoxicity				
ALT/AST elevation	17 (60.71)	1 (3.57)	40 (60.61)	1 (1.52)
Bilirubin elevation	13 (19.70)	0	32 (48.48)	0

B, Immune-mediated AEs

	With HIFU therapy (N=28)		Systemic therapy with ICI only (N=66)	
Event	Any grade	Grade ≥3	Any grade	Grade ≥3
Thyroid dysfunction	4 (14.29)	0	14 (21.21)	0
Pneumonitis	2 (7.14)	0	2 (3.03)	0
Skin reactions	4 (14.29)	0	12 (18.18)	0
Renal dysfunction	3 (10.71)	0	5 (7.58)	0
Troponin elevation	6 (21.43)	0	13 (19.70)	0
Arthralgia	3 (10.71)	0	5 (7.58)	0
CCEP	2 (7.14)	0	8 (12.12)	0

AEs, adverse events; HIFU, high-intensity ultrasonic focusing; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CCEP, cutaneous capillary hyperplasia.

lesions, making it difficult to count the number. Furthermore, most of these patients also had multiple pulmonary and bone metastases, which further reduced the significance of the size of liver metastases. However, the largest tumor was found in the liver of every patient. Third, due to the gradual onset of immunotherapy, physicians often recommended this treatment for patients with an anticipated survival exceeding two months, thereby introducing a potential selection bias. Fourth, patients who received one or two cycles of ICI but without further imaging review were excluded, as the efficacy of ICI was uncertain in these cases. Finally, as HIFU is a novel method in cancer treatment, limited clinical evidence about its efficiency on the immune system has been reported previously. In the present study, it was not observed that HIFU may improve the immune environment by ablating liver metastases, and this was not included in the lesions' selection items. However, this approach may have inflated the objective response rate. Of note, seven patients with oligometastases were potentially curable according to the guidelines for oligometastasis of lung carcinoma (32), and 2 of 7 accepted HIFU after failing in the pre-treatment evaluation for other local curative treatments. Nonetheless, this study suggests that HIFU may enhance ICI efficacy in patients with LIM, with mild and manageable AEs.

In conclusion, the present retrospective study indicated that HIFU prolonged the PFS and OS of first-line ICI-based treatment in newly diagnosed patients with advanced cancer with LIM, with manageable safety and tolerability. Therefore, the efficacy of HIFU in patients with LIM undergoing ICI treatment warrants further prospective clinical investigation. Given the good safety of this combination strategy and that up to 50% of patients with various cancer types will either present with or develop LIM during the course of their disease, it is indicated that it can be further promoted in clinical practice for liver and extrahepatic lesions. This treatment strategy may also be considered for advanced cancers without LIM. To further clarify the efficacy of HIFU in immunotherapy for LIM, animal studies are in planning in our group to further investigate the efficacy of HIFU in immunotherapy for LIM.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

Conceptualization, XD, GF and WC; methodology, XD and FG; software, JL and YL; validation, DW and XD; formal analysis, JL, YL, YZ and ML; investigation, YL, YZ, XY, BL and LN; resources, ML; data curation, ML, YL and XD; writing-original draft preparation, YL and BL; writing-review and editing, JL, YZ, XD and WC; visualization, DW; supervision, BL and YZ; project administration, BL, GF and JL. All authors have read and agreed to the published version of the manuscript. YL and XD checked and confirmed the authenticity of all the raw data.

