Original Article

Differential organ-specific tumor response to first-line immune checkpoint inhibitor therapy in non-small cell lung cancer—a retrospective cohort study

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Background: Immune checkpoint inhibitors (ICIs) possess remarkable clinical effectiveness in non-small cell lung cancer (NSCLC). Different immune profiles of tumors may play a key role in the efficacy of treatment with ICIs. This article aimed to determine the differential organ responses to ICI in individuals with metastatic NSCLC.

Methods: This research analyzed data of advanced NSCLC patients receiving first-line treatment with ICIs. Major organs such as the liver, lung, adrenal glands, lymph nodes and brain were assessed using the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 and RECIST-improved organ-specific response criteria.

Results: A retrospective analysis was conducted on a total of 105 individuals with advanced NSCLC with programmed death ligand-1 (PD-L1) expression ≥50% who received single agent anti-programmed cell death protein 1 (PD-1)/PD-L1 monoclonal antibodies as first-line therapy. Overall, 105 (100%), 17 (16.2%), 15 (14.3%), 13 (12.4%), and 45 (42.8%) individuals showed measurable lung tumors and liver, brain, adrenal, and other lymph node metastases at baseline. The median size of the lung, liver, brain, adrenal gland, and lymph nodes were 3.4, 3.1, 2.8, 1.9, and 1.8 cm, respectively. The results recorded mean response times of 2.1, 3.4, 2.5, 3.1, and 2.3 months, respectively. Organ-specific overall response rates (ORRs) were 67%, 30.6%, 34%, 39%, and 59.1%, respectively, with the liver having the lowest remission rate and lung lesions having the highest remission rate. There were 17 NSCLC patients with liver metastasis at baseline, and 6 had different responses to ICI treatment, with remission in the primary lung site and progressive disease (PD) in the metastatic liver site. At baseline, the mean progression-free survival (PFS) of the 17 patients with liver metastasis and 88 patients without liver metastasis was 4.3 and 7 months, respectively (P=0.02, 95% CI: 0.691 to 3.033).

Conclusions: The liver metastases of NSCLC may be less responsive to ICIs than other organs. The lymph nodes respond most favorably to ICIs. Further strategies may include additional local treatment in case of oligoprogression in these organs in patients with otherwise sustained treatment benefit.

Keywords: Lung cancer; immune checkpoint inhibitor (ICI); tumor microenvironment (TME); tumor response; organ-specific response rates (OSRRs)

Submitted Dec 08, 2022. Accepted for publication Feb 16, 2023. Published online Feb 25, 2023.
doi: 10.21037/tlcr-23-83
View this article at: https://dx.doi.org/10.21037/tlcr-23-83

Introduction

Lung cancer has the highest morbidity and death rates around the world (1). Among lung cancers, approximately 80–85% are non-small cell lung cancer (NSCLC). Most individuals with NSCLC have already reached an advanced stage by the time of diagnosis and have a poor prognosis. The leading cause of the high mortality of NSCLC is local recurrence and distant metastasis (2). The most common locations for metastasis are the brain, liver, bones, and adrenal gland (3).

Systemic therapy has lately made great strides toward the treatment of advanced NSCLC. Recently, programmed cell death protein 1 (PD-1)/programmed cell death-ligand 1 (PD-L1) as the target of immune checkpoint inhibitors (ICIs) has heralded a revolution in the treatment of driver gene-negative NSCLC, improving the 5-year survival rate of individuals at an advanced stage of this disease (4). Investigations of the action mechanisms of ICIs revealed that they induce anti-tumor effects by reactivating exhausted T cells and therefore, rejuvenating anti-tumor immunity (5,6). In the treatment of metastatic urothelial carcinoma, ICIs can achieve complete remission in lymph node metastases, whereas liver metastases show therapeutic resistance (7). At present, the lymph nodes, lungs, and skin are believed to be the sites that benefit the most from anti-tumor immunity, which may be attributed to increased immune cell infiltration levels in specific organs (8). In a study on the application of ICIs in the treatment of primary liver cancer, the remission of extrahepatic lesions was significantly better than that of intrahepatic lesions (9). Hence, the therapeutic impact of ICIs may possibly be influenced by different tumor microenvironments (TMEs) of different organs.

