SPANDIDOS PUBLICATIONS

ONCOLOGY LETTERS 28: 489, 2024

# Immune checkpoint inhibitors with or without radiotherapy in metastatic non-small cell lung cancer: A meta-analysis and literature review

ISAH ADAMU DANBALA[1,2], SHENGQIAO FU[1], WANYING SHENG[1], HAOWEN TANG[1], MAHMUD ABDULKADIR MAGASHI[2,3] and XU WANG[1]

[1]Department of Radiation Oncology, Institute of Oncology, Affiliated Hospital of Jiangsu University, Zhenjiang, Jiangsu 212001, P.R. China; [2]Overseas Education College, Jiangsu University, Zhenjiang, Jiangsu 212013, P.R. China; [3]Department of Gastrointestinal Surgery, Affiliated People's Hospital of Jiangsu University, Zhenjiang, Jiangsu 212002, P.R. China;

Received January 21, 2024; Accepted July 3, 2024

DOI: 10.3892/ol.2024.14622

**Abstract.** The combination of immune checkpoint inhibitors (ICIs) and radiotherapy has shown promise in the treatment of metastatic non-small cell lung cancer (NSCLC). The present meta-analysis aimed to determine the efficacy and safety of combining radiotherapy (RT) ICIs for the treatment of metastatic NSCLC. PubMed, Google Scholar, the Cochrane Library and Web of Science databases were searched for relevant articles up to February 1, 2023. Post-therapy outcomes such as progression-free survival (PFS), complete response, partial response (PR), progressive disease (PD), stable disease and adverse events (AEs) were analyzed. The meta-analysis was performed using RevMan 5.4 software. A total of seven studies involving 682 patients were included (384 patients who received ICI + RT vs. RT and 298 patients who received ICI + RT vs. ICI alone). No significant difference in PFS was demonstrated between the ICI + RT group and the RT group (heterogeneity: $\chi^2$=2.35; df=1; P=0.13; $I^2$=57% and test for overall effect: Z=0.10; P=0.92). Conversely, patients in the ICI alone group had significantly decreased PR rates (heterogeneity: $T^2$=0.00; $\chi^2$=2.13; df=3; P=0.54; $I^2$=0% and test for overall effect: Z=2.57; P=0.01) compared with patients in the ICI + RT group. The ICI + RT group also had significantly lower rates of PD (heterogeneity: $T^2$=0.00; $\chi^2$=0.91; df=3; P=0.82; $I^2$=0% and test for overall effect: Z=2.52; P=0.01) compared with the ICI alone group. Safety analysis revealed no significant difference between patients who received ICI + RT and those who received RT in terms of grade 1 or 2 AEs. In conclusion, the combination of ICIs + RT demonstrates promising efficacy and safety for patients with metastatic NSCLC. However, clinical trials that have tested this combination are lacking, which emphasizes the need for further research.

*Correspondence to:* Professor Xu Wang, Department of Radiation Oncology, Institute of Oncology, Affiliated Hospital of Jiangsu University, 438 Jiafang Road, Jiangkou, Zhenjiang, Jiangsu 212001, P.R. China
E-mail: jsdxwx@126.com

*Key words:* immune checkpoint inhibitors, stereotactic radiotherapy, non-small cell lung cancer, metastasis, immunotherapy

## Introduction

Lung cancer remains a significant global health challenge. It is the second most common cancer with an estimated 2.2 million cases reported worldwide in 2020. Lung cancer also has the highest mortality rate amongst all cancers, with ~1.8 million deaths recorded globally each year (1). Furthermore, non-small cell lung cancer (NSCLC) accounts for ~85% of all lung cancer cases (2). Recent advancements in cancer immunotherapy have revolutionized the management of metastatic NSCLC (3).

The landscape of advanced NSCLC treatment has undergone a paradigm shift with the advent of immunotherapy. Immune checkpoint inhibitors (ICIs) targeting programmed cell death protein 1 (PD-1), programmed death-ligand 1 (PD-L1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) have emerged as pivotal agents in this regard (4). Key clinical trials, such as KEYNOTE-010, 024 and 042, have established immunotherapy, either as a monotherapy or in combination with chemotherapy, as the standard first-line treatment for advanced NSCLC (5-7). However, the efficacy of immunotherapy remains limited, as only ~20% of unselected patients with NSCLC derive a benefit, which has prompted the exploration of combination strategies (8,9).

Stereotactic radiotherapy (SRT) delivers a precise high radiation dose to a single tumor site and is typically administered in 3-5 fractions with high accuracy. The potential synergistic effects of immunotherapy and SRT have garnered increasing interest and are supported by preclinical evidence that has indicated enhanced tumor antigen release, improved antigen presentation and increased T-cell infiltration in irradiated tumors. Furthermore, several preclinical studies across several solid tumor types, including nonirradiated tumors, have demonstrated more pronounced tumor regression when radiotherapy (RT) is combined with ICIs than with either treatment alone (10-16). However, randomized clinical trials

have yet to assess this synergistic effect on the response of patients with metastatic NSCLC.

Therefore, the aim of the present meta-analysis was to systematically assess the safety and efficacy of ICIs combined with RT for the treatment of metastatic NSCLC.

## Materials and methods

*Study design*. The present meta-analysis compared the effectiveness of combining ICIs with RT vs. RT alone, and ICI + RT vs. ICI therapy alone for metastatic NSCLC. Randomized controlled trials (RCTs) and retrospective studies (RSs) were included and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were followed for methodological consistency (17). Analysis was performed according to the Cochrane Handbook for Systematic Reviews of Interventions, version 5.1 risk of bias tool (www.handbook.cochrane.org). Patient consent and ethical approval were not obtained, as the analysis solely relied on previously published original studies.

*Search strategy*

*Selection of studies*. The research methodology of the present study involved a rigorous and comprehensive search strategy to identify relevant studies that investigated the use of SRT in combination with ICIs in cancer, with a specific focus on metastatic NSCLC. A total of four major databases were searched, namely, PubMed (https://pubmed.ncbi.nlm.nih.gov/), Google Scholar (https://scholar.google.com/), the Cochrane Library (https://www.cochranelibrary.com/) and Web of Science (www.webofscience.com/), to cover literature from database inception to February 1, 2023. To ensure the inclusivity of the search, a range of key terms were used, including 'ICI', 'radiotherapy', 'PD-1', 'PD-L1', 'CTLA-4' and 'NSCLC', as well as specific ICI agents, such as 'pembrolizumab', 'nivolumab', 'ipilimumab', 'atezolizumab', 'durvalumab' and 'tremelimumab'. The search strategy was designed to capture all relevant studies that assessed the efficacy and safety of ICIs combined with SRT in the treatment of NSCLC. The references of the included studies were also screened to identify any additional studies that may have been missed during the initial search. This comprehensive approach ensured that a robust body of evidence was gathered and allowed a thorough analysis of the effectiveness and safety profile of this combined therapy in NSCLC treatment to be performed.

*Selection criteria*. The studies included in the analysis adhered to specific criteria, which were as follows: i) Studies with patients diagnosed with metastatic NSCLC who underwent combination treatment of STR with ICIs targeting PD-1, PD-L1 and CTLA-4; and ii) studies that were RSs or RCTs, which ensured a variety of study designs for a comprehensive analysis. Furthermore, the following exclusion criteria were applied: i) Single-arm studies; ii) systematic reviews; iii) case reports; iv) non-English publications; v) studies lacking sufficient data for outcome estimation; and vi) animal studies.