Ethics approval and consent to participate

The clinical trial protocol was approved by the Ethics Committee of Mianyang Central Hospital (file no. S20240390-01) and conducted in accordance with the principles of the Declaration of Helsinki. The Ethics Committee granted an exemption from informed consent due to the retrospective nature of the study, and no specimens were collected from the patients.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Disibio G and French SW: Metastatic patterns of cancers: Results from a large autopsy study. Arch Pathol Lab Med 132: 931-939, 2008.
2. Tsilimigras DI, Brodt P, Clavien PA, Muschel RJ, D'Angelica MI, Endo I, Parks RW, Doyle M, de Santibañes E and Pawlik TM: Liver Metastases. Nat Rev Dis Primers 7: 27, 2021.
3. Topalian SL, Taube JM and Pardoll DM: Neoadjuvant checkpoint blockade for cancer immunotherapy. Science 367: eaax0182, 2020.
4. Bilen MA, Shabto JM, Martini DJ, Liu Y, Lewis C, Collins H, Akce M, Kissick H, Carthon BC, Shaib WL, *et al*: Sites of metastasis and association with clinical outcome in advanced stage cancer patients treated with immunotherapy. BMC Cancer 19: 857, 2019.
5. Tumeh PC, Hellmann MD, Hamid O, Tsai KK, Loo KL, Gubens MA, Rosenblum M, Harview CL, Taube JM, Handley N, *et al*: Liver metastasis and treatment outcome with anti-PD-1 monoclonal antibody in patients with melanoma and NSCLC. Cancer Immunol Res 5: 417-424, 2017.
6. Welsh JW, Tang C, de Groot P, Naing A, Hess KR, Heymach JV, Papadimitrakopoulou VA, Cushman TR, Subbiah V, Chang JY, *et al*: Phase II trial of ipilimumab with stereotactic radiation therapy for metastatic disease: Outcomes, toxicities, and low-dose radiation-related abscopal responses. Cancer Immunol Res 7: 1903-1909, 2019.
7. Welsh J, Menon H, Chen D, Verma V, Tang C, Altan M, Hess K, de Groot P, Nguyen QN, Varghese R, *et al*: Pembrolizumab with or without radiation therapy for metastatic non-small cell lung cancer: A Randomized Phase I/II Trial. J Immunother Cancer 8: e001001, 2020.
8. Wang X, Ji Q, Yan X, Lian B, Si L, Chi Z, Sheng X, Kong Y, Mao L, Bai X, *et al*: The impact of liver metastasis on anti-PD-1 monoclonal antibody monotherapy in advanced melanoma: Analysis of five clinical studies. Front Oncol 10: 546604, 2020.
9. Vokes EE, Ready N, Felip E, Horn L, Burgio MA, Antonia SJ, Arén Frontera O, Gettinger S, Holgado E, Spigel D, *et al*: Nivolumab versus docetaxel in previously treated advanced non-small-cell lung cancer (CheckMate 017 and CheckMate 057): 3-year update and outcomes in patients with liver metastases. Ann Oncol 29: 959-965, 2018.
10. Chen XJ, Ren A, Zheng L, Zheng ED and Jiang T: Pan-cancer analysis identifies liver metastases as negative predictive factor for immune checkpoint inhibitors treatment outcome. Front. Immunol 12: 651086, 2021.
11. Horst AK, Neumann K, Diehl L and Tiegs G: Modulation of liver tolerance by conventional and nonconventional antigen-presenting cells and regulatory immune cells. Cell Mol Immunol 13: 277-292, 2016.
12. Thomson AW and Knolle PA: Antigen-presenting cell function in the tolerogenic liver environment. Nat Rev Immunol 10: 753-766, 2010.
13. Jenne CN and Kubes P: Immune surveillance by the liver. Nat Immunol 14: 996-1006, 2013.
14. Yu J, Green MD, Li S, Sun Y, Journey SN, Choi JE, Rizvi SM, Qin A, Waninger JJ, Lang X, *et al*: Liver metastasis restrains immunotherapy efficacy via macrophage-mediated T cell elimination. Nat Med 27: 152-164, 2021.
15. Zhou B, He N, Hong J, Yang T, Ng DM, Gao X, Yan K, Fan X, Zheng Z, Chen P, *et al*: HIFU for the treatment of gastric cancer with liver metastases with unsuitable indications for hepatectomy and radiofrequency ablation: A prospective and propensity score-matched study. BMC Surg 21: 308, 2021.
16. Yang T, Ng DM, Du N, He N, Dai X, Chen P, Wu F, Chen B, Fan X, Yan K, *et al*: HIFU for the treatment of difficult colorectal liver metastases with unsuitable indications for resection and radiofrequency ablation: A phase I clinical trial. Surg Endosc 35: 2306-2315, 2021.
17. Quesson B, Vimeux F, Salomir R, de Zwart JA and Moonen CT: Automatic control of hyperthermic therapy based on real-time Fourier analysis of MR temperature maps. Magn Reson Med 47: 1065-1072, 2002.
18. Tillander M, Hokland S, Koskela J, Dam H, Andersen NP, Pedersen M, Tanderup K, Ylihautala M and Kohler M: High intensity focused ultrasound induced in vivo large volume hyperthermia under 3D MRI temperature control. Med Phys 43: 1539-1549, 2016.
19. Coussios CC, Farny CH, Haar GT and Roy RA: Role of acoustic cavitation in the delivery and monitoring of cancer treatment by high-intensity focused ultrasound (HIFU). Int J Hyperthermia 23: 105-120, 2007.
20. Ebbini ES and ter Haar G: Ultrasound-guided therapeutic focused ultrasound: current status and future directions. Int J Hyperthermia 31: 77-89, 2015.
21. Ter Haar G: HIFU Tissue Ablation: Concept and devices. Adv Exp Med Biol 880: 3-20, 2016.
22. Sheybani ND, Witter AR, Thim EA, Yagita H, Bullock TNJ and Price RJ: Combination of thermally ablative focused ultrasound with gemcitabine controls breast cancer via adaptive immunity. J Immunother Cancer 8: e001008, 2020.
23. Silvestrini MT, Ingham ES, Mahakian LM, Kheirolomoom A, Liu Y, Fite BZ, Tam SM, Tucci ST, Watson KD, Wong AW, *et al*: Priming is key to effective incorporation of image-guided thermal ablation into immunotherapy protocols. JCI Insight 2: e90521, 2017.
24. Han X, Wang R, Xu J, Chen Q, Liang C, Chen J, Zhao J, Chu J, Fan Q, Archibong E, *et al*: In situ thermal ablation of tumors in combination with nano-adjuvant and immune checkpoint blockade to inhibit cancer metastasis and recurrence. Biomaterials 224: 119490, 2019.