In the immune system, for T cells to exert cytotoxicity, they must overcome the influence of basal cells, other immune cells, and their secreted factors. This indicates that the immune response of T lymphocytes is regulated by various cells and components in the TME (10). Data obtained from melanoma patients suggests that the function of ICIs depends on the presence or absence of immune cells during tumor metastasis (11). Lymph nodes exhibit significant interactions with the adaptive immune system, numerous immune cells, and specific antigen-presenting cells (APCs). Recent reports have shown that tumor infiltrating lymphocytes (TILs) are linked to a better response rate to inhibitors of cytotoxic T-lymphocyte associated protein-4 (CTLA-4) in lymph node metastases (12). In addition, as an inhibitory immune regulator, the liver can suppress immune responses and lead to immune tolerance (13). Research has found that compared with patients without liver metastases, those with melanoma and NSCLC accompanied by liver metastases show worse response rates to anti-PD-1 inhibition and poor progression-free survival (PFS) (14). Moreover, insufficient responses are associated with a low level of $CD8^+$ infiltration.

In summary, immune cell infiltration varies according to the affected organ. We proposed that the response to ICIs would be different for different organ locations. This study aimed to analyze the ICI response of different organs in individuals with NSCLC. Therefore, we analyzed the organ-specific response rates (OSRRs) to ICIs in a group of individuals with NSCLC. Understanding the ICIs'

Highlight box

Key findings

- NSCLC with liver metastases is less responsive to ICI as compared to other metastatic sites. ICI has a good effect on lymph and lung tumors.

What is known and what is new?

- Patients with melanoma and NSCLC with liver metastases show remarkably worse response rates to anti-PD-1 inhibition and poor PFS.
- The liver metastases of NSCLC may be less responsive to ICIs than other organs. The lymph nodes respond most favorably to ICIs.

What is the implication, and what should change now?

- It can be used to identify patients with metastatic NSCLC who can receive locally additive therapy.

varying activity in different organs is clinically significant for radiotherapy monitoring. It can identify patients with metastatic disease who may benefit from locally additive therapy. We present the following article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-83/rc).

Methods

This was a retrospective, single-center study to explore the response of NSCLC and its recurrence after PD-1/PD-L1 monoclonal antibody treatment. In addition to ORR, PFS, and overall survival (OS), our team also investigated the OSRR and cumulative incidence of organ-specific progression (OSP) in various organs to reveal the potential diversity of PD-1/PD-L1 activity.

Study population

In total, 105 individuals with stage IV NSCLC with PD-L1 expression ≥50% and receiving PD-1/PD-L1 antibody treatment every 3 weeks as first-line therapy were included. All patients were treated at Shanghai Pulmonary Hospital between January 2019 and December 2021. Enrolled patients included only those with measurable diseases. Measurable lesions were defined as those with at least 1 diameter that could be accurately measured, and the maximum diameter of lesions were recorded, with lymph node being the shortest diameter, and imaging studies were utilized to assess efficacy. Other inclusion criteria included an Eastern Cooperative Oncology Group physical status of 0 or 1, no autoimmune disease, and no platinum drug treatment. Enrolled patients had not taken corticosteroids (prednisone of 10 mg or more) or antibiotics for 14 days (or more) prior to treatment. Clinical data were retrieved from medical record systems. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The Ethics Committee of Shanghai Pulmonary Hospital approved this study (No. K22-067Y) and individual consent for this retrospective analysis was waived.

Radiological analysis

Overall response rate (ORR) and OSRR were evaluated on serial computed tomography (CT) scans employing the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (15). CT was scheduled to be performed every 2 months until progressive disease (PD) as per the RECIST, death, or refusal of the patient, whichever occurred first. CT analysis was carried out utilizing a third-generation dual-source CT system (Siemens, Erlangen, Germany). Employing the CareDose and CarekV algorithms, the product of tube voltage and current time could be automatically adjusted according to the patient's habitus. Furthermore, 2 mm thick slices and 1 mm slices were reconstructed using soft tissue convolution filters. According to RECIST 1.1 standards, axial imaging was performed on 5 lesions by two skilled radiologists using an electronic ruler tool with up to 2 measurements per lesion. In OSRR, there are up to 5 targets per organ. Lesions not identified at baseline, including pathological lymph nodes, could be tracked for the presence or absence of established progression. Lymph nodes were divided into organs showing the largest lesion diameter, as defined for other organ locations in RECIST 1.1. Two qualified radiologists assessed the distinction between primary and other organ metastases.