*Data extraction*. Two researchers (SF and WS) independently screened each article based on the title and abstract, and the data collection process relied on preferred literature sources. Table I provides a comprehensive overview of the included studies and provides the following details: First author, year of publication, country of origin, study design, total patient count, type of therapy (ICI + RT vs. RT and ICI + RT vs. ICI), trial registration number, phase and outcomes. Furthermore, information on progression-free survival (PFS), grade 1 and 2 adverse events (AEs; including hypophysitis, uveitis, xerostomia, hypothyroidism, pneumonitis, hepatitis, enterocolitis, pancreatitis, autoimmune diabetes, adrenal insufficiency, arthralgia and dermatitis), complete remission (CR), progressive disease (PD), stable disease (SD) and partial remission (PR) outcomes was collected.

*Statistical analysis*. Statistical analysis was performed using the ReviewManager (RevMan) software, version 5.4 (The Cochrane Collaboration). Dichotomous variables were pooled using odds ratios (ORs) with 95% confidence intervals (CIs). The Mantel-Haenszel method was used to assess random effects models for OR. The inconsistency statistic ($I^2$) was used to evaluate heterogeneity between studies, with pooled results considered significant and heterogeneous if $I^2$>50%; in this case, a random effects model was applied. Additionally, potential publication bias was assessed using funnel plots. P<0.05 was considered to indicate a statistically significant difference.

## Results

*Study selection*. A total of 1,250 records were screened, 85 of which were assessed in full. Moreover, 7 articles involving 682 patients diagnosed with metastatic NSCLC were included in the meta-analysis (Fig. 1). Among these patients, 384 patients were given ICI + RT or RT alone, whilst 298 patients received ICI + RT or ICI alone. The characteristics of the included studies are summarized in Table I. A total of three of the records were phase II trials. The studies included only patients with NSCLC. The ICIs used included anti-PD-1 (pembrolizumab and nivolumab), anti-PD-L1 (atezolizumab and durvalumab) and anti-CTLA-4 (ipilimumab and tremelimumab) agents, whilst SRT was the type of RT administered. Treatment effects were evaluated in individual studies according to Response Evaluation Criteria in Solid Tumours 1.1 (18). Efficacy was classified as CR, PR, SD or PD. PFS was calculated from treatment initiation to the time of disease progression or death. A total of three studies compared the efficacy between the ICI + RT arm and RT-alone arm, among which two studies (19,20) with 260 patients reported PFS, and no significant difference was observed between the two arms (heterogeneity: $\chi$=2.35; df=1; P=0.13; $I^2$=57% and test for overall effect: Z=0.07; P=0.94; Fig. 2A). In another study a subgroup analysis of patients diagnosed with NSCLC revealed a significant improvement in PFS [hazard ratio (HR)=0.49; 95% CI, 0.37-0.64; P<0.00001] in patients <65 years who received ICI + RT, but no significant difference in PFS was reported in patients >65 years (HR=0.86; 95% CI, 0.65-1.16; P=0.43) (21). However, neither grade 1 or 2 AEs recorded in two studies (20,22) that included 333 patients were significantly different after the application of ICI + RT compared with RT alone. However, a notable improvement in grade 1 AEs was recorded for the RT arm. Moreover, no heterogeneity was observed for grade 1 AEs (25 vs. 33%; heterogeneity: $T^2$=0.00; $\chi^2$=0.51; df=1; P=0.47; $I^2$=0%; and test

Table I. Characteristics of the included studies.

| First author/s, year | Country | Study design | Arms (i vs. ii) | Trial registration no. | Phase | No. of patients (arm i/ii) | Outcomes at 12 months, n (arm i/ii) | (Refs.) |
|---|---|---|---|---|---|---|---|---|
| Shepard *et al*, 2019 | USA | RS | ICI (nivolumab, pembrolizumab and atezolizumab) + SRT vs. SRT | - | - | 17/34 | PFS (8/22) | (19) |
| Chen *et al*, 2018 | USA | RS | ICI (ipilimumab, nivolumab and pembrolizumab) + SRT vs. SRT | - | - | 28/181 | PFS (25/148) and AEs: grade 1 (5/58) and grade 2 (10/78) | (20) |
| Theelen *et al*, 2019 | Netherlands | RCT | ICI (pembrolizumab) + SRT vs. ICI | NCT02492568 | II | 36/40 | CR (3/1), PR (14/8), SD (9/10) and PD (10/21) | (23) |
| Tian *et al*, 2020 | USA | RS | SRT + ICI (pembrolizumab or nivolumab) vs. SRT | - | - | 56/68 | AEs: grade 1 (16/24) and grade 2 (20/23) | (22) |
| Pakkala *et al*, 2020 | USA | RCT | ICI (durvalumab and tremelimumab) + SRT vs. ICI | NCT02701400 | II | 9/9 | PR (2/0), SD (1/2) and PD (4/6) | (25) |
| Wang *et al*, 2022 | China | RS | ICI (pembrolizumab) + SRT vs. ICI | - | - | 59/93 | ECOG PS: 0 (24/44) and 1 (35/49), and CR (2/0), PR (28/29), SD (25/52) and PD (4/12) | (24) |
| Schoenfeld *et al*, 2023 | USA | RCT | ICI (durvalumab and tremelim umab) + SRT vs. ICI | NCT02888743 | II | 26/26 | ECOG PS: 0 (9/5) and 1 (17/21), and PR (2/3), SD (12/11) and PD (8/10) | (26) |

ICI, immune checkpoint inhibitor; RT, radiotherapy; RS, retrospective study; SRT, stereotactic radiotherapy; PFS, progression-free survival; AE, adverse event; RCT, randomized controlled trial; CR, complete remission; PR, partial remission; SD, stable disease; PD, progressive disease; ECOG PS, Eastern Cooperative Oncology Group Performance Status.

