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Safety and Efficacy of Radiotherapy Combined With Sintilimab in Advanced NSCLC Patients Who Progressed on First or Second Line Therapy: A Prospective, Multiple Center, and Single-Arm Study

Xiaoyi Feng[1] | Xiaoyan Liu[1] | Hui Guan[2] | Chunhong Chen[3] | Feng Gao[3] | Xiaoxing Gao[1] | Minjiang Chen[1] | Jing Zhao[1] | Yan Xu[1] | Mengzhao Wang[1]

[1]Department of Pulmonary and Critical Care Medicine, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, People's Republic of China | [2]Department of Radiotherapy, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, People's Republic of China | [3]Department of Oncology, Beidahuang Group General Hospital, Heilongjiang, People's Republic of China

Correspondence: Yan Xu (maraxu@163.com) | Mengzhao Wang (mengzhaowang@sina.com)

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ABSTRACT

Background: This study explored the safety and efficacy of combining radiotherapy with sintilimab in non-small cell lung cancer (NSCLC) patients who have progressed after first or second-line therapy.

Methods: In this multicenter, single-arm trial, patients with NSCLC who had progressed after first or second-line therapy were enrolled. Participants received hypofractionated stereotactic body radiotherapy (SBRT) (requiring a single-site biological dose of more than 30 Gy or planned to reach 30 Gy) followed by sintilimab every 3 weeks until disease progression or unacceptable toxicity occurred.

Results: From March 1, 2019, to July 27, 2023, 14 patients were enrolled across two centers. The cohort included 64.3% males and 35.7% females, with a median age of 67 years (range 57–73 years). All participants completed radiation therapy and received at least one cycle of sintilimab. The overall response rate (ORR) was 21.4% (3/14) and the disease control rate (DCR) was 71.4% (10/14). The absent radiation response (ARR) was 14.3% (2/14). The median PFS was 4.17 months (95% CI: 1.15–8.69 months), with a 6-month PFS rate of 42.9%. The median OS was 16.17 months (95% CI: 11.69–20.64 months). Overall, 10 patients (71.4%) experienced at least one treatment-emergent adverse event (TEAE). Grade 3 adverse events included one case each of immune-related myocarditis, thrombocytopenia, and checkpoint inhibitor pneumonitis (CIP). Four patients (28.6%) had immune-related adverse events (irAEs) including skin rash and pruritus (2/14, grade 1), immune-related myocarditis (1/14, grade 3), and CIP (1/14, grade 3).

Conclusions: Radiotherapy combined with sintilimab for NSCLC patients who progressed after first-or second-line therapy showed promising efficacy outcomes.

Xiaoyi Feng and Xiaoyan Liu contributed equally to the study.

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1 | Introduction

Non-small cell lung cancer (NSCLC) remains the leading cause of cancer-related mortality globally, with advanced stages of the disease often exhibiting poor prognosis and limited treatment options [1–3]. Despite significant advancements in first-line treatment, including the integration of targeted therapies and immunotherapy, most patients experience disease progression within the first year [4]. The limited efficacy of subsequent treatment lines for advanced NSCLC underscores the critical need for innovative therapeutic strategies to improve outcomes and enhance the quality of life for this patient population [5, 6].

Recent developments in cancer immunotherapy have led to considerable interest in exploring combinations of immune checkpoint inhibitors (ICIs) with other treatment modalities to maximize the anti-tumor effects [7, 8]. Concurrently, the role of radiation therapy in NSCLC has evolved beyond local disease control [9]. Radiotherapy (RT) has been identified as a potential modulator of the tumor microenvironment, capable of enhancing tumor antigenicity and promoting inflammatory responses that can synergize with immunotherapy [10]. This combination approach, known as immunoradiotherapy, seeks to leverage radiation-induced immune modulation to enhance the efficacy of programmed death-1 (PD-1) inhibitors [11].