Statistical analysis

The reverse Kaplan-Meier method was used to measure the median follow-up time. OS was defined as the time from initiation of treatment to time of death. PFS was measured from the start of the first ICI to the progression according to RECIST1.1 or death due to any reason, whichever occurred first. The duration of treatment (TTD), from the date of the first ICI treatment to the end of the last course of treatment, was determined. Patients who were still alive and having no progression were censored at the last tumor assessment. ORR represented the patients who achieved the best overall response in either complete remission (CR) or partial remission (PR); OSRR was defined as the percentage of patients who had CR or PR as the best response of the target lesions in a specific organ assessed according to RECIST 1.1. The disease control ratio (DCR) was the percentage of individuals with the best overall response in CR, PR, or stable disease (SD). Organ-specific disease control rate (OSDCR) referred to the optimal organ-specific response in individuals with the lowest CR, PR, or SD. Early presentation of RECIST PD or death can avoid the observation of OSP because CT scans are performed before RECIST PD, death, or patient rejection. Therefore, OSP timing is estimated in terms of competing risks, which treat RECIST PD and death as competing risks. The analysis procedure was implemented by R software (version 3.3.3, R Foundation for Statistical Computing, Vienna,

Table 1 Baseline patient characteristics

Characteristic	N (%)
Gender	
Male	62 (59.0)
Female	43 (41.0)
Age (years)	
≥60	67 (64.0)
<60	38 (36.0)
Histological subtype	
Adenocarcinoma	63 (63.2)
Squamous	32 (24.3)
Adenosquamous	10 (12.5)
TNM stage	
I–IIIA	42 (39.7)
IIIB–IV	63 (60.3)
Tobacco	
Current smoker	45 (43.0)
Former smoker	52 (49.0)
Never smoker	8 (8.0)
Median pack years	40
ECOG	
1	70 (66.7)
2	35 (33.3)

TNM, tumor-node-metastasis; ECOG, Eastern Cooperative Oncology Group.

Austria).

Results

Baseline patient characteristics

In total, 105 patients were included in this study, with an average follow-up of 14 months. Most of the individuals had adenocarcinoma (63.2%) and either had previously been a smoker (49%) or were an active smoker (43%), and very few had never smoked (8%). Details of patients and tumors are shown in *Table 1*. Prior to the commencement of ICI treatment, the metastatic target lesions were lymph nodes (42.9%, n=45), liver (16%, n=17), adrenal glands (12%, n=13), and brain (12.3%, n=15). A total of 5 patients (4.8%) were treated for brain metastases, which were considered non-targeted. In bone, 16 (15%) had non-targeted lesions.

Overall and organ-specific responses

Overall, 105 (100%), 17 (16.2%), 15 (14.3%), 13 (12.4%), and 45 (42.8%) individuals showed measurable lung tumors and liver, brain, adrenal, and other lymph node metastases at baseline, respectively. Organ-specific responses were evaluated in these patients. The respective median sizes of the tumors measured in lung tumors and liver, brain, adrenal, and lymph node metastases were 3.4, 3.1, 2.8, 1.9, and 1.8 cm. The organ-specific ORRs of lung tumors and liver, brain, adrenal, and lymph node metastases were 67%, 30.6%, 34%, 39%, and 59.1%, respectively (*Table 2*). The median response time for lung tumors and liver, brain,

Table 2 Median of mean tumor sizes and organ-specific responses to ICIs in NSCLC

Evaluation	Lung (n=105)	Liver (n=17)	Brain (n=15)	Adrenal (n=13)	Lymph node (n=45)
Median tumor size (cm)	3.4	3.1	2.8	1.9	1.8
Organ-specific response, %	67	30.6	34	39	59.1
Complete response, n (%)	0 (0.0)	0 (0.0)	1 (6.7)	1 (7.7)	3 (6.7)
Partial response, n (%)	65 (61.9)	4 (29.4)	5 (33.3)	5 (38.4)	20 (44.4)
Stable disease, n (%)	30 (28.6)	3 (17.6)	4 (26.7)	6 (46.1)	10 (22.2)
Progressive disease, n (%)	10 (9.5)	10 (58.8)	6 (40.0)	2 (15.4)	12 (26.7)

ICIs, immune checkpoint inhibitors; NSCLC, non-small cell lung cancer.

