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RESEARCH PAPER

Metastatic sites as predictors in advanced NSCLC treated with PD-1 inhibitors: a systematic review and meta-analysis

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ABSTRACT

Background: Programmed cell death protein 1 (PD-1) inhibitors are the first-line treatment for advanced non-small-cell lung cancer (NSCLC) patients. However, their efficacy in metastatic NSCLC patients remains controversial.

Aim of the study: The aim of our study was to evaluate the prognosis of advanced metastatic NSCLC patients treated with PD-1 inhibitors, and discuss the predictive effect of metastatic site on the long-term outcome.

Methods: The Embase, Ovid Medline, Cochrane Central Register of Controlled Trials, and PubMed databases were systematically screened up to February 10, 2020. Twenty-five eligible studies, involving 8,067 patients that assessed the impact of metastatic sites on survival outcome were incorporated in our study. Overall survival (OS) and progression-free survival (PFS) were described as hazard ratio (HR) with 95% confidence interval (CI).

Results: Among the advanced NSCLC patients, the median proportion of brain, liver, bone, and adrenal gland metastases were 21%, 17%, 35%, and 21%, respectively. Patients with metastases to the brain, liver, and bone had worse OS compared to patients without these metastases when treated with PD-1 inhibitors. Similarly, patients with metastasis to the brain and liver were more likely to progress when treated with PD-1 inhibitors. Besides, patients with multiple metastatic sites had worse PFS compared to patients with one metastatic site, while no significant difference was found in terms of OS.

Conclusions: Based on the findings of our systematic review and meta-analysis, metastatic sites were independent predictors of the survival outcome for advanced NSCLC patients treated with PD-1 inhibitors.

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Introduction

Lung cancer is the most common malignancy worldwide and has the highest mortality rate among all types of malignant tumors.[1,2] Non-small-cell lung cancer (NSCLC) accounts for approximately 80% of all lung cancers.[3] Due to the lack of early symptoms, 70–80% of patients are diagnosed in advanced stages and lose the opportunity for surgery. Chemo-, radio-, and molecular targeted-therapies remain the main treatment options for such patients, but the 5-y survival rate is <50%.[4] The main limitation of chemo- and radiotherapy is that they often cause serious adverse reactions and affect the quality of life of the patient.[5] In the past decade, molecular targeted-therapy has become a hot spot with a low incidence of adverse reactions, although the problem of drug resistance has gradually become apparent.[6] Due to the limitations of the above treatment modalities, immunotherapy has gained considerable attention for the treatment of NSCLC.

Programmed cell death protein 1 (PD-1) is an important immunosuppressive molecule, which is expressed on T cells, and regulates its activity in the peripheral tissues.[7] PD-1 has two ligands, PD-L1 and PD-L2, which are widely expressed on a variety of immune effector, antigen-presenting, and tumor cells.[8] According to previous studies, the PD-1/PD-L1 signaling pathway is overexpressed in the tumor microenvironment, and tilts the immune balance in favor of immunosuppression, abnormally strengthens the negative immune effect, and inhibits T cell activation.[8,9] Thus, the tumor cells escape from immune cell-mediated cell death, and proliferate and metastasize without being controlled by the body's defense mechanism.[10] In recent years, PD-1/PD-L1 inhibitors have made breakthrough progress in the treatment of NSCLC. Randomized controlled clinical trials such as the CheckMate017, CheckMate057, KEYNOTE010, and OAK have made nivolumab, pembrolizumab, and atezolizumab the second-line treatment options for advanced NSCLC.[11–14] Pembrolizumab has also changed the first-line treatment model for advanced lung cancer and has become one of the first-line treatment drugs for NSCLC recommended by the National Comprehensive Cancer Network clinical practice guidelines.[15]

Currently, PD-1/PD-L1 inhibitors are approved for first-line or second-line treatment of advanced NSCLC, and relevant clinical trials have been carried out widely. However, data pertaining to their safety and effectiveness in the treatment of NSCLC are still contentious. Whether PD-1 treatment is

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advantageous, especially in patients with metastasized NSCLC, remains controversial. Therefore, in this systematic review and meta-analysis, we aimed to explore the relationship between metastatic sites prior to PD-1 treatment and the long-term survival of those NSCLC patients.

Methods

This study was designed and reported in accordance with the preferred reporting items for systematic review and meta-analysis (PRISMA) guidelines.[16]

Study search strategy and identification

The Embase, Ovid Medline, Cochrane Central Register of Controlled Trials, and PubMed databases were systematically searched up to February 10, 2020. A comprehensive search was performed using the following search terms: PD-1, pembrolizumab, nivolumab, atezolizumab, durvalumab, JS001, IBI308, immune checkpoint inhibitor, immune checkpoint blockade, immune checkpoint therapy, and NSCLC. Both keywords and medical sub-headings terms were used in the search. All studies containing titles and abstracts were imported into Endnote for deleting duplications and screening the literature.