25. Chavez M, Silvestrini MT, Ingham ES, Fite BZ, Mahakian LM, Tam SM, Ilovitsh A, Monjazeb AM, Murphy WJ, Hubbard NE, *et al*: Distinct immune signatures in directly treated and distant tumors result from TLR adjuvants and focal ablation. Theranostics 8: 3611-3628, 2018.
26. Karwacki J, Kiełbik A, Szlasa W, Sauer N, Kowalczyk K, Krajewski W, Saczko J, Kulbacka J, Szydełko T and Małkiewicz B: Boosting the immune response-combining local and immune therapy for prostate cancer treatment. Cells 11: 2793, 2022.
27. Sinha M, Zhang L, Subudhi S, Chen B, Marquez J, Liu EV, Allaire K, Cheung A, Ng S, Nguyen C, *et al*: Pre-existing immune status associated with response to combination of sipuleucel-T and ipilimumab in patients with metastatic castration-resistant prostate cancer. J Immunother Cancer 9: e002254, 2021.
28. Wu YL, Planchard D, Lu S, Sun H, Yamamoto N, Kim DW, Tan DSW, Yang JC, Azrif M, Mitsudomi T, *et al*: Pan-Asian adapted clinical practice guidelines for the management of patients with metastatic non-small-cell lung cancer: A CSCO-ESMO initiative endorsed by JSMO, KSMO, MOS, SSO and TOS. Ann Oncol 30: 171-210, 2019.
29. Wang FH, Zhang XT, Li YF, Tang L, Qu XJ, Ying JE, Zhang J, Sun LY, Lin RB, Qiu H, *et al*: The Chinese Society of Clinical Oncology (CSCO): Clinical guidelines for the diagnosis and treatment of gastric cancer, 2021. Cancer Commun (Lond) 41: 747-795, 2021.
30. Tang LL, Chen YP, Chen CB, Chen MY, Chen NY, Chen XZ, Du XJ, Fang WF, Feng M, Gao J, *et al*: The Chinese Society of Clinical Oncology (CSCO) clinical guidelines for the diagnosis and treatment of nasopharyngeal carcinoma. Cancer Commun (Lond) 41: 1195-1227, 2021.
31. Muro K, Lordick F, Tsushima T, Pentheroudakis G, Baba E, Lu Z, Cho BC, Nor IM, Ng M, Chen LT, *et al*: Pan-Asian adapted ESMO clinical practice guidelines for the management of patients with metastatic oesophageal cancer: A JSMO-ESMO initiative endorsed by CSCO, KSMO, MOS, SSO and TOS. Ann Oncol 30: 34-43, 2019.
32. Dingemans AC, Hendriks LEL, Berghmans T, Levy A, Hasan B, Faivre-Finn C, Giaj-Levra M, Giaj-Levra N, Girard N, Greillier L, *et al*: Definition of synchronous oligometastatic non-small cell lung Cancer-A consensus report. J Thorac Oncol 14: 2109-2119, 2019.
33. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, *et al*: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 45: 228-247, 2009.
34. National Cancer Institute: Terminology Criteria for Adverse Events (CTCAE). Version 4.0. 2009. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_40.
35. Ajani JA, D'Amico TA, Bentrem DJ, Chao J, Cooke D, Corvera C, Das P, Enzinger PC, Enzler T, Fanta P, *et al*: Gastric cancer, version 2.2022, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 20: 167-192, 2022.
36. Japanese Gastric Cancer Association: Japanese gastric cancer treatment guidelines 2021 (6th edition). Gastric Cancer 26: 1-25, 2023.