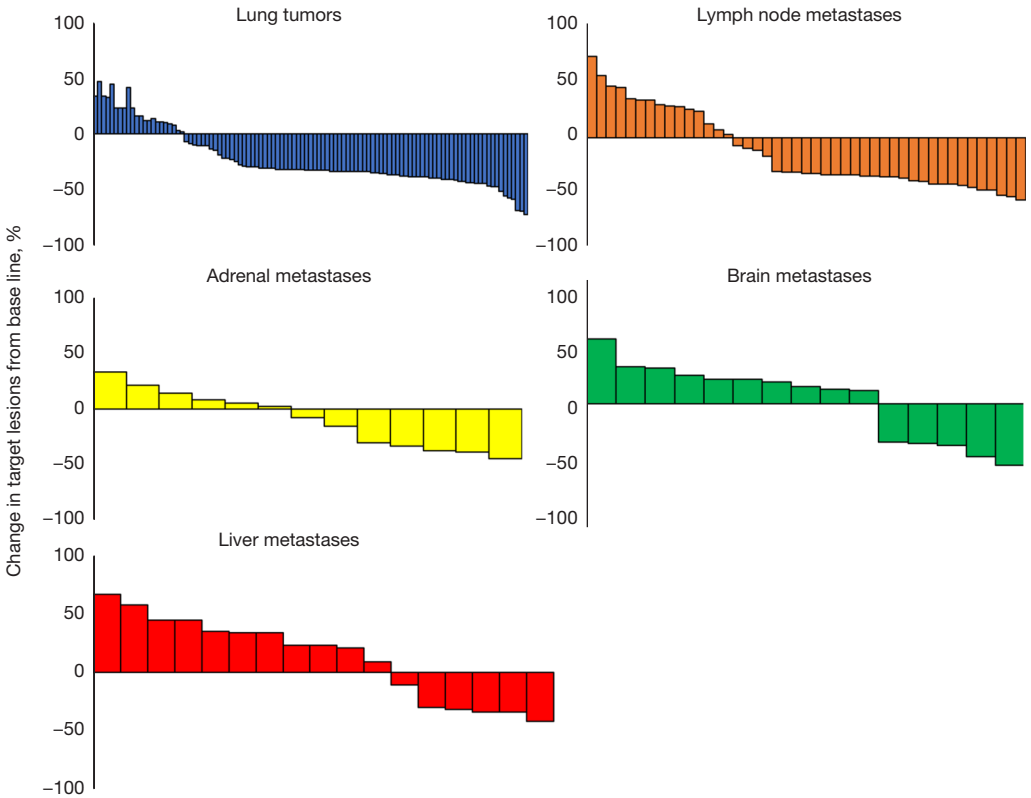

Figure 1 Best percentage change over time (month, from baseline) in tumor burden in various organ systems.

adrenal, and lymph node metastases were 2.5, 3.1, and 2.3 months, respectively. *Figure 1* is the best percentage change over time (from baseline) in tumor burden in various organ systems. For bone metastases, there was no formal response assessment because only unmeasured non-target lesions were included; however, 9 out of 12 cases experienced progressive changes throughout the study.

At baseline, the median PFS of the 17 patients with liver metastasis and 88 patients without liver metastasis was 4.3 and 7 months, respectively (P=0.02, 95% CI: 0.691–3.033). The median PFS of patients with adrenal metastasis and without adrenal metastasis at baseline was 5 and 7 months, respectively (P=0.001, 95% CI: 0.012–0.154). The median PFS of individuals with and without brain metastasis at baseline was 5.9 and 7 months, respectively (P=0.01, 95% CI: 0.441–1.618). The median PFS of the individuals with lymph node metastasis and without lymph node metastasis at baseline was 6.5 and 7 months, respectively (P=0.31, 95% CI: 6.084–6.310 (*Figure 2*).

In total, the cumulative incidence probability of OSP at 6 months was 31% in the brain, 34% in the liver, 32% in adrenal, and 47% in lymph node metastases (*Figure 3*).