Sintilimab, a PD-1 inhibitor, can specifically bind to PD-1 and effectively block the interaction between PD-1 and programmed death-ligand 1 (PD-L1), enhancing T cell response activation and producing anti-tumor effects [10]. Sintilimab has a higher monovalent affinity to human PD-1 than pembrolizumab and nivolumab [12]. In China, sintilimab in combination with chemotherapy has been approved for the first-line treatment of non-squamous/squamous NSCLC, and it is the first PD-1 inhibitor approved for patients with EGFR-mutated non-squamous NSCLC that progressed after EGFR-TKI therapy [13–15]. Furthermore, sintilimab in combination with docetaxel, radiation therapy, or anlotinib has also shown promising anti-tumor efficacy, and is therefore worth further exploration [16].

Given the pressing need for more effective treatments in the second-line or later setting for NSCLC, our study investigated the safety and efficacy of combining radiation therapy with sintilimab in patients who have progressed on first or second-line therapy. This prospective multicenter single-arm study aimed to establish a potential new standard in the therapeutic regimen for these patients.

2 | Patients and Methods

2.1 | Study Design and Patients

This prospective multicenter single-arm trial evaluated the safety and efficacy of RT in combination with sintilimab in NSCLC patients, who progressed following first or second-line systemic treatment. Eligible patients were aged 18 years or older, had histologically or cytologically confirmed NSCLC, at least one measurable tumor lesion per RECIST 1.1 criteria [17], at least one lesion eligible for radiation, an Eastern Cooperative Oncology Group (ECOG) performance status score of ≤ 1, stage IIIB to IV [18], and disease progression or recurrence after receiving first/s line systemic therapy for advanced or metastatic disease or intolerance to chemotherapy. Additionally, patients had to have a normal left ventricular ejection fraction, a life expectancy of ≥ 3 months, and adequate hematologic, hepatic, and renal function.

Key exclusion criteria included EGFR-sensitive mutation or ALK/ROS1 rearrangement, prior exposure to an immunotherapy agent, active infection (including HBV, HCV, and HIV), history of autoimmune disease, interstitial lung disease (including drug-induced ILD, radiation pneumonitis requiring corticosteroids, or any clinical implication for active ILD), prior radiation therapy to the lung, unstable central nervous system (CNS) metastasis or requiring corticosteroids to control CNS symptoms, pregnant or lactating women, and any condition necessitating treatment with continuous systemic corticosteroids > 10 mg/day prednisone or an equivalent dose of other steroids.

All study procedures adhered to the ethical standards set forth in the 1964 Declaration of Helsinki and its later amendments. The Ethical Review Committee of Peking Union Medical College Hospital approved the study (HS-1856), and all participants provided written informed consent before screening. This trial was registered with ClinicalTrials.gov (NCT04167657).

2.2 | Treatments

Participants underwent hypofractionated stereotactic body radiotherapy (SBRT), requiring a single-site biological dose of more than 30 Gy (6Gy × 5, or other) or planned to reach 30 Gy, followed by sintilimab administered at 200 mg intravenously every 3 weeks until progressive disease (PD), intolerable toxicity, or a maximum of 24 months. Radiotherapy can be performed for primary lung lesions or metastatic lesions, such as bone metastases, adrenal lesions, and so on, excluding CNS lesions.

Preclinical studies have shown that fractionated but not single-dose radiotherapy in mice induces immune-mediated distant effects [19]. More than 12 Gy radiation dose can lead to a significant reduction in cytoplasmic double-stranded DNA, and the total dose of radiotherapy should be at least 30 Gy to facilitate T cell infiltration [20]. At the same time, early clinical studies in advanced NSCLC have shown that high-dose hypofractionated SBRT (50Gy/4f) combined with PD-1 inhibitors is superior to traditional radiotherapy (45Gy/15f) combined with PD-1 inhibitors in multiple efficacy endpoints [21]. Hypofractionated SBRT has stronger mechanistic and clinical support for immune synergy. Therefore, we chose hypofractionated radiotherapy with a total dose of at least 30 Gy to trigger its regulation of the immune response.

Image-guided radiotherapy (IGRT) was performed using cone-beam CT (CBCT) for all patients. The clinical target volume (CTV) encompassed the gross tumor volume (GTV) and its

margins of 5–10 mm of possible tumor invasion. The planning target volume (PTV) included an additional 3–5 mm margin to the CTV for setup uncertainty. Sintilimab initiation occurred no later than 3 weeks after completing radiation therapy, which was based on preclinical and clinical evidence suggesting that radiation-induced immunogenic effects peak within 1–3 weeks post-radiation, and initiating immunotherapy within this timeframe may enhance the synergistic antitumor effects [22, 23]. Radiotherapy could be performed on the same day as sintilimab administration.