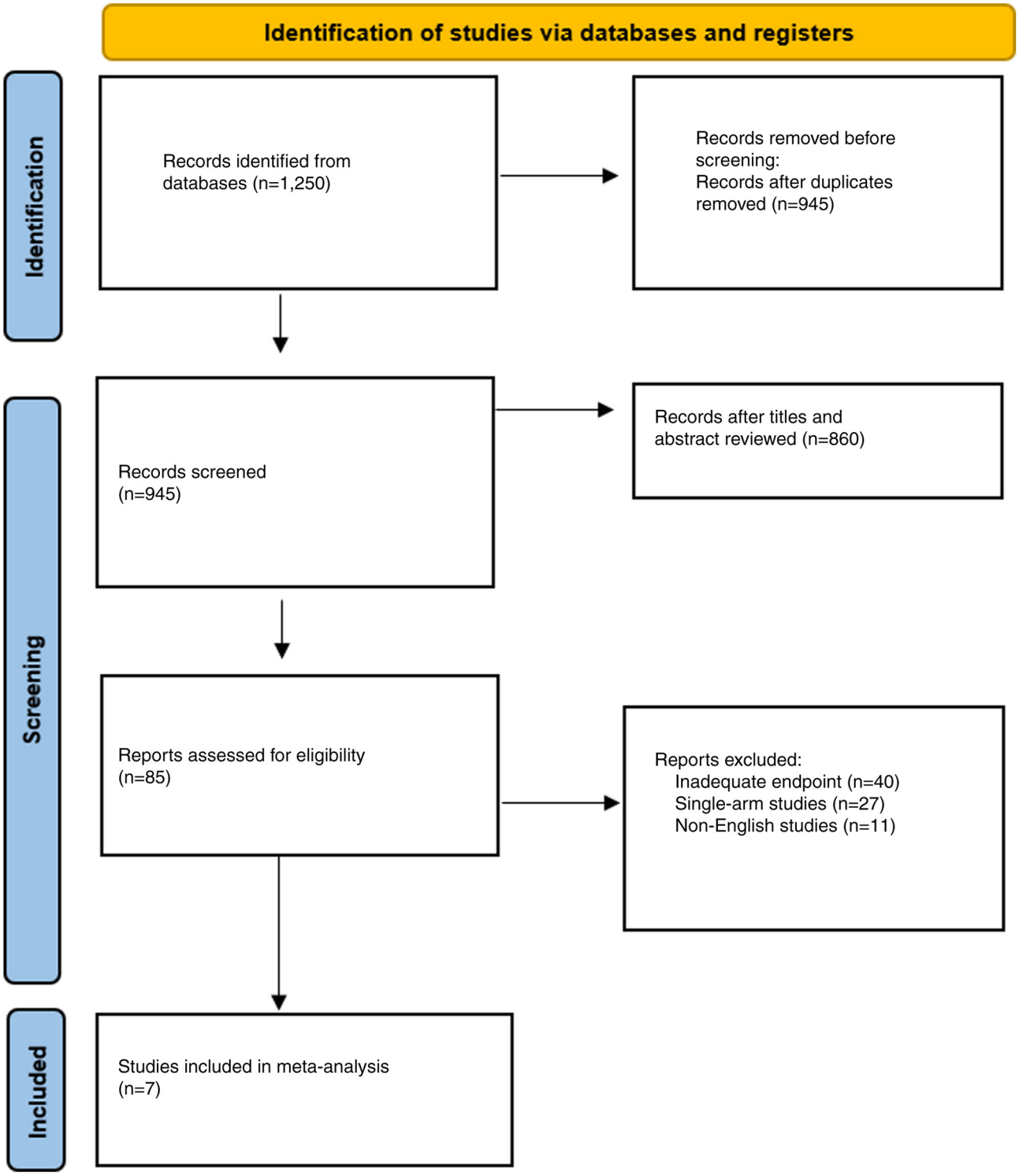


Figure 1. Preferred reporting items for systematic reviews and meta-analyses flowchart of the included studies.

for overall effect: Z=1.53; P=0.13) or grade 2 AEs (heterogeneity: $\chi^2$=0.48; df=1; P=0.49; $I^2$=0% and test for overall effect: Z=0.34; P=0.74; Fig. 2B and C). The results indicate that the use of RT alone led to an increase in grade 1 AEs.

A total of four studies including 298 patients evaluated the use of ICI + RT and ICI alone, with two studies (23,24) with 228 patients reporting the CR rate. A pooled analysis of CRs was performed using a random effects model, and no significant difference was observed between the two arms (heterogeneity: $\chi^2$=0.18; df=1; P=0.67; $I^2$=0% and test for overall effect: Z=1.71; P=0.10; Fig. 3A). The PR rate of patients who were treated with a combination of ICI + RT compared with ICI alone was retrieved from four studies (23-26). Compared with patients who received ICI + RT, patients who received ICI alone achieved a significant PR (heterogeneity: $\chi^2$=2.13; df=3; P=0.54; $I^2$=0% and test for overall effect: Z=2.66; P=0.01; Fig. 3B). A total of four studies (23-26) reported the SD rate, and no significant

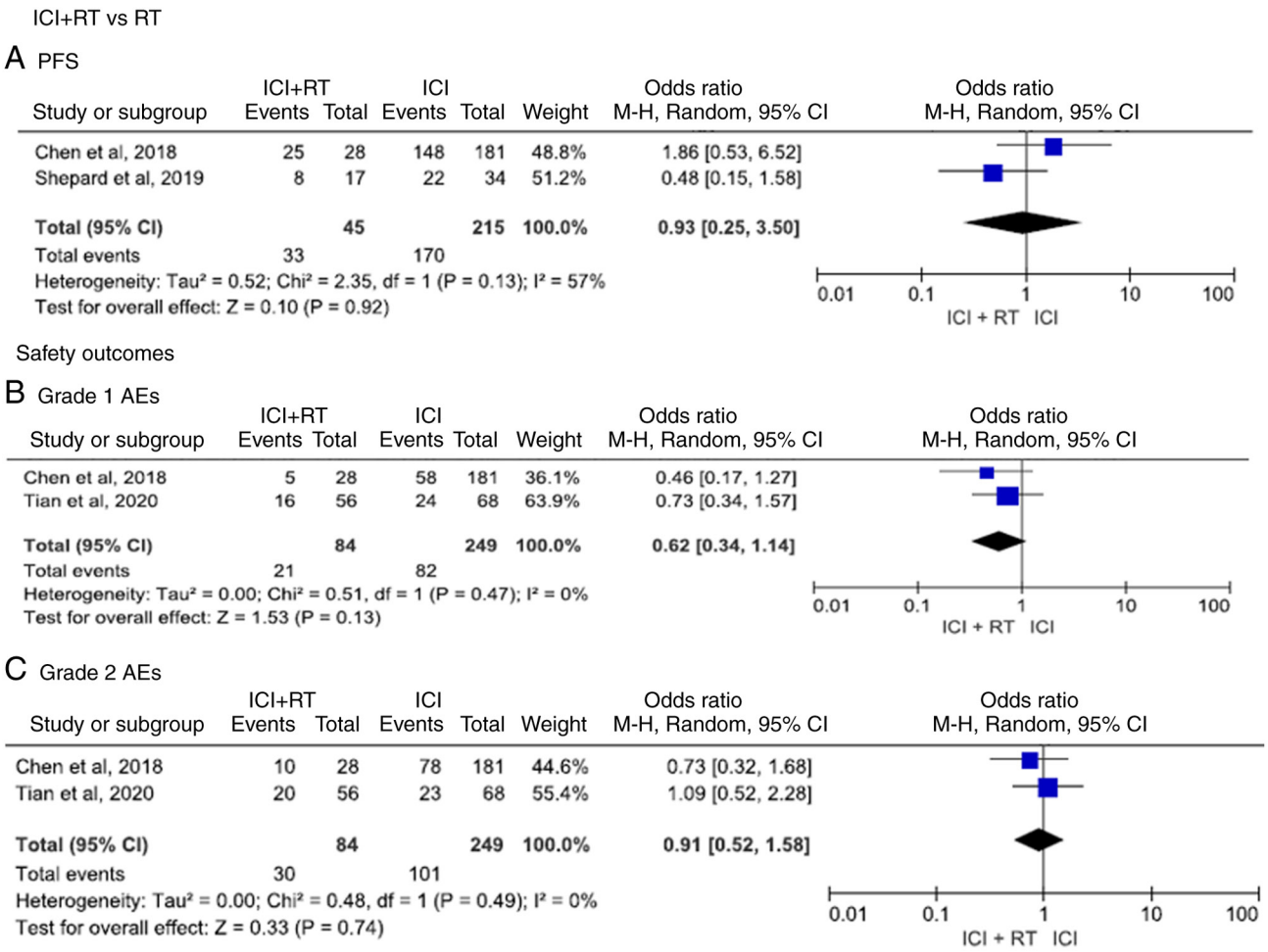


Figure 2. Forest plot of ICI + RT vs. RT. (A) PFS. (B) Grade 1 AEs. (C) Grade 2 AEs. ICI, immune checkpoint inhibitor; RT, radiotherapy; PFS, progression-free survival; AE, adverse event; df, degrees of freedom; M-H, Mantel-Haenszel; CI, confidence interval.