Inclusion and exclusion criteria

Studies satisfying the following inclusion criteria were selected for the analysis:[1] Clinical trials investigating advanced NSCLC treated with PD-1 inhibitors;[2] Studies discussing the impact of different metastatic sites on survival outcome;[3] Patients diagnosed with metastases prior to treatment with PD-1 inhibitors;[5] Overall survival (OS) and progression-free survival (PFS) were described as hazard ratio (HR) with 95% confidence interval (CI) or the HR could be extracted by survival plots;[4] If the same population was used by different studies, only study with the longest follow-up time or with the largest sample size was included.

The exclusion criteria were as follows:[1] Study type was a review, comments, and case report;[2] NSCLC patients were not treated with PD-1 inhibitors;[3] Studies included other types of cancer;[4] Metastases data or survival outcome data could not be extracted;[6] Publication in a language other than English.

Data extraction

Two reviewers independently evaluated the titles and abstracts according to the inclusion and exclusion criteria. Disagreement between the two reviewers was resolved by a third reviewer.

The following information was extracted independently from each included studies: Author, publication year, publication center and country, recruitment period, study type, anti-PD-1 treatment, patient characteristics (patient sample, age, gender, smoking status, histology of cancer, tumor stage), metastatic site and patient number, HRs and 95% CIs associated with OS and PFS from univariate or multivariate COX regression analyses.

Quality assessment

The quality of the prognostic studies was evaluated as reported previously.[17] Two researchers (ZL Zhang and WJ Li) independently assessed the quality of the included studies following the criteria:[1] Representativeness of the population;[2] Exposed cohort;[3] Ascertainment of exposure;[4] Outcome assessment;[5] Appropriate measurement and account;[6] Measurement of outcomes;[7] Completeness of follow-up. Studies with a score of >7 were regarded as high-quality studies.

Statistical analysis

Statistical analysis was performed using the Stata 15.1 software (Stata Corporation, College Station, Texas, USA). We used the method of random-effects and fixed-effects model to pool outcomes, which is calculated by HR and 95% CI to estimate the predictor value of different metastatic sites on long-term outcome. The I^2 statistic and χ^2 test were used for heterogeneity assessment between studies. Heterogeneity was considered to exist between studies if $I^2 \geq 50\%$ and the random-effect model would be used. A statistical test with $P < .05$ was considered significant.

Result

Selection of eligible studies

A total of 3,252 articles were identified from the online database search. Figure 1 shows the flowchart of the study selection process. After screening the titles and abstracts, 324 studies were selected for full-text review. Following further assessment of the full-texts, 299 studies were excluded based on the inclusion and exclusion criteria. Finally, 25 studies that met all the criteria were included in the systematic review and meta-analysis.[3,7,18–40]

Characteristics of the studies included and quality assessment

The baseline characteristics of the 25 studies included in the analysis are listed in Tables 1 and 2. A total of 8,067 patients were included in our systematic review. The search was limited to publications between 2017 and 2020, with the recruitment period ranged from 2013 to 2019. The recruited patients were from Europe, Asia, South and North America, and eight studies were from multicenter data. A total of 67% of the patients (range: 23–80%) were males with a median age of 64 y. In terms of the tumor histology, 27% of patients were diagnosed with squamous NSCLC, and 66% were diagnosed with adenocarcinoma. Among the patients, 19% did not have a history of smoking.

Table 2 summarizes the common metastatic sites in advanced NSCLC patients treated with PD-1 inhibitors. The median proportion of brain, liver, bone, and adrenal gland metastases were 21%, 17%, 35%, and 21%, respectively. Five studies reported the proportion of lymph node metastases (median proportion: 57%), three studies reported pleural invasion (median proportion: 30%), and six studies reported intrapulmonary metastases (median proportion: 49%).