2.3 | Endpoints and Assessments

Following the initiation of treatment, tumor response assessments will be conducted in patients with measurable disease every 6 weeks (±1 week) using radiographic imaging, in accordance with the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria [17], until disease progression is documented or a new cancer treatment is initiated. The primary endpoint is the Overall Response Rate (ORR), which includes target lesions within the radiation field. The ORR is determined by the proportion of patients achieving a Complete Response (CR) or Partial Response (PR). Secondary endpoints include Progression-Free Survival (PFS), Overall Survival (OS), 1-year survival rate, Disease Control Rate (DCR) and safety. The DCR comprises the proportion of patients with CR, PR, or Stable Disease (SD) as determined by radiographic assessment. The ORR excluding the radiation field lesions is defined as the Absent Radiation Response (ARR). The DCR excluding the radiation field lesions is defined as the Absent Control Rate (ACR). The ARR and ACR are only defined for lesions not irradiated by radiotherapy. The ORR and DCR include lesions irradiated by radiotherapy. OS was defined as the time from the date of first protocol treatment (radiotherapy or sintilimab, whichever came first) to death from any cause or the last contact date for patients lost to follow-up. PFS was measured from the date of first protocol treatment to the first observed disease progression or death from any cause, or the last contact date of the patient who lost follow-up, whichever occurred first.

Safety was assessed in all participants who received at least one dose of the study drug (safety population) through evaluations of adverse events (AEs), clinical laboratory results, physical examinations, and vital sign measurements conducted at baseline, prior to each treatment cycle, and continued until 30 days following the final dose of the trial medication. Patients were monitored until the resolution of any treatment-related toxicities. Adverse events were classified using the Medical Dictionary for Regulatory Activities (MedDRA) version 22.0 [24] and graded according to the National Cancer Institute's Common Terminology, version 4.0 [25]. Radiation pneumonitis was diagnosed based on the temporal relationship to radiotherapy (typically occurring within 6 months), radiographic changes confined to the irradiated field, and exclusion of infectious causes. Immune-related pneumonitis was identified by diffuse or multifocal infiltrates outside the radiation field and response to corticosteroids. During the clinical trial, each AE event was clinically evaluated and diagnosed by at least one respiratory physician and one radiotherapy physician to ensure the smooth progress of the experiment.

2.4 | Statistical Analyses

Descriptive statistics were utilized to summarize patient characteristics, treatment administration, and adverse events (AEs). Quantitative variables approximately following a normal distribution were expressed as means and standard deviations; those with a non-normal distribution were presented as medians and ranges. Qualitative variables were reported as frequencies and percentages. The Kaplan–Meier method was employed to estimate survival times. Statistical analyses were conducted using SPSS 26.0 (SPSS Inc., Chicago, IL, USA) and the R program (version 4.2.0).

3 | Results

3.1 | Patients and Treatment

From March 1, 2019, to July 27, 2023, the study enrolled 14 patients across two centers. The median follow-up duration was 40.1 months (95% confidence interval [CI]: 24.74–55.46 months). The baseline characteristics of the enrolled patients are presented in Table 1. The cohort included 64.3% males and 35.7% females, with a median age of 67 years (range, 57–73 years). The majority of patients were former or current smokers (71.4%), and adenocarcinoma was the most common histological type (71.4%), followed by squamous cell carcinoma (28.6%). Most patients had an ECOG performance status score of 1 (64.3%) and were diagnosed with stage IV disease (85.7%). Overall, 12 patients received platinum-based chemotherapy, while two received a combination of chemotherapy and anti-vascular targeted therapy. All subjects experienced disease progression after first-line or second-line systemic treatment for advanced or metastatic tumors. The median interval from the last dose of prior chemotherapy to the first protocol treatment (radiotherapy or sintilimab, whichever occurred first) was 2.3 months (range, 1.3–3.9) (Table 1).