heterogeneity was observed among the studies ($\chi^2$=2.89; df=3; P=0.41; $I^2$=0% and test for overall effect: Z=1.32; P=0.19; Fig. 3C). The pooled incidence of PD was reported in four studies (23-26) and the estimate favored ICI + RT, which was associated with a significantly decreased PD rate compared with ICI therapy alone (heterogeneity: $T^2$=0.00; $\chi^2$=0.91; df=3; P=0.82; $I^2$=8% and test for overall effect: Z=2.52; P=0.01; Fig. 3D).

*Sequence of ICI and RT combinations*. The optimal sequencing of RT and ICIs remains a topic of ongoing investigation. Emerging research suggests that ICIs may exhibit maximal efficacy when administered either concurrently with or close to the time RT is given, as this approach helps to mitigate delayed antigen presentation in an immunotolerant environment. Moreover, the synergistic mechanism appears to vary depending on the specific type of ICI used. Anti-PD-1/PD-L1 agents are believed to enhance the activation of new T cells, whilst anti-CTLA4 antibodies function within the lymphatic system to suppress regulatory T cells and restore costimulatory signals, thereby enabling T cells to respond effectively to antigen presentation (27). Consequently, these processes have the potential to synergize with the T-cell activation and proliferation induced by RT, which culminates in a more robust immune response. Dovedi *et al* (12) compared RT administered concurrently with anti-PD-L1 therapy vs. RT followed by a 7-day interval before initiation of anti-PD-L1 treatment. The latter approach resulted in the ineffective activation of effector T cells and poor survival outcomes. Similarly, Young *et al* (28) evaluated the administration of RT (20 Gy x1) alongside anti-CTLA4 at several time points relative to RT. Their findings revealed markedly improved survival rates when anti-CTLA4 was administered 7 days prior to RT. Furthermore, the study explored the use of anti-OX40, a secondary costimulatory checkpoint inhibitor, in conjunction with RT and reported optimal survival outcomes when ICI was given 1 day after RT. These findings underscore the importance of tailoring the sequencing of RT and ICIs based on the specific agent used. Currently, ongoing clinical trials, such as the RT sequence phase I trial (trial registration no. NCTO3307759), are assessing the optimal sequence of RT and ICIs, particularly in the context of metastatic NSCLC. In clinical practice, ICIs may be administered before, during or after SRT, with concurrent use defined as the administration of ICIs within 2-4 weeks before or after SRT. Favorable outcomes have been observed with this approach in terms of local control and overall survival (28,29). Based on current medical evidence, an interval of ≤4 weeks between SRT and ICI administration is recommended. Notably, the efficacy of ICIs may

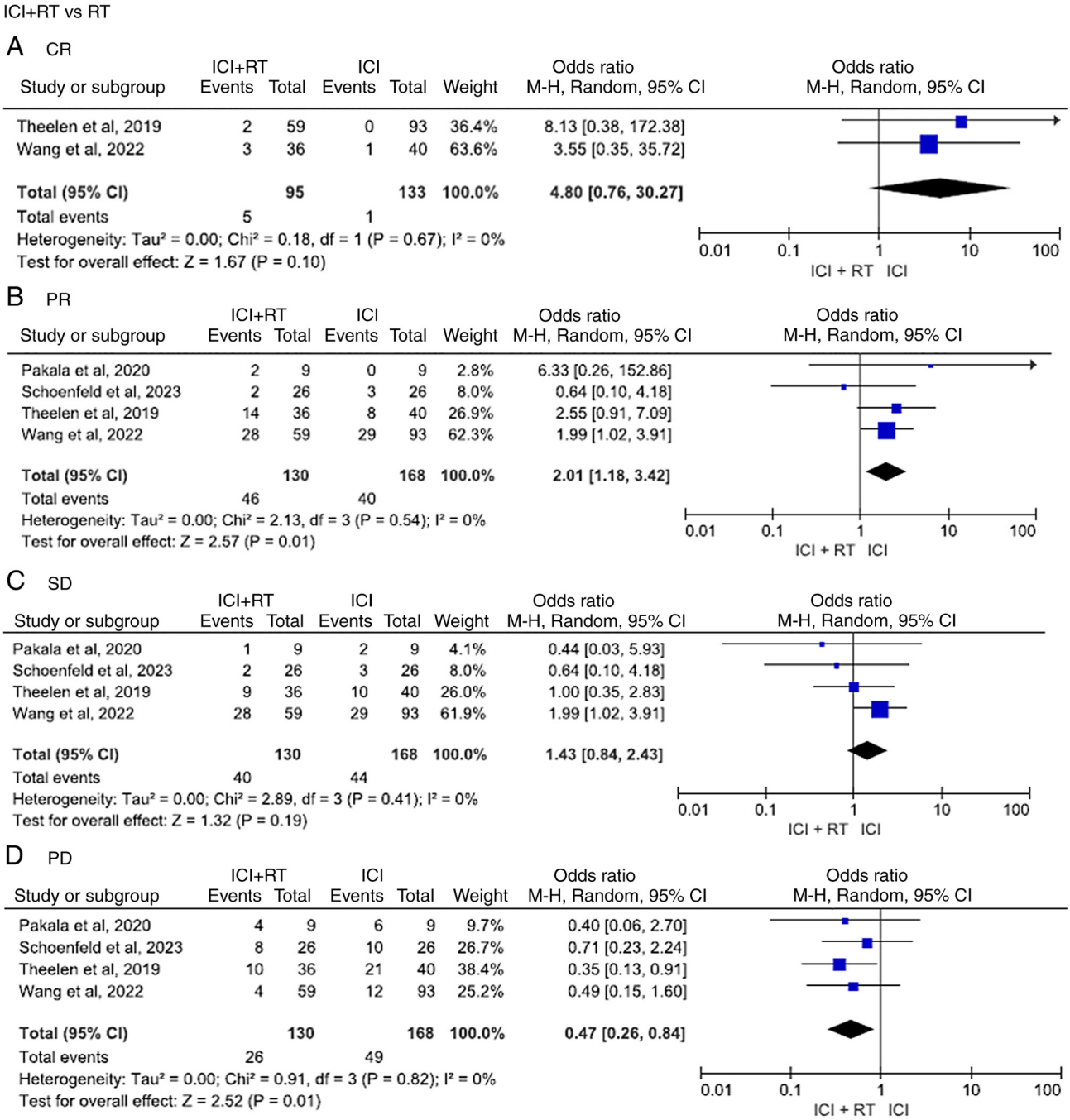


Figure 3. Forest plot of ICI + RT vs. ICI. (A) CR. (B) PR. (C) SD. (D) PD. ICI, immune checkpoint inhibitor; RT, radiotherapy; CR, complete remission; PR, partial remission; SD, stable disease; PD, progressive disease.

vary depending on the order and timing of their delivery in conjunction with SRT (28,29). Therefore, continued research in this area is essential to optimize treatment strategies and improve patient outcomes.