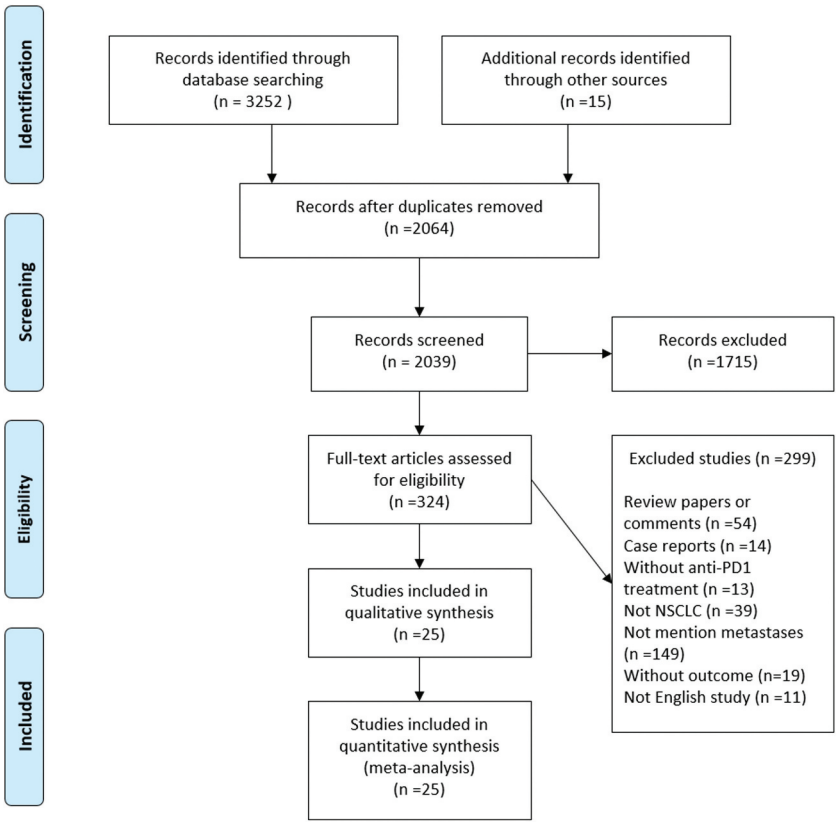

Figure 1. A flowchart of literature screening method.

The assessment of quality between studies was based on the Newcastle Ottawa Scale, which is shown in Table 1. Nine studies were regarded as median quality with scores of 5–6, and remaining sixteen studies were regarded as high-quality with a score of >7.

Survival outcome based on different metastatic site in advanced NSCLC

The impact of various metastatic sites in advanced NSCLC, prior to PD-1 inhibitor treatment, on the OS and PFS is shown in Figure 2 (OS) and Figure 3 (PFS). In terms of OS, the number of studies that discussed the predictive impact of brain, liver, bone, and adrenal gland metastases on OS following immune checkpoint inhibitor treatment was 15, 9, 5, and 1, respectively. The results of meta-analysis showed that patients with metastasis to the brain (HR = 1.25, 95% CI = 1.09–1.44, I^2 = 43.8%, P < .001), liver (HR = 1.73, 95% CI = 1.35–2.20, I^2 = 69.4%, P < .001), and bone (HR = 1.67, 95% CI = 1.30–2.16, I^2 = 64.7%, P < .001) had worse OS than patients without these metastases when treated with PD-1 inhibitors. Similarly, patients with metastasis to the brain (HR = 1.33, 95% CI = 1.14–1.55, I^2 = 48.0%, P < .001) and liver (HR = 1.40, 95% CI = 1.07–1.83, I^2 = 74.7%, P = .015) were more likely to progress than patients without these metastases, when treated with PD-1 inhibitors. There was no significant difference in the PFS when patients were diagnosed with bone, adrenal, or lymph node metastases prior to treatment with PD-1 inhibitors (all P > .05).

Moreover, we summarized the impact of the number of metastatic sites on the OS and PFS (Figure 4). Forest plots showed that patients with multiple metastatic sites had worse PFS than patients with one metastatic site (HR = 1.58, 95% CI = 1.32–1.90, I^2 = 0%, P < .001), while no significant difference was found in terms of OS (HR = 1.43, 95% CI = 0.87–2.34, I^2 = 0%, P = .154). Besides, three studies compared the overall response rate (ORR) in terms of brain metastases, and patients with brain metastases had a lower ORR compared to those without metastases (OR = 1.58, 95% CI = 1.27–1.97, P < .001).

Discussion

To the best of our knowledge, this is the first and largest scale meta-analysis (number of included studies) to analyze the impact of metastatic sites on the prognosis of NSCLC patients. Although several previous studies concluded that tumor metastasis is not a predictor for advanced NSCLC patients when treated with PD-1 inhibitors, [3,18,22] in this review we demonstrate that metastatic site is an important factor related to long-term survival, especially in patients with brain and liver metastasis.

The results of our meta-analysis showed that patients with brain, liver, and bone metastases had worse OS. Similarly, patients with brain and liver metastases were more likely to progress than patients without metastases when treated with PD-1 inhibitors. In addition, we found that patients with brain metastases had a lower response rate than patients without metastases. The findings from our analysis suggest that the

Table 1. The characteristics of included studies.

