



Efficacy of single-site radiotherapy plus PD-1 inhibitors vs PD-1 inhibitors for oligometastatic non-small cell lung cancer

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Abstract

Purpose Growing numbers of clinical trials test the efficacy of radiotherapy (RT) plus immune checkpoint inhibitors (ICIs), but the number of irradiated sites is not uniform. We aimed to evaluate the efficacy of single-site RT plus immunotherapy in oligometastatic non-small cell lung cancer (NSCLC) with smaller disease burdens and low tumor heterogeneity.

Methods We retrospectively identified oligometastatic NSCLC (< 4 metastatic sites) patients treated with PD-1 pathway inhibitors with or without RT to a single lesion in our institution between 2018 and 2020. The primary endpoints were the best objective response rate (ORR) and progression-free survival (PFS).

Results Of the 152 patients enrolled, 93 and 59 were identified as the ICI alone group and the ICI plus RT group, respectively. The addition of RT to ICI therapy significantly increased the best ORR from 31.2% to 50.8% ($p=0.015$). The out-of-field (abscopal effect) response rate could reach 41.3% (95%CI 26.5%–56.1%) in the ICI plus RT group. Median PFS was 8.9 months (95%CI 4.7–13.1 months) with ICI alone versus 13.8 months (95%CI 9.5–18.1 months) with ICI plus radiotherapy (hazard ratio [HR] 0.556; $p=0.035$). In an exploratory subgroup analysis of PFS, the addition of RT brought greater benefits in patients aged < 65 years ($p=0.016$), patients with ECOG PS = 0 ($p=0.048$), and patients with 1–2 metastatic sites ($p=0.024$). No unexpected adverse events or significantly increased toxicities were observed in the experimental arm.

Conclusion Single-site RT plus anti-PD-1 inhibitors significantly increased systemic responses and improved survival outcomes in oligometastatic NSCLC patients.

Keywords Oligometastatic · PD-1 · Immune checkpoint inhibitors · Radiotherapy · NSCLC

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Background

The introduction of immunotherapy has transformed the treatment paradigm for advanced non-small cell lung cancer (NSCLC). Immunotherapy mainly refers to checkpoint inhibitors, such as PD-1, PD-L1, and CTLA-4. Chemotherapy combined with PD-1/PD-L1 inhibitors immunotherapy or immunotherapy alone has been approved as the standard first-line treatment for advanced NSCLC based on the results of the KEYNOTE (010, 024, 042) (Herbst et al. 2016; Mok et al. 2019; Reck et al. 2016). Unfortunately, only approximately 20% of unselected NSCLC patients could benefit from immunotherapy, spurring efforts to explore combination strategies (Borghaei et al. 2015; Gandhi et al. 2018).

Radiotherapy (RT) increases the expression of tumor-associated antigens and causes tumor cell immunogenic death, which promotes migration of T lymphocytes to tumor sites, thereby enhancing the local antitumor effects (Deng et al. 2014; Formenti and Demaria 2013; Verbrugge et al.

2012). Furthermore, RT can cause the decrease or regression of tumor outside the irradiation field. This phenomenon called the abscopal effect is because local RT causes a systemic immune response (Formenti et al. 2018; Khalife et al. 2019; Sezen et al. 2021; Theelen et al. 2020; Zhuang 2020).

However, data on the efficacy of the anti-PD-1 treatment with RT among metastatic NSCLC patients generally do not show better results than those among patients who have received immune checkpoint.

Inhibitors (ICI) alone (Samuel et al. 2020; Theelen et al. 2019). The reason for the inconsistent outcomes may be the single-site irradiation in these studies. Given the larger tumor burden and non-equal immunogenicity in metastatic NSCLC, irradiating only a single lesion in patients with multiple metastases might not be sufficient to induce systemic responses (Brooks and Chang 2019).

In metastatic NSCLC patients, approximately 25–50% of patients presented with oligometastatic disease (Parikh et al., 2014). (Bauml et al. 2019) conducted a single-arm phase II trial specifically focusing on oligometastatic NSCLC patients treated with local ablative therapies at all sites, plus pembrolizumab. The results with a 19.1-month median PFS-P (from the start date of pembrolizumab use) were significantly better than the historical control, with a PFS of 6.6 months. Despite this success, the irradiation of a single lesion continues to be the cornerstone of current strategies designed to test the efficacy of RT in combination with immunotherapy. Moreover, no prospective studies have been conducted on this trial design for oligometastatic NSCLC.