*Clinical implications of ICIs and RT in cancer treatment.* ICIs have revolutionized the management of NSCLC by targeting CTLA-4 and PD-1, along with their corresponding ligands B7-1 (CD-80)/B7-2 (CD-86) and (PD-L1)/PD-L2 (30). In a comprehensive analysis by Chicas-Sett *et al* (31), which included 18 publications and encompassed 1,736 patients who underwent treatment with SRT and ICIs, this combination demonstrated notable success rates, with a 71% local control rate and a 41% success rate in eliciting the abscopal effect. Furthermore, combination treatment led to a significant improvement in overall survival (OS; (12.4 months; P=0.006). Clinical trials evaluating several combinations of SRT and ICIs in patients with metastasis are supported by theoretical and preclinical evidence that has shown a synergistic relationship between these modalities. However, controversies persist regarding the optimal sequence of administration, SRT fractionation patterns and dosages, selection of appropriate ICIs, therapeutic effects and side effects, among other factors. Although most studies have reported enhanced local control and OS with acceptable AE rates, it is essential to note that these findings primarily stem from retrospective

cohort analyses with a limited population size; these studies have predominantly included patients with primary histology indicative of malignant melanoma and have used ipilimumab more than other ICIs. These inherent limitations pose challenges in extrapolating published results and understanding their true impact, especially for brain metastases originating from other primary tumors (32).

*AEs associated with ICIs and RT.* Immunotherapy (IT) and ICIs have revolutionized cancer treatment, but they also cause a range of AEs. Common AEs associated with IT and ICIs include fatigue, cutaneous eruptions, pruritus and hormonal imbalances, such as hypophysitis and thyroid dysfunction, particularly with anti-CTLA-4 agents, as well as gastrointestinal issues (primarily colitis). Respiratory complications that range from mild coughing or shortness of breath to pneumonia are also prevalent (33). Moreover, reports have indicated potential detrimental effects on the heart and nervous system and the likelihood of experiencing these AEs appears to increase with the combination of RT and IT (33). In one study, AEs exceeding grade 3 with RT + ICI combination therapy ranged from 10-17% and 29-38% in patients who received anti-PD-1/PD-L1 therapy and anti-CTLA-4 therapy, respectively (31). However, these findings did not significantly differ from those observed with IT alone. For instance, in the PACIFIC trial, the incidence of grade 3-4 AEs was greater in the durvalumab group than in the placebo group, as patients treated with durvalumab also had a greater incidence of lung disease (34). Early discontinuation of durvalumab was primarily attributed to grade 3-4 lung disease and radiation-induced lung disease. Additional randomized trials have further supported these findings and have shown no significant difference in grades ≥3 and ≥4 pulmonary AEs when RT/IT was compared with placebo/RT (31,35). Nevertheless, caution is warranted due to the potential AEs of the RT + IT combination, such as inflammation in the colon with abdominopelvic RT or nerve damage with RT of brain metastases. SRT may mitigate certain AEs compared with conformal RT (36).

*Publication bias assessment.* No indication of publication bias was found as every study fell within the 95% CI range (Fig. 4). Subsequently, Egger's test demonstrated statistical evidence of funnel plot symmetry. However, the results did not show any evidence of publication bias for SD (heterogeneity: $\chi^2$=2.89; df=3; P=0.41; $I^2$=0; Fig. 3C).

*Quality assessment.* In the present study, the Cochrane Handbook for Systematic Reviews of Interventions, Version 5.1 risk of bias tool (The Cochrane Collaboration) was used to objectively assess the quality of the trials. The potential for bias was evaluated in the following areas: i) Sequence generation; ii) allocation concealment; iii) blinding; iv) incomplete data; v) selective reporting; and vi) other factors (Fig. 5). 'High-risk' trials were those with risks of bias for ≥1 important domains. A trial was deemed to be 'low risk' if it had a low bias risk across all important domains. Alternatively, the trial was deemed 'unclear'. Disagreements between the researchers were resolved by discussion with the corresponding author.

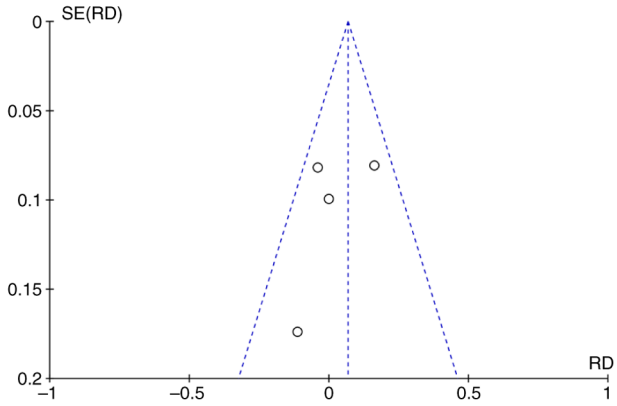


Figure 4. Funnel plot of stable disease. SE, standard error, RD risk difference.

## Discussion

The human immune system serves a crucial role in mounting an antitumoral immune response, with T cells being particularly instrumental in shouldering a significant portion of this immunological workload. The balance between stimulatory and inhibitory signals, including ICIs, ultimately governs the effectiveness of the immune response, which is triggered by T-cell recognition of specific antigens (37,38). In addition to the immune system itself, tumors and surrounding tissues can also provoke immune responses. When T cells fail to respond, it is often because their receptors do not recognize any antigens. Key ICIs, such as CTLA-4 and PD-1, are pivotal in cancer treatment due to their ability to modulate immune responses at several stages through distinct mechanisms. Examples of CTLA-4 and PD-1 ICIs include ipilimumab, nivolumab and pembrolizumab. These antibodies function by blocking inhibitory receptors on T cells, thereby enhancing their effectiveness against tumors. This unique mechanism of action prevents the transmission of inhibitory signals, which enables T cells to effectively eliminate cancer cells (39). According to preclinical models, checkpoint agents that target the PD-1 and CTLA-4 pathways may be more effective when immunogenic radiation doses are added (11,40).

The present meta-analysis aimed to demonstrate the safety and efficacy of the administration of ICIs that target PD-1 and CTLA-4 in conjunction with RT in individuals with metastatic NSCLC. An analysis of 10 studies revealed no significant difference in PFS between the ICI + RT group and the RT-alone group (heterogeneity: $\chi^2$=2.35; df=1; P=0.13; $I^2$=57%). Out of the studies analyzed, only one conducted a comparison between patient groups that were administered radiation and those that were not, and showed a favorable effect of RT on the best objective response but no significant difference in PFS or OS (41). Moreover, a meta-analysis performed by Ma *et al* (42) demonstrated that combination therapy including ICIs significantly prolonged PFS compared with ICI monotherapy (HR=0.83; 95% CI, 0.74-0.94; P=0.003). However, notably, this analysis revealed significant heterogeneity (P<0.0001; $I^2$=85%). Furthermore, Xu *et al* (21) highlighted a significant improvement in PFS when ICIs were combined with RT therapy, particularly in younger patients (<65 years of age) with NSCLC (vs. ≥65 years of age: HR=0.49; 95% CI,