Author	Publish year	Country	Study type	Anti-PD-1 treatment	Sample	Male, %	Median age	Squamous, %	Adenocarcinoma, %	Never smoking, %	Quality score
Zhang, G. et al.	2020	China	Retrospective	Nivolumab	73	55 (75)	NG	27 (37)	42 (58)	NG	8
Zhang, F. et al.	2020	China	Retrospective	Pembrolizumab, nivolumab	55	41 (75)	55	20 (36)	35 (64)	25 (45)	7
Ruiz-Patino, A. et al.	2020	Multicenter	Retrospective	ICIs	296	177 (60)	64	28 (9)	232 (78)	34 (11)	7
Morita, R. et al.	2020	Multicenter in Japan	Retrospective	Nivolumab	901	651 (72)	67	221 (25)	610 (68)	181 (20)	6
Kawachi, H. et al.	2020	Multicenter	Retrospective	Pembrolizumab	213	176 (83)	71	55 (26)	129 (61)	20 (9)	7
Ruiz-Banobre, J. et al.	2019	Multicenter in Spain	Retrospective	Nivolumab	153	119 (78)	NG	51 (33)	102 (67)	12 (8)	6
Ren, F. et al.	2019	China	Retrospective	Pembrolizumab, nivolumab	147	34 (23)	57	62 (42)	85 (58)	56 (38)	5
Prelaj, A. et al.	2019	Italy	Retrospective	ICIs	193	120 (62)	65	44 (23)	144 (75)	43 (22)	6
Lang, D. et al.	2019	Austria	Retrospective	Nivolumab, pembrolizumab, atezolizumab	153	91 (59)	66	53 (35)	100 (65)	20 (13)	7
Landi, L. et al.	2019	Multicenter in Italy	Prospective	Nivolumab	1788	1029 (58)	66	0	1788 (100)	360 (20)	8
					371	298 (80)	67	371 (100)	0	31 (8)	8
Kuo, C. H. S. et al.	2019	China	Retrospective	Pembrolizumab, nivolumab, atezolizumab, durvalumab	119	87 (73)	59	33 (28)	76 (64)	46 (39)	7
Hendriks, L. E. L. et al.	2019	Multicenter in Europe	Prospective	ICIs	1025	646 (63)	64	268 (26)	681 (66)	77 (8)	7
Gao, G. et al.	2019	China	Retrospective	ICIs	178	74 (42)	64	34 (19)	55 (31)	31 (17)	7
Gadgeel, S. M. et al.	2019	Multicenter	Prospective	Atezolizumab	425	261 (61)	NG	112 (26)	313 (74)	84 (20)	8
Fukui, T. et al.	2019	Japan	Prospective	Nivolumab	52	37 (71)	69	16 (31)	33 (63)	10 (19)	6
Ahn, B. C. et al.	2019	Korea	Retrospective	Pembrolizumab, nivolumab	155	113 (73)	64	47 (30)	105 (68)	51 (33)	7
Tournoy, K. G. et al.	2018	Belgium	Retrospective	Nivolumab	267	193 (72)	66	71 (27)	196 (73)	16 (6)	7
Suh, K. J. et al.	2018	Korea	Retrospective	Pembrolizumab, nivolumab	54	42 (78)	68	17 (31)	37 (69)	15 (28)	8
Tamiya, M. et al.	2018	Japan	Retrospective	Nivolimanb	201	135 (67)	68	42 (21)	142 (71)	44 (22)	6
Shiroyama, T. et al.	2018	Japan	Retrospective	Nivolimanb	201	135 (67)	68	42 (21)	142 (71)	44 (22)	6
Mezquita, L. et al.	2018	Multicenter in Europe	Retrospective	Nivolumab, pembrolizumab, atezolizumab, durvalumab	466	301 (65)	62	159 (34)	270 (58)	NG	7
Garde-Noguera, J. et al.	2018	Spain	Retrospective	Nivolumab	175	128 (73)	61	40 (23)	135 (77)	16 (9)	7
Dumenil, C. et al.	2018	France	Prospective	Nivolumab	67	46 (69)	NG	17 (25)	47 (70)	9 (13)	6
Dudnik, E. et al.	2018	Israel	Retrospective	Nivolumab	260	176 (68)	67	59 (23)	183 (70)	40 (15)	7
Funazo, T. et al.	2017	Korea	Retrospective	Nivolimanb	79	NG	NG	NG	NG	NG	5

Abbreviation: NG: not given; ICIs: immune checkpoint inhibitors.

Table 2. The reported metastatic sites of advanced NSCLC in different studies.