All patients were immunotherapy-naive and completed the planned RT with at least one cycle of sintilimab (median, 3 cycles; range: 1–35 cycles). Nine patients (9/14, 64.3%) initiated sintilimab concurrently on the first day of radiotherapy. Five patients (5/14, 35.7%) began to receive sintilimab treatment within 3 weeks after the end of radiotherapy. A total of 21.4% (3/14) of patients completed 10 or more treatment cycles. Four patients received local radiotherapy for metastatic lesions, while the remaining 10 patients received radiotherapy for primary lung tumor lesions. All patients discontinued treatment before the cut-off date on April 30, 2024.

3.2 | Efficacy Outcomes

Figure 1A illustrated the waterfall plot showing the best response of all evaluable patients, including those with lesions within the radiation field, along with follow-up imaging data. Figure 1B, on the other hand, presents the best response when assessing lesions excluding the radiation field. One of the patients did not have a CT scan after the disease progressed, so it was not included in the waterfall plot. Figure 2 displayed a swimmer plot of the duration of treatment response. The primary reasons for treatment discontinuation were disease

TABLE 1 | Baseline demographic and clinical characteristics in the included population, *n* (%).

Characteristics	*N* (%)
Sex	
Men	9 (64.3)
Women	5 (35.7)
Age, *y*, median (range)	67 (57, 73)
> 65	7 (50.0)
≤ 65	7 (50.0)
Smoking history	
Never smoke	4 (28.6)
Current / former smoker	10 (71.4)
ECOG	
0	5 (35.7)
1	9 (64.3)
Histology	
Adenocarcinoma	10 (71.4)
Squamous cell carcinoma	4 (28.6)
Staging	
IIIB / IIIC	2 (14.3)
IVA	5 (35.7)
IVB	7 (50.0)
Distant metastasis	12 (85.7)
Intrapulmonary	6 (50.0)
Pleural	5 (41.7)
Brain	2 (16.7)
Bone	7 (58.3)
Liver	1 (8.3)
Adrenal gland	1 (8.3)
Prior cancer therapies	
Chemotherapy	12 (85.7)
Chemotherapy combined with anti – vascular therapy	2 (14.3)
Response to prior chemotherapy	
CR / PR	3 (21.4)
SD	11 (78.6)
PD	0 (0)
Time since prior treatment (months), median (range)	2.3 (0.3, 4.1)
Radiotherapy site	
Primary lung tumor	10 (71.4)
Distant metastasis	4 (28.6)
Bone metastasis	3 (21.4)
Subcutaneous soft tissue	1 (7.2)
The order of receiving radiotherapy and immunotherapy	
Concurrent	8 (57.1)
Sequential	6 (42.9)

Abbreviations: CR: complete response; ECOG: Eastern Cooperative Oncology Group; PD: progressive disease; PR: partial response; SD: stable disease.

progression (12/14, 85.7%) and adverse reactions (2/14, 14.3%). Among the 14 patients evaluated, the ORR, including target lesions within the radiation field, was 21.4% (3/14), and the DCR was 71.4% (10/14), with best responses of PR in three cases (21.4%), SD in seven cases (50.0%), and PD in four cases (28.6%). The ARR, excluding the radiation field, was 14.3% (2/14), and the ACR was 71.4% (10/14), with two cases (14.3%) showing PR, eight cases (57.1%) showing SD, and four cases (28.6%) showing PD (Table 2). The median OS was 16.17 months (95% CI: 11.69–20.64 months), and the median PFS was 4.17 months (95% CI: 1.15–8.69 months) (Figure 3). The PFS rates at 6 months and 1 year were 42.9% and 21.4%, respectively, and the OS rate at 1 year was 57.1%.

After disease progression, 64.3% (9/14) of patients received at least one subsequent anti-tumor treatment, while the remaining five patients received palliative care. Specifically, 18.2% (2/9) of patients received subsequent chemotherapy combined with immunotherapy, including pembrolizumab. Subsequent single-agent chemotherapy was administered to 18.2% (4/9) of patients. Subsequent targeted therapies, including furmonertinib and anlotinib, were given to 27.3% (3/9) of patient.