Individuals with organ-specific differential responses

In total, 17 patients at baseline had both lung and liver metastases. Different responses were shown by 6 patients to ICI treatment. A total of 13 individuals showed disease control (CR, PR, or SD) in lung tumors, whereas 6 patients had PD in liver tumors. The median lung tumor size was smaller in the 6 patients with PD in the liver (2.0 cm, range, 1.0–13.1 cm) than in the 4 patients with PD in both lung and liver metastases sites (2.7 cm, range, 1.1–6.1 cm). Differential responses to ICI treatment shown by some typical cases are demonstrated in *Figure 4*.

Discussion

Response patterns to ICIs therapy are clinically relevant due to their ability to guide the progression of radiological monitoring and determination of oligonucleotides. The understanding of tumor response patterns to ICIs in different organs of metastasis NSCLC is insufficient. We retrospectively analyzed the data from 105 patients with metastatic NSCLC who received ICIs and found that the

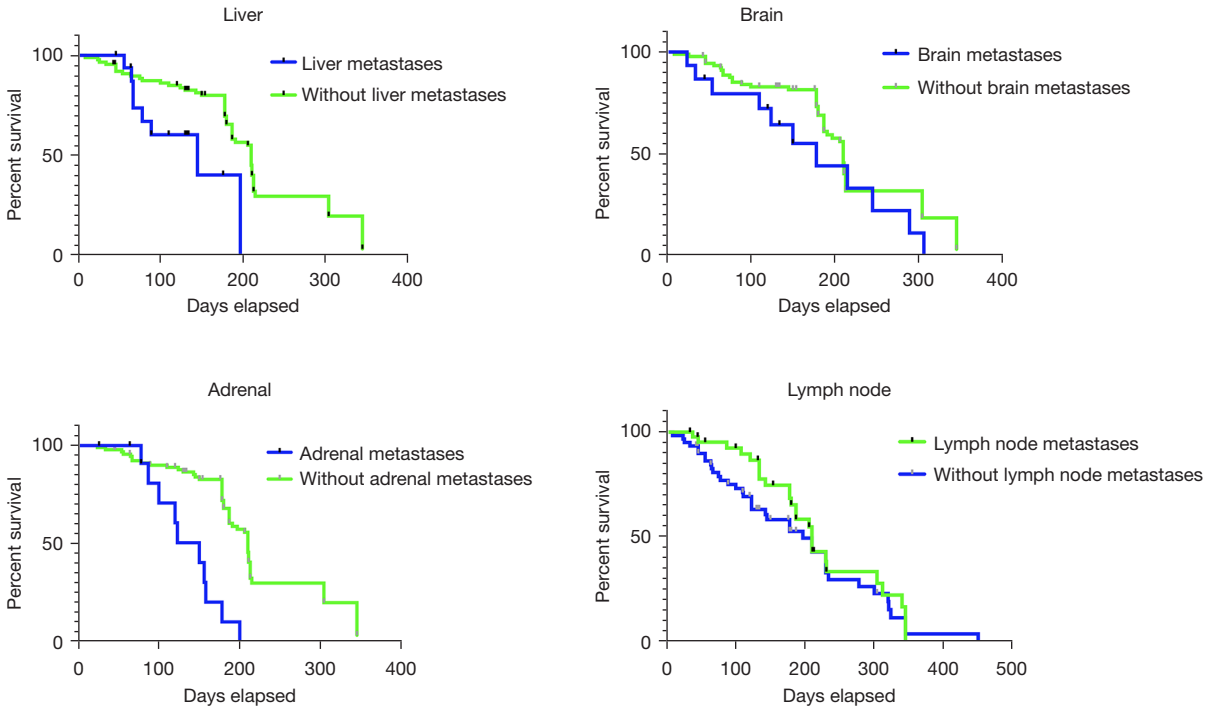

Figure 2 Kaplan-Meier curves of PFS of individuals with advanced NSCLC treated with ICIs. PFS, progression-free survival; NSCLC, non-small cell carcinoma; ICIs, immune checkpoint inhibitors.

tumor response to ICIs varied significantly depending on the tumor site. This study also indicated that individuals with NSCLC treated with ICIs showed an ORR of 67% and a median PFS of 7 months, which is consistent with the published literature (16-18).