Author	Publish year	Recruitment year	Stage III, %	Stage IV, %	Brain, %	Liver, %	Bone, %	Adrenal gland, %	Lymph node, %	Pleural invasion, %
Zhang, G. et al.	2020	2016–2018	3 (4)	70 (96)	32 (44)	NG	NG	NG	NG	NG
Zhang, F. et al.	2020	2015–2017	NG	NG	17 (31)	9 (16)	16 (29)	NG	NG	NG
Ruiz-Patino, A. et al.	2020	2013–2018	NG	NG	68 (23)	62 (21)	136 (46)	62 (21)	226 (76)	86 (10)
Morita, R. et al.	2020	2016	102 (11)	497 (55)	201 (22)	104 (12)	256 (28)	309 (34)	NG	NG
Kawachi, H. et al.	2020	2017–2018	38 (18)	144 (68)	39 (18)	28 (13)	59 (28)	32 (15)	163 (77)	56 (37)
Ruiz-Banobre, J. et al.	2019	2015–2017	49 (32)	104 (68)	33 (22)	NG	NG	NG	NG	NG
Ren, F. et al.	2019	2013–2017	61 (41)	86 (59)	NG	28 (19)	NG	NG	NG	NG
Prelaj, A. et al.	2019	2013–2019	5 (3)	188 (97)	44 (23)	38 (20)	87 (45)	NG	NG	NG
Lang, D. et al.	2019	2015–2018	19 (12)	134 (88)	31 (20)	NG	NG	NG	NG	NG
Landi, L. et al.	2019	2015–2016	NG*	NG	191 (11)	178 (10)	626 (35)	NG	NG	NG
			NG§	NG	37 (10)	63 (17)	120 (32)	NG	NG	NG
Kuo, C. H. S. et al.	2019	2015–2018	16 (13)	103 (87)	25 (21)	NG	NG	NG	NG	NG
Hendriks, L. E. L. et al.	2019	2012–2018	NG	NG	255 (25)	NG	NG	NG	NG	NG
Gao, G. et al.	2019	2016–2019	NG	NG	12 (7)	13 (7)	NG	NG	NG	NG
Gadgeel, S. M. et al.	2019	2014–2015	NG	NG	61 (14)	NG	NG	NG	NG	NG
Fukui, T. et al	2019	2016–2017	13 (25)	29 (56)	8 (15)	10 (19)	16 (31)	NG	NG	NG
Ahn, B. C. et al.	2019	2014–2019	NG	NG	61 (39)	24 (15)	51 (33)	28 (18)	NG	NG
Tournoy, K. G. et al.	2018	2016	12 (4)	255 (96)	46 (17)	55 (21)	115 (43)	46 (17)	64 (24)	NG
Suh, K. J. et al.	2018	2013–2016	NG	NG	9 (17)	10 (19)	NG	NG	NG	NG
Tamiya, M. et al.	2018	2015–2016	NG	NG	51 (25)	29 (14)	66 (33)	NG	105 (52)	89 (44)
Shiroyama, T. et al.	2018	2015–2016	NG	NG	NG	29 (14)	NG	NG	NG	NG
Mezquita, L. et al.	2018	2012–2016	130 (28)	296 (64)	59 (13)	94 (20)	130 (28)	NG	NG	NG
Garde-Noguera, J. et al.	2018	2015–2016	23 (13)	150 (86)	38 (22)	39 (22)	67 (38)	31 (18)	100 (57)	NG
Dumenil, C. et al.	2018	2015–2016	12 (18)	55 (82)	11 (16)	NG	NG	NG	NG	NG
Dudnik, E. et al.	2018	2015–2016	NG	NG	55 (21)	55 (21)	NG	NG	NG	NG
Funazo, T. et al.	2017	2015–2016	NG	NG	NG	22 (28)	NG	NG	NG	NG

Abbreviation: NG: not given; *: adenocarcinoma cohort; §: squamous.