3.3 | Toxicity

The combination therapy of radiation and sintilimab was generally well tolerated among the study population. A total of 71.4% (10/14) of patients experienced at least one treatment-emergent adverse event (TEAE). Notably, none of the events reached Grade 4 or 5 severity. Three patients experienced Grade 3 adverse events, including one case each of immune-related myocarditis, thrombocytopenia, and checkpoint inhibitor pneumonitis (CIP). Additionally, one patient had a Grade 2 event, and six patients encountered Grade 1 events. Dermatological toxicity was the most frequently observed, affecting 21.4% (3/14) of the patients, with all cases being Grade 1 and primarily presenting as rash and pruritus. Neutropenia was detected in 14.3% of the patients, corresponding to two Grade 2 cases. Furthermore, 28.6% (4/14) of patients were identified to have immune-related adverse events (irAEs) based on the investigators' assessment, including skin rash and pruritus in two patients (Grade 1), immune-related myocarditis in one patient (Grade 3), and CIP in another patient (Grade 3) (Table 3). There were no treatment-related fatalities. Immune-related adverse events were effectively managed with corticosteroids and temporary cessation of sintilimab.

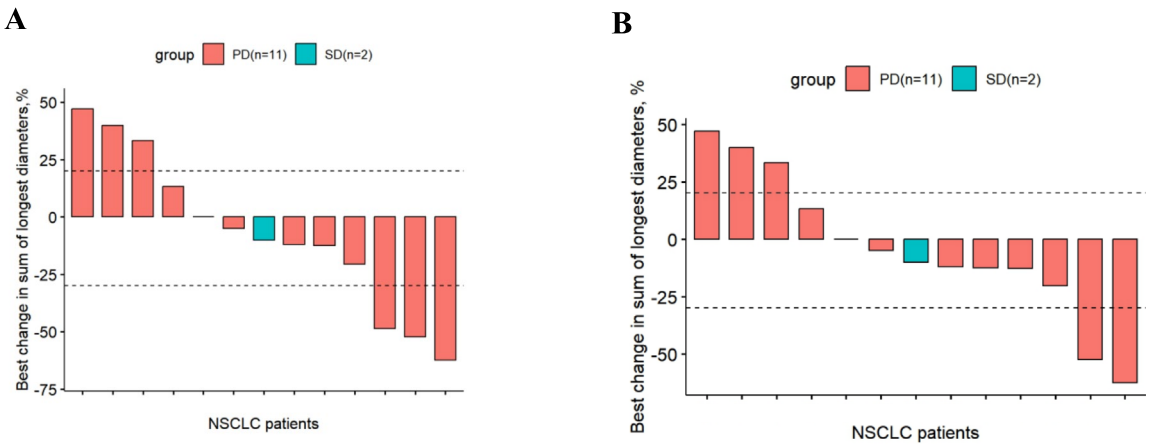

FIGURE 1 | Waterfall plots of best response in individual patients. (A) Illustrated the best response of all evaluable patients, including those with lesions within the radiation field. (B) Presented the best response when assessing lesions excluding the radiation field. One patient who did not undergo radiological scans after disease progression was therefore not included in the waterfall plot. NSCLC: non-small cell lung cancer; PD: progressive disease; SD: stable disease.

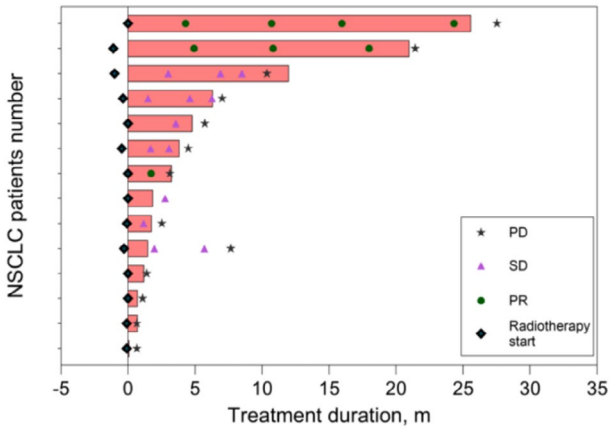

FIGURE 2 | A swimmer plot of duration of response in individual patients. m: month; NSCLC: non-small cell lung cancer; PD: progressive disease; PR: partial response; SD: stable disease.