Therefore, we conducted a retrospective study of immunotherapy with or without irradiation of a single lesion for oligometastatic NSCLC. This study evaluated whether single-site RT was sufficient to enhance the systemic response of immunotherapy.

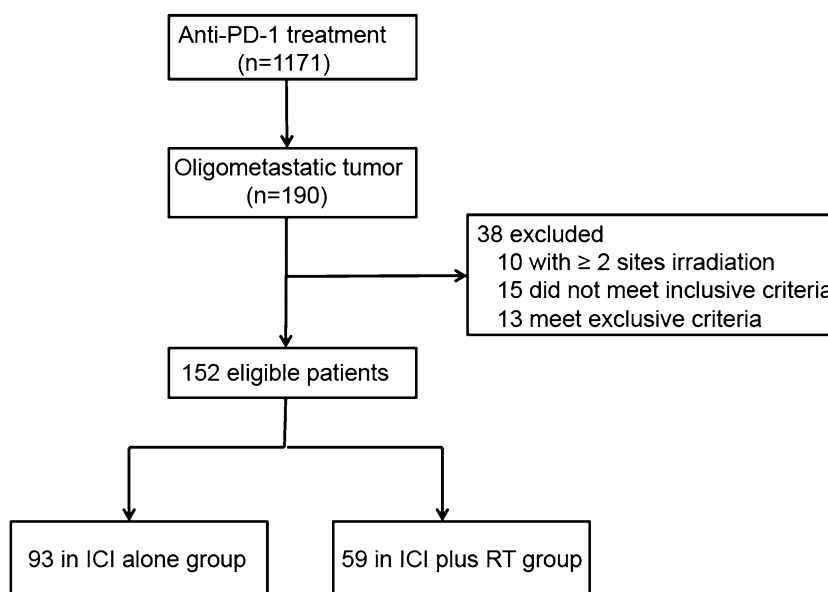
Materials and methods

Patient selection

Management of oligometastatic disease in patients with limited metastases is supported by relatively high-level evidence. In our institution, local therapies are recommended in combination with systemic therapy in well-selected patients. Gains in survival due to the ICIs therapy have further inspired research into the oligometastatic paradigm. We retrospectively reviewed the data of patients with oligometastatic NSCLC (defined as having < 4 metastases) (Bauml et al. 2019) treated in our institution (2018–2020) with immunotherapy (PD-1 checkpoint inhibitors) combined with or without RT (Fig. 1). The RT was limited to single-site irradiation in this treatment phase. Other key eligibility criteria included: (1) At least 1 separate lesion was required, which was measurable according to the Response Evaluation Criteria in Solid Tumors version 1.1; (2) ≥ 2 cycles of anti-PD-1 treatment; and (3) no epidermal growth factor receptor (EGFR) and/or anaplastic lymphoma kinase (ALK) targetable mutations. Patients were ineligible if they had (1) prior treatment with immunotherapy and (2) no complete clinical and follow-up data. Patients were divided into two groups based on whether they received RT or not: ICI alone and ICI plus RT groups. The collected data included baseline demographics, ECOG performance status, prior systemic treatment, immunotherapy regimens and RT details, treatment-related toxicities, and follow-up data.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Research Ethics Board of Shandong Cancer Hospital, and individual consent was waived owing to its retrospective nature. The authors are accountable for all

Fig. 1 The flow chart of patient selection



aspects of the work in ensuring that questions relating to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Treatment and outcomes

Patients received one of the following anti-PD-1 agents every two or three weeks with or without chemotherapy: sintilimab (Innovent Biologics, China), toripalimab (Shanghai Merck & Co.), camrelizumab (Jiangsu Hengrui Medicine, China), nivolumab (Bristol-Myers Squibb, USA), or pembrolizumab (Merck & Co., USA) (Supplementary Table 1). In the anti-PD-1 plus RT group, the radiation sites included primary tumors and metastatic lesions. Tumor response was assessed using radiographic imaging by the investigators according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1), and adverse events (AEs) were evaluated using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, with causality to treatment recorded. In particular, the response of unirradiated lesions (out-of-field) was also evaluated in the anti-PD-1 plus RT group.