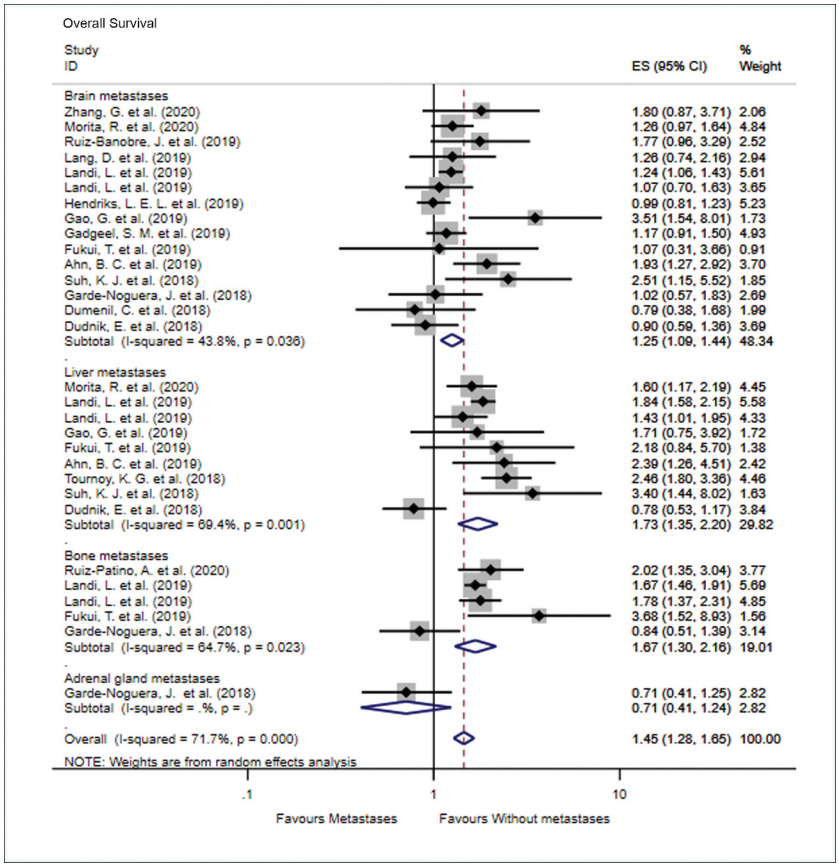

Figure 2. Forest plot of the impact of different metastatic sites on overall survival following PD-1 therapy.

efficacy of treatments may differ depending on the metastatic site.

How metastatic sites contribute to the patient's response to PD-1 inhibitors remains unclear. Metastatic spread of cancers to distant organs is the main cause of cancer-related mortality. NSCLC is prone to intrathoracic dissemination, such as intrapulmonary metastases, pleura, and pericardial invasion. The common distant organs of metastases include bone, brain, liver, and adrenal glands. Some studies have indicated that tumors may exhibit four different biological behavior metastases: tumors that mainly metastasize to local lymph nodes; tumors that are mainly involved in direct invasion; tumors that metastasize into the lung, and those that metastasize through systemic seeding.[41] Oikawa et al. reported that distant organ metastases in lung cancer are nonrandom, and there may be specific patterns of distant metastases in lung cancer patients.[42] Another study showed that when compared to patients with wild-type EGFR, ALK, or KRAS, higher incidence of pericardial, pleural dissemination, and liver metastasis was observed in ALK-positive patients and patients with EGFR mutations had higher incidence of liver metastasis.[43] However, there are limited studies on the correlation between metastatic organs, clinicopathological characteristics, and oncogenes, and the correlations remain inconclusive. Thus, considerable heterogeneity exists among studies that evaluated the relationship between metastatic sites and the long-term outcome following PD-1 inhibitor treatment.

Brain is one of the common metastatic sites in NSCLC. Previous studies have shown that brain metastases from NSCLC account for approximately half of all solid tumors metastasized to the brain.[44] According to statistics, approximately 16–22% of lung cancer patients develop brain metastases.[45] At the same time, brain metastases are also a leading cause of death in patients with NSCLC.[46] Previous studies have reported that patients with lung metastases from lung cancer have a very high mortality rate and their 1-y survival rate is low at approximately 10%.[45,46] Due to the abundant pulmonary blood vessels and lymphatic networks that exist at the NSCLC development site, the cancer cells can enter the skull through the collateral circulation and carotid artery. Besides, lung cancer has the characteristics of a neutrophilic tissue structure and a strong affinity for the brain. Theoretically, the blood-brain barrier is damaged or affected to a certain extent in patients with brain metastases. Most chemotherapeutic drugs, however, are still unable to enter the brain due to their large molecular structure, and so they remain less effective in treating brain metastases.[47] The combination treatment of PD-1 inhibitors with radiotherapy has been a novel attempt at treating brain metastases in NSCLC patients. Schapira et al. conducted a clinical trial in NSCLC patients with brain metastases by treating them with concurrent stereotactic radiosurgery (SRS) and PD-1 inhibitors and showed that the concurrent treatment effectively controlled locoregional disease progression and therefore prolonged long-term OS.[45] Similarly, Shepard et al. demonstrated that concurrent treatment with SRS and PD-1 inhibitors was tolerated and provided more rapid brain metastasis regression.[48] Although several attempts have been undertaken in treating patients with