TABLE 2 | Patient's response according to RECIST v1.1, *n* (%).

Best overall response	Including radiotherapy lesions	Except for radiotherapy lesions
PR	3 (21.4)	2 (14.3)
SD	7 (50.0)	8 (57.1)
PD	4 (28.6)	4 (28.6)

Abbreviations: PD: progressive disease; PR: partial response; RECIST: response evaluation criteria in solid tumors; SD: stable disease; v1.1: version 1.1.

4 | Discussion

Our study demonstrates that RT combined with sintilimab shows manageable safety and promising efficacy in NSCLC patients who have failed first- or second-line treatments. The observed ORR and DCR are consistent with the hypothesized benefits of radiotherapy-induced modulation of the tumor microenvironment to enhance PD-1 inhibition. Survival outcomes suggest that this combination therapy may offer more durable benefits compared with existing second-line treatment options.

The CHECKMATE017/057 and KEYNOTE-010 trials established nivolumab and pembrolizumab as effective second-line therapies for NSCLC, with median PFS of 2.7 ~ 3.5 months and 3.9 months, respectively, showing benefits in patients without EGFR mutations [6, 26–28]. However, the ORR of PD-1/PD-L1 inhibitors is typically less than 20%, highlighting the need for more effective treatments. Our study indicates that combining RT with immunotherapy extends median OS to 16 months, surpassing the 10–12 months typically seen with monotherapy. With an ORR of 21.4%, a DCR of 71.4%, and a median duration of response (DoR) approaching 20 months, our findings suggest the potential for sustained benefits in a subset of patients, underscoring the value of this therapeutic approach.

RT can reshape the tumor microenvironment and reactivate immune-suppressed conditions, thereby enhancing the efficacy of immunotherapy in cancer patients [11, 29–31]. The randomized PEMBRO-RT study, involving NSCLC patients who had failed two or more prior treatments, compared pembrolizumab with and without SBRT. The study showed that the ORR in the combination group was double that of the monotherapy group (36% vs. 18%), without an increase in toxicity. Although the median PFS and OS did not reach statistical significance, the separation of survival curves was evident [32]. A pooled analysis of two randomized studies (PEMBRO-RT and the MDACC study) also showed that ORR was significantly higher with pembrolizumab combined with RT than with drug monotherapy [21]. Similar to the present study, PEMBRO-RT also used a single dose of ≥ 5 Gy of hypofractionated SBRT (e.g., 30 Gy/3–5 fractions). Although conventional fractionated radiotherapy (e.g., 2 Gy × 15f) is preferred for extensive disease because of the lower risk of toxicity, low-fractionated SBRT offers significant advantages in immunotherapy. Larger fractions (≥ 5 Gy) are more effective in inducing immune cell death by generating cell membrane DNA fragments that can activate innate immune signaling pathways [11, 25]. Preclinical studies have shown that 6–10 Gy per fraction optimally activates the cGAS-STING pathway, maximizes