The primary endpoints were the best objective response rate (ORR) and progression-free survival (PFS). Secondary endpoints included safety and disease control rates. PFS was defined as the time between the commencement of anti-PD-1 treatment to the date of progression or death, whichever occurred first.

Statistical analyses

Baseline characteristics and quality-of-life measures were summarized by descriptive statistics and compared using χ^2 contingency analyses. The Kaplan–Meier method and log-rank test were used to evaluate PFS. In the subgroup analyses, the effect on PFS of the addition of RT to immunotherapy was assessed among the subgroups using Cox proportional hazard models presented in a forest plot. Statistical significance was set at $P < 0.05$. Analyses were conducted using the Statistical Package for the Social Sciences software package, version 23.0 (SPSS Inc., Chicago, IL, USA) and GraphPad Prism, version 7.00 for Windows (GraphPad Software).

Results

Patient characteristics and disposition

Between July 2018 and March 2020, 152 eligible patients were retrospectively identified and assigned to the ICI alone group ($n = 93$) and the ICI plus RT group ($n = 59$). Figure 1 shows the selection of patients and patient characteristics are summarized in Table 1. The median age of these patients was 62 years (range, 34–81 years), and 128 (84%) were

male. There were 39 (42.0%) patients in the ICI alone group and 21 (35.6%) patients in the ICI plus RT group receiving PD-1 inhibitor as first-line therapy. The PD-L1 status was collected in 50 patients. Patient demographics, including

Table 1 Patient baseline clinical and treatment characteristics

Demographic or Characteristic	PD-1 ($n = 93$)	PD-1 plus RT ($n = 59$)	<i>P</i> value
<i>Age</i>			0.474
< 65	59	34	
≥ 65	34	25	
<i>Gender</i>			0.442
Male	80	48	
Female	13	11	
<i>Smoking, pack-years</i>			0.231
< 10	35	28	
≥ 10	58	31	
<i>ECOG PS</i>			0.423
0	44	24	
1–2	49	35	
<i>Histology</i>			0.132
Adenocarcinoma	55	42	
Squamous	38	17	
<i>Metastatic timing</i>			0.159
Synchronous	55	28	
Metachronous	38	31	
<i>Number of metastases</i>			0.241
1	33	28	
2	29	20	
3	23	8	
4	8	3	
<i>Lines of previous chemotherapy</i>			0.436
0	39	21	
1–3	54	38	
<i>PD-L1 status</i>			0.573
Negative	10	4	
Positive (≥ 1%)	20	16	
Unknown	63	39	
<i>Systemic treatment options</i>			0.138
Anti-PD-1 monotherapy	27	24	
Anti-PD-1 and chemotherapy	66	35	
<i>Irradiated tumor site</i>			
Lung, primary tumor	–	12	–
Lung/Pleural, metastasis	–	5	–
Brain	–	26	–
Bone	–	11	–
Adrenal	–	1	–
Liver	–	1	–
Lymph node(s)	–	3	–

Abbreviations ECOG PS Eastern Cooperative Oncology Group performance status, PD-L1 programmed death ligand 1

age, gender, smoking status, ECOG PS, histology, metastatic timing, number of metastases, previous chemotherapy, and systemic treatment options, were well balanced between the two groups (Table 1).

Efficacy

At the cutoff date of February 2021, the median follow-up time was 8.1 months (range, 1.3–29.9 months). In the ICI alone group, no complete response was observed, 29 (31.2%) patients had confirmed partial response, and 52 (55.9%) patients had stable disease (Table 2). In the ICI plus RT group, 2 (3.4%) patients had confirmed complete response, 28 (47.5%) patients achieved partial response, and 25 (42.4%) had stable disease (Table 2). Best ORR was significantly higher with ICI plus RT compared with ICI alone (50.8% vs. 31.2%; odds ratio [OR] 2.28, 95% CI 1.17–4.48; $p=0.015$) (Table 2 and Fig. 2A). In the out-of-field evaluable population ($n=46$) of the ICI plus RT group, the out-of-field ORR was 41.3% (95% CI, 26.5–56.1%), which is higher than an ORR of 31.2% in the ICI alone group ($p=0.238$) (Table 2). Kaplan–Meier analysis indicated a significantly better PFS in the ICI plus RT group compared with the ICI alone group (median PFS, 13.8 vs. 8.9 months; HR, 0.556; 95% CI, 0.330–0.937; $p=0.035$, Fig. 2B).