In addition to lung cancer, other solid tumors have also shown mixed responses to immunotherapy (19-22). In the phase I KEYNOTE-001 study, the subgroup of individuals with metastatic melanoma was analyzed; the highest rate of CR (42.3%) was in lung lesions, followed by peritoneal (37.3%) and liver (24.4%) (23). The findings of this research are in line with the recently published NSCLC cohort by researchers demonstrating higher OSRR and OSDCR in patients with lymph node metastases, also supporting the concept of better response in organs with postulated high pre-treatment immune cell infiltration (24). In addition, the discoveries in this study substantiate previously published studies reporting poorer activities in liver metastases (25), where the liver exhibits suppressive immune modulation attributes (13).

Lymph nodes have a higher response rate and disease control compared to other organs, with a lower cumulative incidence of OSP probabilities before overall progression or death. According to RECIST, despite overall progression, disease control continued in most patients with lymph node metastases and, in most organ locations, there was overall high concordance with OSRR. As the organs involved are small and the number of targets in these regions is small, little is known about the response rates of the brain, adrenal glands, and soft tissues. The adrenal glands are believed to have immunomodulatory functions (26,27), and a cohort study by Nishino *et al.* showed that the adrenal glands had a higher RR on a pathological basis (28). In contrast to these findings, both OSRR and OSDCR were low in the adrenals in our cohort, though the small number of patients with adrenal metastasis prohibited a conclusive statement. Compared with other organs, the effect of ICI on adrenal metastasis needs to be further explored.

The lungs are constantly in contact with pollutants and pathogens. Therefore, they are rich in specific alveolar macrophages and dendritic cells (DCs). Specific APCs promote T-cell responses to viral and bacterial infections. Therefore, this research group believes that in terms of immunity, OSRR and OSDCR have high biological activity in primary lung tumors. However, the role of ICIs in lung metastases and primary lung tumors remains a mystery.

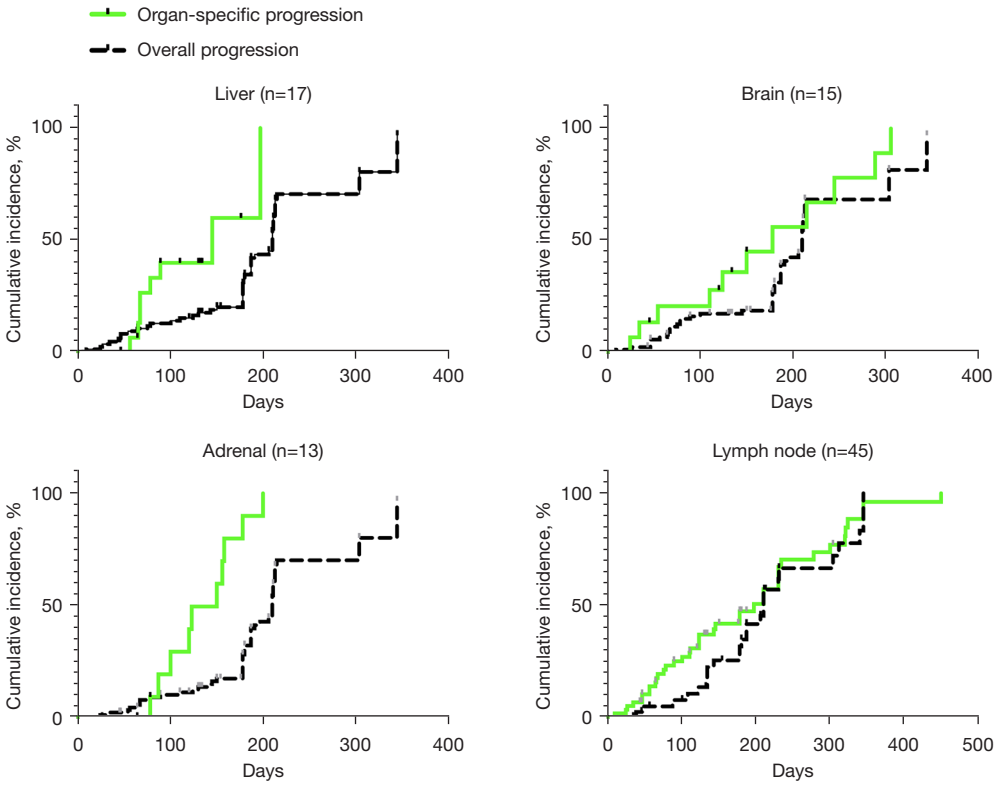

Figure 3 Cumulative incidence probability of organ-specific progression employing competing risk approach.