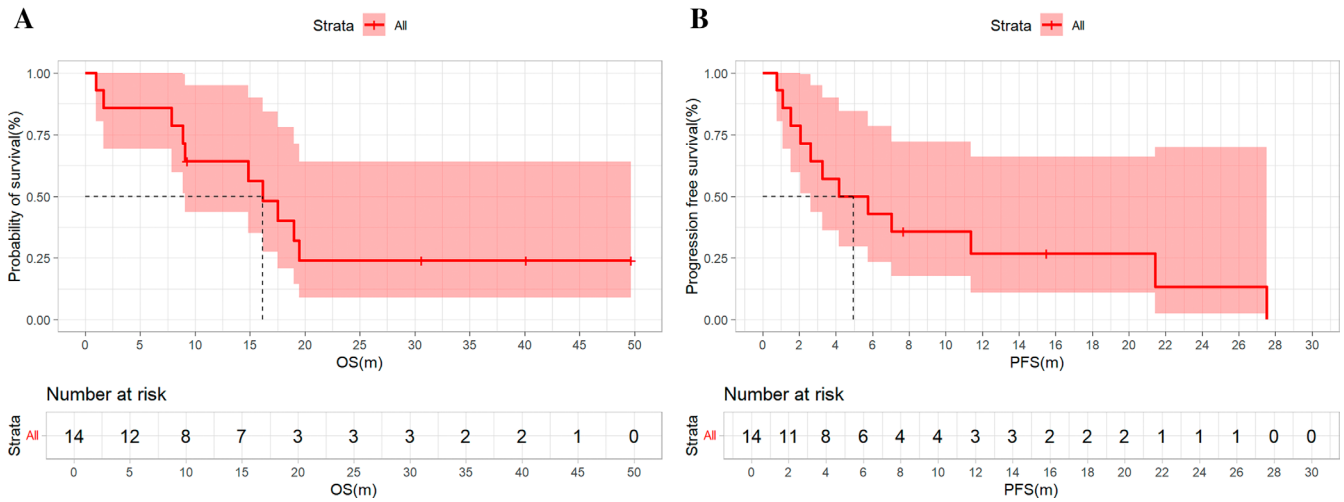

FIGURE 3 | Kaplan–Meier estimates of (A) OS and (B) PFS for the 14 enrolled patients. m, month; OS, overall survival; PFS, progression-free survival.

TABLE 3 | Treatment-emergent adverse events in all treated patients.

AE	*N* (%)
Any TRAEs	10 (71.4)
Dermatological toxicity	3 (21.4)
Neutropenia	2 (14.3)
Anemia	1 (7.1)
Thrombocytopenia	1 (7.1)
Immune – related myocarditis	1 (7.1)
CIP	1 (7.1)
Radiation pneumonitis	1 (7.1)
Any AE	
Leading to any study drug interruption	1 (7.1)
Leading to any study drug withdrawal	3 (21.4)
Grade AE	
1	6 (42.9)
2	1 (7.1)
3	3 (21.4)
4	0 (0)
Any irAEs	
Skin rash and pruritus	2 (14.3)
Immune – related myocarditis	1 (7.1)
CIP	1 (7.1)

Abbreviations: CIP: checkpoint inhibitor pneumonitis; irAEs: immune-related adverse events; TRAEs: treatment-related adverse events.

STING-dependent γ-interferon production, promotes dendritic cell maturation, and enhances CD8+ T-cell infiltration, thereby creating a pro-inflammatory tumor microenvironment that acts synergistically with PD-1 inhibitors [24, 26]. This mechanistic synergy is likely to underlie the improved ORR observed in PEMBRO-RT and in our study. The relatively low ORR in this study may be related to the small sample size. Larger randomized trials are needed to verify whether the 30 Gy/5-fraction regimen is the optimal dose-fraction regimen for immunomodulation. In addition, although low-fraction SBRT has practical advantages (e.g., shorter treatment time, reduced normal tissue exposure), its applicability to patients with multifocal or bulky disease needs to be further explored.

The combination of SBRT and immunotherapy can enhance antitumor effects, though the abscopal effect is relatively rare [33]. Brooks and colleagues emphasized the need for multi-site irradiation to enhance the abscopal effect and maximize the efficacy of I-SBRT treatment [22]. The COSINR study, which mirrors our study in the timing of RT and immunotherapy, allowed SBRT to be delivered to 1–4 isocenters. The study found that multisite SBRT combined with immunotherapy enhanced both intra- and extra-tumoral immune responses, showing significant efficacy and good tolerability in first-line NSCLC treatment [34]. Similarly, Luke et al. reported safety data in 73 patients with solid tumors who received pembrolizumab following SBRT to 2–4 tumor sites. Doses ranged from 30 to 50 Gy over 3 to 5 fractions, with an overall ORR of 13.2%, a median OS of 9.6 months, and a median PFS of 3.1 months. They concluded that multisite SBRT is well tolerated before pembrolizumab treatment [35]. Given that our study involved patients with advanced disease who progressed after first- or second-line therapy, toxicity concerns may limit the use of SBRT at multiple tumor sites. However, applying SBRT to a single site (primary or metastatic) combined with immunotherapy still showed good efficacy, with an ORR of 21.4% and a DCR of 71.4%. More prospective studies with larger sample sizes are needed to determine the optimal choice of RT site in this therapeutic strategy.