Among the 60 patients who have received PD-1 inhibitors as first-line treatment, the ORR observed were 38.5% in the anti-PD-1 alone group ($n=39$) and 57.1% in the anti-PD-1 plus RT group ($n=21$) (Fig. 3A). In the 92 patients receiving PD-1 inhibitors as second- or later-line treatment, the ORRs observed were 25.9% in the anti-PD-1 alone group ($n=54$) and 47.3% in the anti-PD-1 plus RT group ($n=38$) (Fig. 3B).

Efficacy by primary tumor and brain metastases

Of the 59 patients in the ICI plus RT group, 12 had primary tumor RT, and 26 had brain RT. Compared with patients in the ICI alone group, primary tumor RT showed an improved ORR (31.2% vs. 50.0%; OR, 0.453, 95% CI 0.14–1.53; $p=0.453$ Fig. 4A) and a better PFS (HR, 0.441, 95% CI 0.187–1.041; $p=0.062$ Fig. 4B).

Table 2 Investigator-assessed best overall tumor response

Group	No. (%)	No. (%)					ORR
		Total	CR	PR	SD	PD	
Anti-PD-1 monotherapy	93 (100.0)	0 (0.0)	29 (31.2)	52 (55.9)	12 (12.9)	29 (31.2)	
Anti-PD-1 plus radiotherapy	59 (100.0)	2 (3.4)	28 (47.5)	25 (42.4)	4 (6.8)	30 (50.8)	
All sites evaluation	46 (100.0)	0 (0.0)	19 (41.3)	23 (50.0)	4 (8.7)	19 (41.3)	

Abbreviations CR complete response, PR partial response, SD stable disease, PD progressive disease, ORR objective response rate

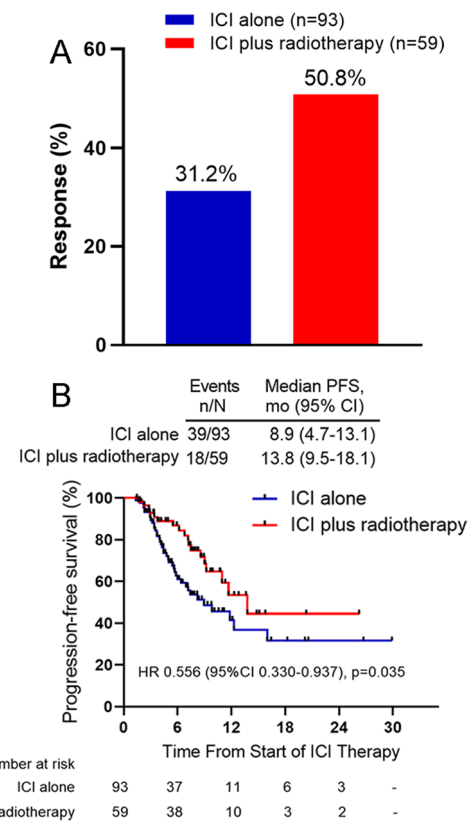


Fig. 2 Best objective response rate (ORR) in patients for the ICI alone treatment versus ICI plus RT treatment comparison (A). Kaplan–Meier estimates of progression-free survival (PFS) in patients for the ICI alone versus ICI plus RT treatment comparison (B). ICI Immune checkpoint inhibitor, mo months, HR Hazard ratio, CI Confidence interval

In the patients with brain metastasis, brain RT also had a better ORR (36.0% vs. 53.8%; OR, 0.200, 95% CI 0.16–1.48; $p=0.200$ Fig. 4C) and PFS (HR, 0.224, 95% CI 0.082–0.606; $p=0.003$ Fig. 4D) compared with brain metastases in ICI alone group.