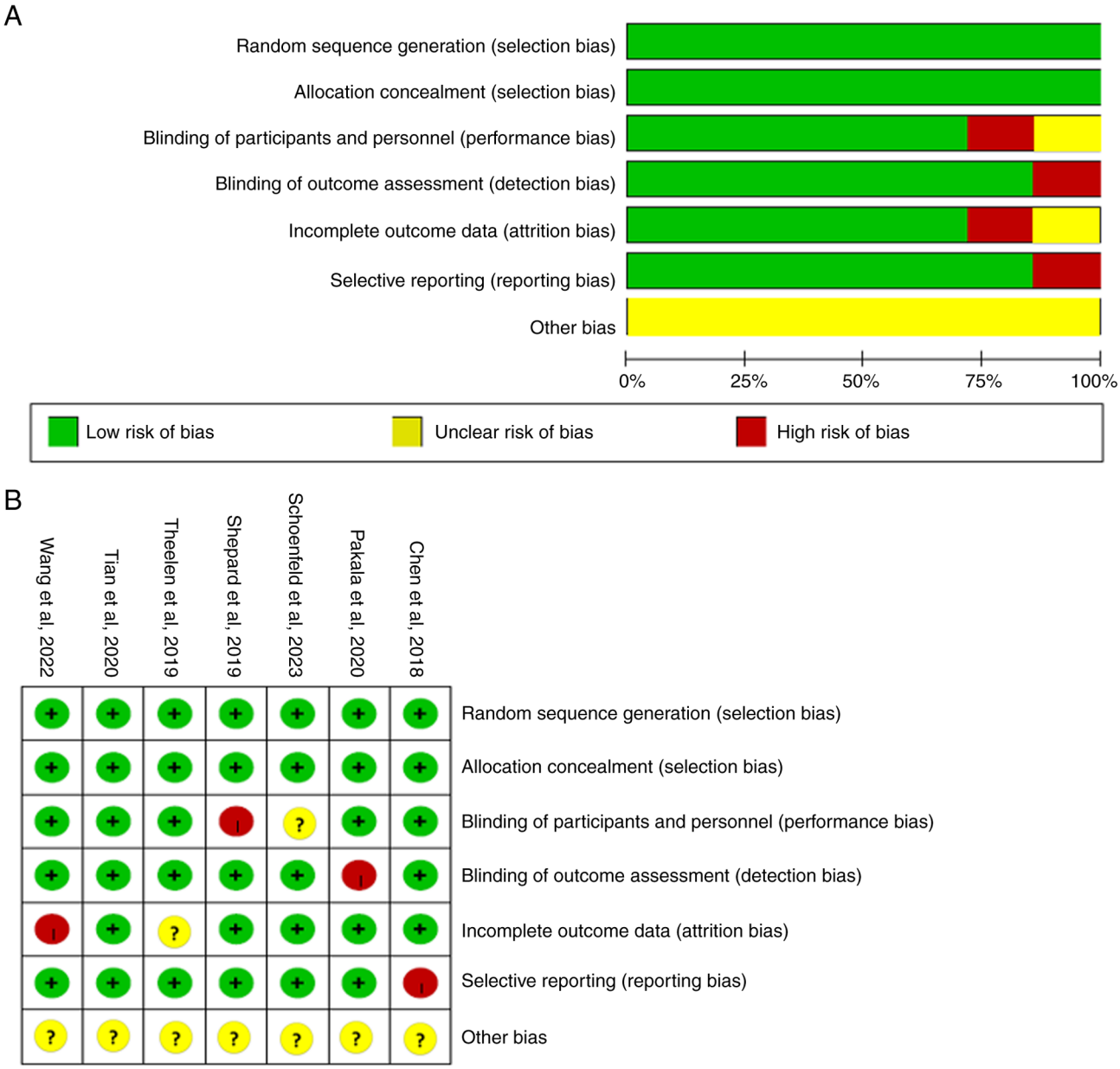


Figure 5. Risk of bias summary. (A) Likelihood of potential bias: Evaluation of each bias item is presented as % for all studies included in the present review. (B) Summary of potential bias: Assessment of each bias item for each study included in the present review.

0.37-0.64; P<0.00001). Ongoing clinical trials, such as trial registration nos. NCT02562625 and NCT02730130, are expected to provide further insights (43).

A comparison between patients who received ICIs + RT and patients who received ICIs alone revealed a significant difference in the rates of PR and PD. PR was significantly higher in the ICI arm (P=0.01), whilst combination therapy was associated with a significantly decreased PD rate compared with ICI therapy alone (P=0.01). However, no significant differences were observed between the two treatment modalities with respect to the CR and SD rates. Moreover, an assessment of the association between the timing of IT and SRT revealed that 167 patients received concurrent IT (within 4 weeks of SRT), whilst 124 patients received nonconcurrent IT. However, no difference was reported between the two groups in terms of the proportion of patients that achieved CR or PR (concurrent, 94.6% vs. nonconcurrent, 94.4%; P=0.5) (44).

No difference was observed in the occurrence of AEs between patients treated with ICIs + RT and those treated with RT alone, as indicated by the absence of heterogeneity in patients with grade 1 (heterogeneity: $\chi^2$=0.51; df=1; P=0.47; $I^2$=0%) and grade 2 (heterogeneity: $\chi^2$=0.48; df=1; P=0.49; $I^2$=0%) AEs. Hwang *et al* (45) reported that patients diagnosed with NSCLC who had previously received thoracic RT did not experience any distinct immune-related AEs compared with those who had received ICI treatment. However, a study involving multiple institutions and 915 patients revealed a significantly greater susceptibility to pneumonitis when patients were treated with a combination of RT + ICIs compared with when patients were treated with monotherapy (10 vs. 3%; P<0.01), which corroborates the pattern observed in the present case (46).

Compared with other studies, the present research provides a distinct contribution in that it addresses a unique aspect of treatment by exploring the combined use of ICIs + RT specifically for metastatic NSCLC. Whilst Kim *et al* (47) assessed the efficacy of ICI therapy with or without RT for NSCLC brain metastases and Liu *et al* (48) evaluated the outcomes of adding RT to ICIs in metastatic NSCLC, the present study provides insights into the effectiveness of this combination therapy for metastatic NSCLC as a whole. Additionally, the present meta-analysis approach allows for a systematic synthesis and analysis of existing data, offering an evaluation of post-therapy outcomes such as PFS, response rates and AEs for the combination of ICIs + RT. By providing evidence of the promising efficacy and safety of this combined treatment modality, the present study sets the stage for further research and potential advancements in the management of patients with metastatic NSCLC.

The present meta-analysis aimed to assess the efficacy and safety of RT + ICIs for the treatment of NSCLC. Whilst the importance of addressing the variability among ICIs is acknowledged, considering that differences exist in the mechanisms of action, pharmacokinetics and patient responses, the present study chose a broader approach to provide a comprehensive evaluation of the combined therapy strategy as a whole. Despite the technical complexities involved in analyzing multiple subgroups based on several ICIs, such as differences in study designs, dosages and patient characteristics, maintaining the integrity and robustness of the primary analysis was prioritized. However, it is crucial to note certain limitations of the present meta-analysis. First, the inclusion of both RSs and RCTs implies that a certain level of bias between the groups was unavoidable. Second, whilst the time interval for the concurrent group in the present study may have been standardized, the same cannot be said for the combined RT + ICI group, as most of the original studies did not define this interval. Third, outcomes may vary depending on the specific ICI and RT protocols used in each study. Further RCTs are necessary to validate and strengthen the conclusions regarding the use of ICIs and RT in the treatment of metastatic NSCLC.