The liver is a specialized organ that is persistently subjected to multiple digestive tract antigens. Therefore, the liver possesses many cellular or molecular mechanisms in its tolerance microenvironment (29). Preclinical and clinical research has demonstrated that macrophages residing in the liver and Kupffer cells can induce T-cell inhibition in the liver (30). Other immunosuppressive cells, such as regulatory T cells, myeloid-derived suppressor cells (MDSCs), tumor-associated macrophages, hepatic stellate cells, hepatocytes, and other similar cells have also been demonstrated to play a role in liver immunosuppression (31). Previous study has shown that among liver cancer patients receiving systemic chemotherapy, patients without intrahepatic lesions had higher ORR values (32). How to overcome the unfavorable immunosuppressive mechanisms in the microenvironment of the liver to improve the efficacy of immunotherapy needs further investigation.

Immune-linked response criteria have been introduced in melanoma (33), which have not been used in NSCLC studies. RECIST 1.1 does not incorporate different treatment activities into different organ sites, which has important clinical implications in the context of the minimal progression of bone or adrenal metastases, as it might help in the identification of a number of individuals who could benefit from the continued ICIs therapy to control disease, such as those with lymph nodes metastases. Local ablative therapies such as radiotherapy to the site of the progressive organ and continued ICIs therapy may be applied. This strategy maximizes the benefit of immunotherapy in patients with molecule-driven changes in *EGFR* and *ALK* (34). In addition, retrospective data and a recently published small randomized prospective phase II trial (35,36) show that radiotherapy can enhance tumor antigen release, antigen presentation, and T-cell infiltration. Therefore, the application of stereotactic radiotherapy for individual cancer progression sites will be a very meaningful research direction.

This study has certain shortcomings. First, the number of subjects was limited. Therefore, this study needs to be validated with a larger population. Second, it is essential to give particular attention to one of the endpoints, the cumulative incidence of OSP. Since CT was not analyzed in this retrospective study and the patient had RECIST PD prior to OSP, a competing-risk survival analysis was