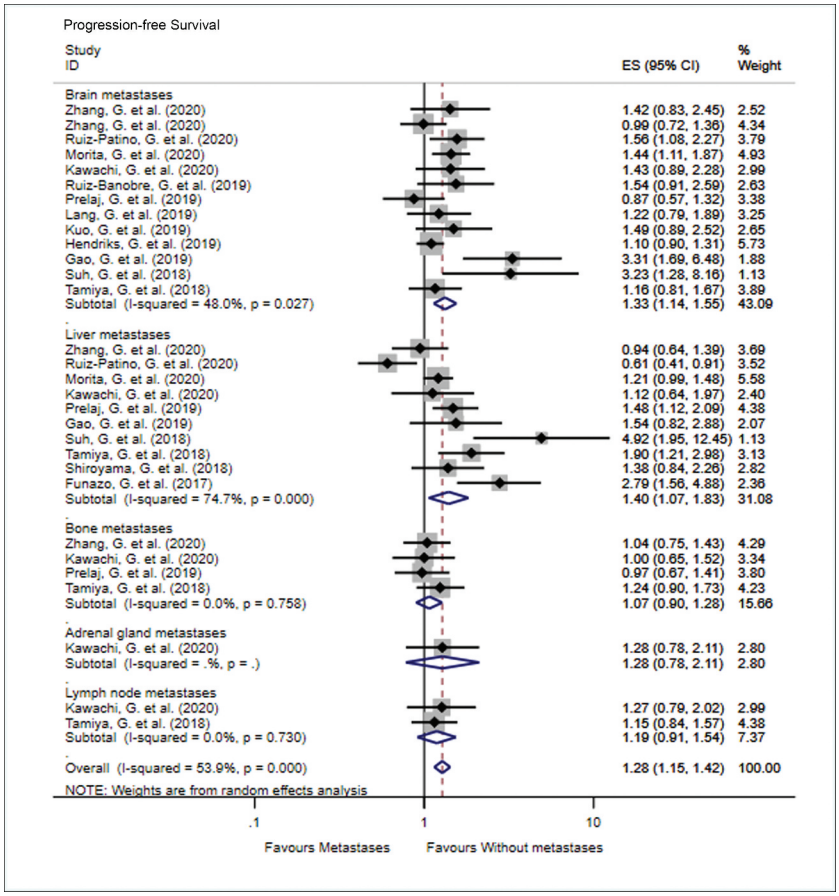

Figure 3. Forest plot of the impact of different metastatic sites on progression-free survival following PD-1 therapy.

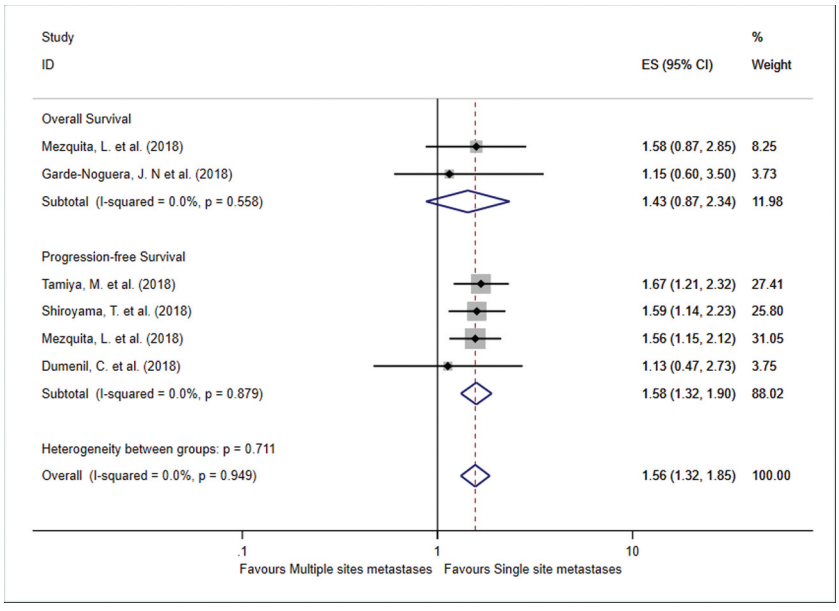

Figure 4. Forest plot of the impact of the number of metastatic sites on survival outcome following PD-1 therapy.

brain metastases, brain metastases remain a predictor for both progression and OS in our meta-analysis.

Bone is another common metastatic site in NSCLC patients, and the incidence of bone metastasis in NSCLC patients is approximately 30–40%.[49] Bone metastases most often involve the central axis bones, including the spine, pelvis, proximal limb bones, and skull, and mainly manifests as osteolytic destruction, which can lead to pain and pathological fractures.[49] Following bone metastasis, the median survival time of NSCLC patient is 6–10 months and the 1-y survival rate after treatment is 40–50%.[49] The bone metastasis cascade is a multi-step process, which mainly includes the following

steps: escape of tumor cells with metastatic ability from the primary tissues and entry into the circulatory system, chemotactic 'homing' and 'settling' to the bone marrow, with active invasion.[50] Besides, the interaction between the metastatic tumor cells and the bone microenvironment plays a vital role in the occurrence and development of bone metastasis.[51] It is now clear that bone marrow can supplant the secondary lymphoid tissue as either a primary immune response or memory response. Further, the bone marrow itself serves as an immune regulatory organ, which affects systemic immunity and therapeutic efficacy of PD-1 inhibitors.[3] Although we did not find a clear association between bone metastases and either OS or PFS, the risk of bone metastases still needs to be considered when PD-1 inhibitors are used for treatment.