In conclusion, the present study revealed that ICIs, either used alone or in combination with RT, are safe and effective for treating patients with metastatic NSCLC. However, further RCTs are needed to gain a deeper understanding of the long-term outcomes, response rates, survival rates and safety profiles.

## Acknowledgements

Not applicable.

## Funding

The present study was supported by grants from the Chinese National Natural Science Foundation (grant no. 32170910), the Jiangsu Provincial Natural Science Foundation (grant no. BK20211124) and the Zhenjiang Key Research and Development Program (grant no. SH2021037).

## Availability of data and materials

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

## Authors' contributions

IAD was involved in the conceptualization and design the work and wrote the manuscript. SF, WS, HT and MAM were responsible for acquiring, analyzing and interpreting the data. SF and WS confirm the authenticity of all the raw data. XW interpreted the data and designed the study, and all of the authors carefully reviewed the manuscript. All authors have read and approved the final manuscript.

## Ethics approval and consent to participate

Not applicable.

## Patient consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

## References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A and Bray F: Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 71: 209-249, 2021.
2. Ernani V and Stinchcombe TE: Management of brain metastases in non-small-cell lung cancer. J Oncol Pract 15: 563-570, 2019.
3. Planchard D, Popat S, Kerr K, Novello S, Smit E, Faivre-Finn C, Mok TS, Reck M, Van Schil PE, Hellmann MD, *et al*: Metastatic non-small cell lung cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 29: iv192-iv237, 2018.
4. de Jong D, Das JP, Ma H, Valiplackal JP, Prendergast C, Roa T, Braumuller B, Deng A, Dercle L, Yeh R, *et al*: Novel targets, novel treatments: The changing landscape of non-small cell lung cancer. Cancers (Basel) 15: 2855, 2023.
5. Herbst RS, Baas P, Kim DW, Felip E, Pérez-Gracia JL, Han JY, Molina J, Kim JH, Arvis CD, Ahn MJ, *et al*: Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): A randomised controlled trial. Lancet 387: 1540-1550, 2016.
6. Mok TS, Wu YL, Kudaba I, Kowalski DM, Cho BC, Turna HZ, Castro G Jr, Srimuninnimit V, Laktionov KK, Bondarenko I, *et al*: Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): A randomised, open-label, controlled, phase 3 trial. Lancet 393: 1819-1830, 2019.
7. Reck M, Rodríguez-Abreu D, Robinson A, Hui R, Csőszi T, Fülöp A, Gottfried M, Peled N, Tafreshi A, Cuffe S, *et al*: 2016. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. N Engl J Med 375: 1823-1833, 2016.
8. Gandhi L, Rodrguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, Domine M, Clingan P, Hochmair MJ, Powell SF, *et al*: Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. N Engl J Med 378: 2078-2092, 2018.
9. Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, Chow LQ, Vokes EE, Felip E, Holgado E, *et al*: Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. N Eng J Med 373: 1627-1639, 2015.
10. Demaria S and Formenti SC: Radiation as an immunological adjuvant: Current evidence on dose and fractionation. Front Oncol 2: 153, 2012.
11. Deng L, Liang H, Burnette B, Beckett M, Darga T, Weichselbaum RR and Fu YX: Irradiation and anti-PD-L1 treatment synergistically promote antitumor immunity in mice. J Clin Invest 124: 687-695, 2014.
12. Dovedi SJ, Adlard AL, Lipowska-Bhalla G, McKenna C, Jones S, Cheadle EJ, Stratford IJ, Poon E, Morrow M, Stewart R, *et al*: Acquired resistance to fractionated radiotherapy can be overcome by concurrent PD-L1 blockade. Cancer Res 74: 5458-5468, 2014.