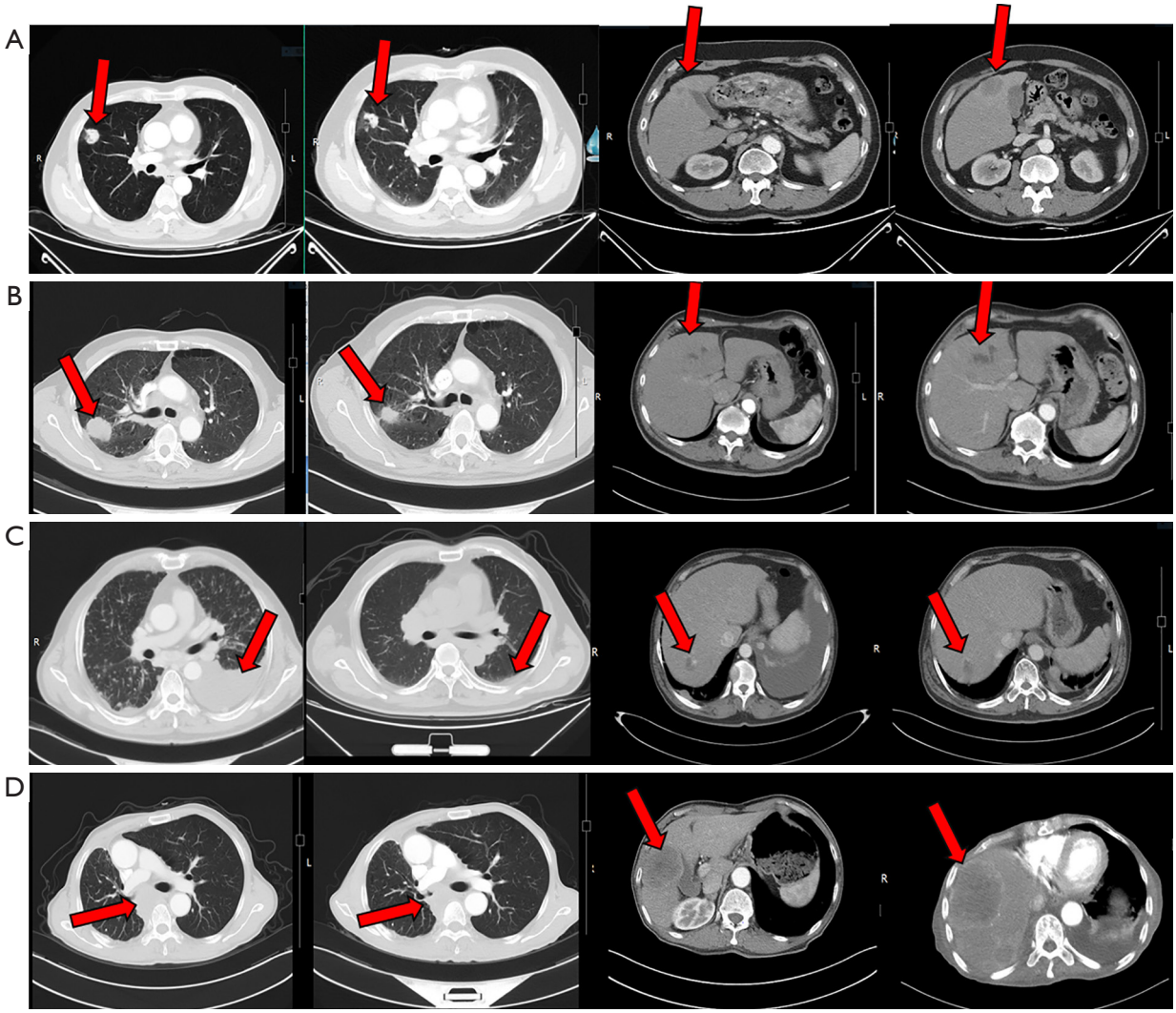

Figure 4 Representative images show differential responses in different organ systems. Four individuals (A-D) had regressed lung metastases but progressed hepatic tumors after being treated with ICIs. The left and right panels demonstrate image studies carried out before and after ICI treatment, respectively. Arrows point to tumor sites with differential responses. ICI, immune checkpoint inhibitor.

selected to calculate RECIST PD or OSP before death, which is slightly different from the cumulative incidence of OSP. Finally, this study did not explore the mechanisms underlying the abnormal response of different organs to ICI. It is a difficult task to simultaneously extract tumor specimens from different human tissues. The use of various preclinical models can assist in the local identification of cellular and molecular mechanisms.

Conclusions

In summary, we discovered that the response of ICI to different organs in advanced NSCLC was different. NSCLC with liver metastases is less responsive to ICI as compared to other metastatic sites. ICIs have a good effect on lymph and lung tumors, and their basic mechanism needs to be further explored.

Acknowledgments

The authors appreciate the academic support from the AME Lung Cancer Collaborative Group.

Funding: This study was supported by grants from the "Dream Tutor" New Person Cultivation Program of

Shanghai Pulmonary Hospital (No. fkxr1907), National Natural Science Foundation of China (No. 81803101 and No. 82072568), and Science and Technology Commission of Shanghai Municipality (No. 19411950300).

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-83/rc

Data Sharing Statement: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-83/dss

Peer Review File: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-83/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-83/coif). MP serves as an unpaid editorial board member of *Translational Lung Cancer Research* from October 2021 to September 2023. MP reports grants from BMS, AZ, MSD, Lilly, Janssen, Roche. In-Jae Oh reports consulting fees from Merck Sharp & Dohme, Ono Pharma, and Roche. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The Ethics Committee of Shanghai Pulmonary Hospital approved this study (No. K22-067Y) and individual consent for this retrospective analysis was waived.

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Cite this article as: Wang Q, Fang Y, Li C, Leong TL, Provencio M, Oh IJ, Zhang Z, Su C. Differential organ-specific tumor response to first-line immune checkpoint inhibitor therapy in non-small cell lung cancer—a retrospective cohort study. Transl Lung Cancer Res 2023;12(2):312-321. doi: 10.21037/tlcr-23-83