Evidence suggests that radiation-induced immunogenic effects peak within 1–3 weeks after radiation, and generally gradually decrease to baseline levels within 7–14 days after radiation, which emphasizes the importance of the best time between radiotherapy and immunotherapy [23]. In most studies, patients received immunotherapy within 1 week after completing RT.

Bestvina et al. reported a phase I trial of NSCLC patients receiving concurrent or sequential ipilimumab, nivolumab, and SBRT, showing no increased toxicity in the concurrent group and good tolerance in patients with widespread metastases, with no significant difference in best response rates between the two groups [36]. In our study, some patients received concurrent RT and immunotherapy, demonstrating good tolerance without an increase in severe adverse events. Determining the optimal timing strategy for integrating these treatments will be crucial in future research.

The manageable safety profile of this combination therapy is noteworthy, as it did not result in a significant increase in severe adverse events compared to the expected profile of PD-1 inhibitors alone. The incidence of grade ≥3 adverse events in our study was 21.4%, similar to the results of the PEMBRO-RT and MDACC studies [21, 32]. The low incidence of immune-related adverse events (irAEs) underscores the potential for broad clinical application of this combined therapy without undue concerns about patient safety. The ability to manage irAEs with standard interventions such as corticosteroids further supports the feasibility of this therapeutic approach in routine clinical practice.

During the recruitment phase of our study, we observed a pivotal finding that the combination of sintilimab with SBRT and low-dose radiation therapy (LDRT) as a first-line treatment demonstrated high ORR and PFS, along with favorable tolerability in advanced NSCLC patients who were negative for driver genes and positive for PD-L1 [10]. This development suggests that the immunoradiotherapy regimen may advance from a second-line to a first-line treatment option, offering earlier intervention for patients with advanced NSCLC. In light of these findings, we halted patient enrollment in October 2023 to prevent redundancy with established treatment protocols and to reassess our strategic approach to ensure patients receive the most up-to-date care. This aligns with the efficacy of the immunoradiotherapy combination, further validating our study's outcomes.

Despite the promising results, our study has limitations, including the small sample size and single-arm design, which may affect the generalizability of the findings. Future studies should focus on expanding patient recruitment and include control groups to validate and extend our findings. Additionally, several factors affecting the combination of RT and immunotherapy need to be addressed. Issues such as RT techniques, dose and volume, fractionation method, irradiation site, timing of immunotherapy initiation, and choice of immunotherapeutic agents all require further clinical trial data to be fully elucidated. It is also necessary to further explore the mechanistic basis of the synergy between RT and PD-1 inhibition. Moreover, identifying predictive biomarkers for response to combination therapy may allow for more precise patient selection, improving clinical outcomes while minimizing unnecessary exposure to potential side effects, thereby personalizing and optimizing treatment interventions.

5 | Conclusion

The integration of RT with sintilimab may represent a significant advancement in NSCLC treatment. This approach not only offers potential efficacy improvements over standard treatments but also maintains a favorable safety profile, which is critical for patients with advanced disease. These findings support further exploration of immuno-radiotherapy combinations and may set new standards in clinical practice.

Author Contributions

Xiaoyi Feng: conceptualization, data curation, formal analysis, writing – original draft. **Xiaoyan Liu:** conceptualization, data curation, formal analysis, writing – original draft. **Hui Guan:** methodology, resources, validation. **Chunhong Chen:** investigation, project administration. **Feng Gao:** investigation, project administration. **Xiaoxing Gao:** investigation, software, visualization. **Minjiang Chen:** investigation, software, visualization. **Jing Zhao:** investigation, software, visualization. **Yan Xu:** funding acquisition, supervision, writing – review and editing, final approval of the manuscript. **Mengzhao Wang:** funding acquisition, supervision, writing – review and editing, final approval of the manuscript. All authors have read and approved the final version.

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Ethics Statement

All study procedures adhered to the ethical standards set forth in the 1964 Declaration of Helsinki and its later amendments. The Ethical Review Committee of Peking Union Medical College Hospital approved the study (HS-1856), and all participants provided written informed consent before screening. This trial was registered with ClinicalTrials.gov (NCT04167657).

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author.

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