13. Victor CTS, Rech AJ, Maity A, Rengan R, Pauken KE, Stelekati E, Benci JL, Xu B, Dada H, Odorizzi PM, *et al*: Radiation and dual checkpoint blockade activate non-redundant immune mechanisms in cancer. Nature 520: 373-377, 2015.
14. Gong X, Li X, Jiang T, Xie H, Zhu Z, Zhou F and Zhou C: Combined radiotherapy and anti-PD-L1 antibody synergistically enhances antitumor effect in non-small cell lung cancer. J Thor Oncol 12: 1085-1097, 2017.
15. Zeng J, See AP, Phallen J, Jackson CM, Belcaid Z, Ruzevick J, Durham N, Meyer C, Harris TJ, Albesiano E, *et al*: Anti-PD-1 blockade and stereotactic radiation produce long-term survival in mice with intracranial gliomas. Int J Radiat Oncol Biol Phys 86: 343-349, 2013.
16. Dovedi SJ, Cheadle EJ, Popple AL, Poon E, Morrow M, Stewart R, Yusko EC, Sanders CM, Vignali M, Emerson RO, *et al*: Fractionated radiation therapy stimulates antitumor immunity mediated by both resident and infiltrating polyclonal T-cell populations when combined with PD-1 blockade. Clin Cancer Res 23: 5514-5526, 2017.
17. Moher D, Liberati A, Tetzlaff J and Altman DG; PRISMA Group: Preferred Reporting items for systematic reviews and meta analyses: The PRISMA statement. PloS Med 6: e123-e130, 2009.
18. Grimaldi S, Terroir M and Caramella C: Advances in oncological treatment: Limitations of RECIST 1.1 criteria. Q J Nucl Med Mol Imaging 62: 129-139, 2017.
19. Shepard MJ, Xu Z, Donahue J, Muttikkal TJE, Cordeiro D, Hansen L, Mohammed N, Gentzler RD, Larner J, Fadul CE and Sheehan JP: Stereotactic radiosurgery with and without checkpoint inhibition for patients with metastatic non-small cell lung cancer to the brain: A matched cohort study. J Neurosurg 133: 685-692, 2019.
20. Chen L, Douglass J, Kleinberg L, Ye X, Marciscano AE, Forde PM, Brahmer J, Lipson E, Sharfman W, Hammers H, *et al*: Concurrent immune checkpoint inhibitors and stereotactic radiosurgery for brain metastases in non-small cell lung cancer, melanoma, and renal cell carcinoma. Int J Radiat Oncol Biol Phys 100: 916-925, 2018.
21. Xu Z, Feng J, Weng Y, Jin Y and Peng M: Combination of immune checkpoint inhibitors and radiotherapy for advanced non-small-cell lung cancer and prostate cancer: A meta-analysis. J Oncol 2021: 6631643, 2021.
22. Tian S, Switchenko JM, Buchwald ZS, Patel PR, Shelton JW, Kahn SE, Pillai RN, Steuer CE, Owonikoko TK, Behera M, *et al*: Lung stereotactic body radiation therapy and concurrent immunotherapy: A multicenter safety and toxicity analysis. Int J Radiat Oncol Biol Phys 108: 304-313, 2020.
23. Theelen WS, Peulen HM, Lalezari F, van der Noort V, de Vries JF, Aerts JG, Dumoulin DW, Bahce I, Niemeijer AN, de Langen AJ, *et al*: Effect of pembrolizumab after stereotactic body radiotherapy vs pembrolizumab alone on tumor response in patients with advanced non-small cell lung cancer: Results of the PEMBRO-RT phase 2 randomized clinical trial. JAMA Oncol 5: 1276-1282, 2019.
24. Wang P, Yin T, Zhao K, Yu J and Teng F: Efficacy of single-site radiotherapy plus PD-1 inhibitors vs PD-1 inhibitors for oligometastatic non-small cell lung cancer. J Cancer Res Clin Oncol 148: 1253-1261, 2022.
25. Pakkala S, Higgins K, Chen Z, Sica G, Steuer C, Zhang C, Zhang G, Wang S, Hossain MS, Nazha B, *et al*: Durvalumab and tremelimumab with or without stereotactic body radiation therapy in relapsed small cell lung cancer: A randomized phase II study. J Immunother Cancer 8: e001302, 2020.
26. Schoenfeld JD, Giobbie-Hurder A, Ranasinghe S, Kao KZ, Lako A, Tsuji J, Liu Y, Brennick RC, Gentzler RD, Lee C, *et al*: Durvalumab, tremelimumab alone or in combination with low-dose or hypofractionated targeted radiotherapy in metastatic non-small cell lung cancer refractory to Prior PD-1 therapy: A multicentre, open-label, randomized, phase 2 trial. Lancet Oncol 23: 279-291, 2022.
27. Seidel JA, Otsuka A and Kabashima K: Anti-PD-1 and anti-CTLA-4 therapies in cancer: Mechanisms of action, efficacy, and limitations. Front Oncol 8: 86, 2018.
28. Young KH, Baird JR, Savage T, Cottam B, Friedman D, Bambina S, Messenheimer DJ, Fox B, Newell P, Bahjat KS, *et al*: Optimizing timing of immunotherapy improves control of tumors by hypofractionated radiation therapy. PLoS One 11: e0157164, 2016.
29. ElJalby M, Pannullo SC, Schwartz TH, Parashar B and Wernicke AG: Optimal timing and sequence of immunotherapy when combined with stereotactic radiosurgery in the treatment of brain metastases. World Neurosurg 127: 397-404, 2019.
30. Bockel S, Antoni D, Deutsch É and Mornex F: Immunotherapy and radiotherapy. Cancer Radiother 21: 244-255, 2017 (In French).
31. Chicas-Sett R, Morales-Orue I, Castilla-Martinez J, Zafra-Martin J, Kannemann A, Blanco J, Lloret M and Lara PC: Stereotactic ablative radiotherapy combined with immune checkpoint inhibitors reboots the immune response assisted by immunotherapy in metastatic lung cancer: A systematic review. Int J Mol Sci 20: 2173, 2019.
32. Trapani S, Manicone M, Sikokis A, D'Abbiero N, Salaroli F, Ceccon G and Buti S: Effectiveness and safety of 'real' concurrent stereotactic radiotherapy and immunotherapy in metastatic solid tumors: A systematic review. Crit Rev Oncol Hematol 142: 9-15, 2019.
33. Perrinjaquet C, Zaher M, Ferraro DA, Comte D, Trueb L, Zimmermann S, Coukos G and Orcurto A: Side effects of immune checkpoint inhibitors: Diagnosis and management. Revue Med Suisse 15: 1010-1016, 2019.
34. Vanpouille-Box C, Diamond JM, Pilones KA, Zavadil J, Babb JS, Formenti SC, Barcellos-Hoff MH and Demaria S: TGFβ is a master regulator of radiation therapy-induced antitumor immunity. Cancer Res 75: 2232-2242, 2015.
35. Gray JE, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, Kurata T, Chiappori A, Lee KH, Cho BC, *et al*: Three-year overall survival with durvalumab after chemoradiotherapy in stage III NSCLC-update from PACIFIC. J Thorac Oncol 15: 288-293, 2020.
36. Ross HJ, Kozono DE, Urbanic JJ, Williams TM, DuFrane C, Bara I, Schulze K, Brockman JM, Wang XF, Gao J, *et al*: AFT-16: Phase II trial of neoadjuvant and adjuvant atezolizumab and chemoradiation (CRT) for stage III non-small cell lung cancer (NSCLC). Wolters Kluwer Health; 2021.
37. Greenwald RJ, Freeman GJ and Sharpe AH: The B7 family revisited. Annu Rev Immunol 23: 515-548, 2005.
38. Zou W and Chen L: Inhibitory B7-family molecules in the tumour microenvironment. Nat Rev Immunol 8: 467-477, 2008.
39. Kucuk A, Topkan E, Durankus NK, Senyurek S, Akdemir EY, Sezen D, Bolukbasi Y, Selek U, Pehlivan B and Sergi CM: Combined stereotactic radiosurgery and immune checkpoint inhibitors for the treatment of brain metastasis. Exon Publications: 57-74, 2023.
40. Deng L, Liang H, Burnette B, Weicheslbaum RR and Fu YX: Radiation and anti-PD-L1 antibody combinatorial therapy induces T cell-mediated depletion of myeloid-derived suppressor cells and tumor regression. Oncoimmunology 3: e28499, 2014.
41. Knispel S, Stang A, Zimmer L, Lax H, Gutzmer R, Heinzerling L, Weishaupt C, Pföhler C, Gesierich A, Herbst R, *et al*: Impact of a preceding radiotherapy on the outcome of immune checkpoint inhibition in metastatic melanoma: A multicenter retrospective cohort study of the DeCOG. J Immunother Cancer 8: e000395, 2020.
42. Ma X, Zhang Y, Wang S, Wei H and Yu J: Immune checkpoint inhibitor (ICI) combination therapy compared to monotherapy in advanced solid cancer: A systematic review. J Cancer 12: 1318-1333, 2021.
43. Shevtsov M, Sato H, Multhoff G and Shibata A: Novel approaches to improve the efficacy of immuno-radiotherapy. Front Oncol 9: 156, 2019.
44. Singh C, Qian JM, James BY and Chiang VL: Local tumor response and survival outcomes after combined stereotactic radiosurgery and immunotherapy in non-small cell lung cancer with brain metastases. J Neurosurg 132: 512-517, 2019.
45. Hwang WL, Niemierko A, Hwang KL, Hubbeling H, Schapira E, Gainor JF and Keane FK: Clinical outcomes in patients with metastatic lung cancer treated with PD-1/PD-L1 inhibitors and thoracic radiotherapy. JAMA Oncol 4: 253-255, 2018.
46. Naidoo J, Wang X, Woo KM, Iyriboz T, Halpenny D, Cunningham J, Chaft JE, Segal NH, Callahan MK, Lesokhin AM, *et al*: Pneumonitis in patients treated with anti-programmed death-1/programmed death ligand 1 therapy. J Clin Oncol 35: 709-717, 2017.
47. Kim DY, Kim PH, Suh CH, Kim KW and Kim HS: Immune checkpoint inhibitors with or without radiotherapy in non-small cell lung cancer patients with brain metastases: A systematic review and meta-analysis. Diagnostics (Basel) 10: 1098, 2020.
48. Liu Z, Xu T, Chang P, Fu W, Wei J, Xia C, Wang Q, Li M, Pu X, Huang F, *et al*: Efficacy and safety of immune checkpoint inhibitors with or without radiotherapy in metastatic non-small cell lung cancer: A systematic review and meta-analysis. Front Pharmacol 14: 1064227, 2023.