37. Lorusso D, Xiang Y, Hasegawa K, Scambia G, Leiva M, Ramos-Elias P, Acevedo A, Sukhin V, Cloven N, Pereira d e Santana Gomes AJ, *et al*: Pembrolizumab or placebo with chemoradiotherapy followed by pembrolizumab or placebo for newly diagnosed, high-risk, locally advanced cervical cancer (ENGOT-cx11/GOG-3047/KEYNOTE-A18): A randomised, double-blind, phase 3 clinical trial. Lancet 403: 1341-1350, 2024.
38. Lim M, Weller M, Idbaih A, Steinbach J, Finocchiaro G, Raval RR, Ansstas G, Baehring J, Taylor JW, Honnorat J, *et al*: Phase III trial of chemoradiotherapy with temozolomide plus nivolumab or placebo for newly diagnosed glioblastoma with methylated MGMT promoter. Neuro Oncol 24: 1935-1949, 2022.
39. Zhang ZY, Jiang AN, Yang W, Yan K, Wu W, Wang S, Jiang BB, Sun LQ, Zhao K and Chen MH: Percutaneous radiofrequency ablation is an effective method for local control of liver metastases from lung cancer. Front Oncol 12: 877273, 2022.
40. Bachu VS, Kedda J, Suk I, Green JJ and Tyler B: High-Intensity focused ultrasound: A review of mechanisms and clinical applications. Ann Biomed Eng 49: 1975-1991, 2021.
41. Zhou Q, Zhu XQ, Zhang J, Xu ZL, Lu P and Wu F: Changes in circulating immunosuppressive cytokine levels of cancer patients after high intensity focused ultrasound treatment. Ultrasound Med Biol 34: 81-87, 2008.
42. Zhu XQ, Lu P, Xu ZL, Zhou Q, Zhang J, Wang ZB and Wu F: Alterations in immune response profile of tumor-draining lymph nodes after high-intensity focused ultrasound ablation of breast cancer patients. Cells 10: 3346, 2021.
43. Eranki A, Srinivasan P, Ries M, Kim A, Lazarski CA, Rossi CT, Khokhlova TD, Wilson E, Knoblach SM, Sharma KV, *et al*: High-Intensity Focused Ultrasound (HIFU) triggers immune sensitization of refractory murine neuroblastoma to checkpoint inhibitor therapy. Clin Cancer Res 26: 1152-1161, 2020.
44. Yang X, Liao Y, Fan L, Lin B, Li J, Wu D, Liao D, Yuan L, Liu J, Gao F, *et al*: High-intensity focused ultrasound ablation combined with immunotherapy for treating liver metastases: A prospective non-randomized trial. PLoS One 19: e0306595, 2024.
45. Dupré A, Pérol D, Blanc E, Peyrat P, Basso V, Chen Y, Vincenot J, Kocot A, Melodelima D and Rivoire M: Efficacy of high-intensity focused ultrasound-assisted hepatic resection (HIFU-AR) on blood loss reduction in patients with liver metastases requiring hepatectomy: Study protocol for a randomized controlled trial. Trials 18: 57, 2017.
46. Dupré A, Rivoire M, Metzger S, Cropet C, Vincenot J, Peyrat P, Chen Y, Pérol D and Melodelima D: Intra-operative high-intensity focused ultrasound in patients with colorectal liver metastases: A prospective ablate-and-resect study. Ultrasound Med Biol 49: 1845-1851, 2023.
47. Fu J, Li WZ, McGrath NA, Lai CW, Brar G, Xiang YQ and Xie C: Immune checkpoint inhibitor associated hepatotoxicity in primary liver cancer versus other cancers: A systematic review and meta-analysis. Front Oncol 11: 650292, 2021.
48. Li L, Li G, Rao B, Dong AH, Liang W, Zhu JX, Qin MP, Huang WW, Lu JM, Li ZF and Wu YZ: Landscape of immune checkpoint inhibitor-related adverse events in Chinese population. Sci Rep 10: 15567, 2020.