Liver metastasis occurs when NSCLC cells that are shed from the primary site enter the liver through blood circulation and continue to grow following liver colonization. Therefore, liver metastases can be single or multiple nodule metastases. Liver metastasis rate of NSCLC at autopsy is 40–61%. Approximately 38–44% of NSCLC patients develop liver metastases throughout the development and progression of the disease.[52] Compared to other metastases, patients with liver metastases respond poorly to chemotherapy, have shorter survival, and poor prognosis. Therefore, liver metastasis is an important factor affecting the prognosis of NSCLC. Currently, several studies have reported that patients with liver metastases may benefit from combined treatment of PD-1 inhibitors with chemotherapy.[53,54] However, in our meta-analysis, liver metastases remained a risk factor associated with worse survival outcome.

Currently, PD-1/PD-L1 inhibitors are used to treat several types of malignancies. In melanoma, the main research focus is currently on PD-1 inhibitors as single agent or combined with Ipilimumab for pre- and post-(neo) adjuvant treatment of high-risk melanoma of stage IIB to III. Although many Phase III clinical trials are still in progress, the current results of PD-1 inhibitors used in adjuvant treatment of middle-advanced resectable melanoma significantly prolonged PFS and reduced the incidence of grade 3 to 4 adverse reactions.[55] More recently, Warner et al. conducted a cohort study and summarized that majority of melanoma patients with confirmed complete response chose to discontinue the PD-1 treatment and the complete response was mostly durable.[56] In bladder cancer, several PD-1 inhibitors were approved by FDA as a second-line treatment in 2017.[57] A Phase I trial (NCT01375842) involving 95 patients with metastatic bladder cancer showed that the partial response rate of the patients was 26%, the median PFS was 2.7 months, and the median survival time was 10.1 months. Among them, 40% had PD-LI expression of ≥5%, and their median survival time was 14.6 months, [58] which indicated that detection of PD-L1 expression level is of considerable significance for tumor immunotherapy. More recently, Phase 1b trials published the efficacy of combination of lenvatinib plus pembrolizumab in patients with unresectable hepatocellular carcinoma, which indicated that the combination treatment could prolong the lifespan of advanced liver cancer patients with median PFS of 9.3 months.[59] Besides, a single-arm, Phase 1b-2 trial (CP-MGAH22-05) was conducted to treat HER2-positive gastroesophageal adenocarcinoma patients and the combination of anti-HER2 agent and anti-PD-1 checkpoint blockade was found to be safe and well tolerated, and ORR was observed in 18% of the patients with malignancy.[60] Nevertheless, treatment with PD-1/PD-L1 inhibitors remains promising although attention must be paid to the associated toxicity.

Some limitations of our study need to be acknowledged. First, although we used the random-effect model to decrease the effect of weight in different studies, we could not entirely eliminate the heterogeneity between studies. The heterogeneity existed in two parts: (a) PD-1 expression may be different between primary tumors and metastatic sites. Generally, the inclusion criteria in different studies may consider tumors expressing higher PD-1 expression were, the better the response may the patients have. However, majority of advanced stage patients were biopsied in the primary tumors. Thus, primary tumors with high expression of PD-1 may be cured by PD-1 inhibitors, however, whether the metastatic sites have the same expression of PD-1 as the primary tumor remains controversial. (b) Metastatic sites may have a different genetic profile compared to the primary site. Different PD-1 inhibitors may be effective in different kinds of mutations or mismatches. Thus, the primary tumors may benefit from one PD-1 inhibitor, while the metastatic sites may benefit from another. Second, most of the studies were retrospective studies and very few studies were prospectively designed for advanced metastatic NSCLC patients treated with PD-1 inhibitor. Besides, chemotherapy and radiotherapy were used in the treatment in some studies, which may increase the bias between different studies. Further multicenter and prospective studies need to be undertaken in NSCLC patients with metastases.

Conclusion

Our systematic meta-analysis suggests that metastatic sites are independent predictors of survival outcome in advanced NSCLC patients treated with PD-1 inhibitors. Combination of treatments is needed to target the different metastatic sites.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

Author's contribution

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