Subgroup analysis

In the subgroup analysis, the combination of ICI plus RT seemed most beneficial among patients aged < 65 years

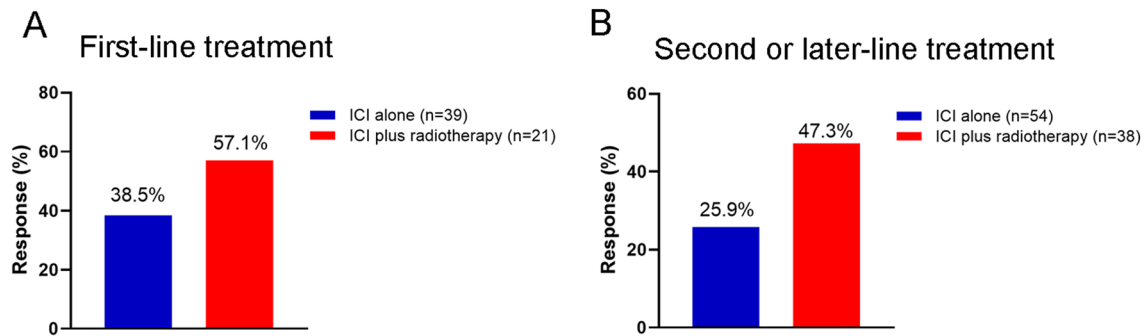


Fig. 3 Comparison of best objective response rate (ORR) between the ICI alone group and the ICI plus radiotherapy group in first-line setting (A) and second or later-line setting (B). *ICI* Immune checkpoint inhibitor

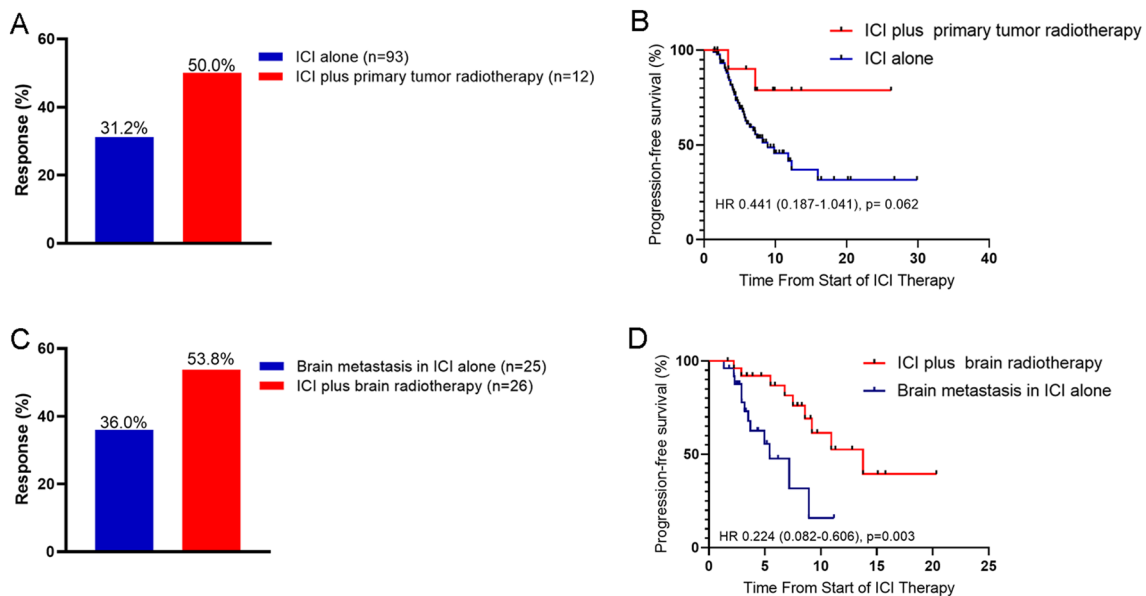


Fig. 4 Objective response rate (ORR) and progression-free survival (PFS) categories by primary tumor RT and brain RT (A) Best ORR in patients received ICI alone vs. primary tumor RT plus ICI. B Kaplan-Meier estimates of PFS in patients for the ICI alone vs. primary tumor RT plus ICI treatment comparison. C Best ORR

in patients with brain metastasis received ICI alone vs. RT plus ICI. D Kaplan-Meier estimates of PFS in patients with brain metastases for the ICI alone versus brain RT plus ICI treatment comparison. *ICI* Immune checkpoint inhibitor

($p=0.016$), female patients ($p=0.015$), ECOG PS = 0 patients ($p=0.048$), synchronous metastases patients ($p=0.012$), patients with 1–2 metastatic sites ($p=0.024$), and patients who received PD-1 inhibitor as first-line therapy ($p=0.009$) (Fig. 5). A trend toward greater clinical benefit from the addition of RT was seen in the PD-L1-negative subgroup vs. the PD-L1-positive subgroup (Fig. 5).

We performed an exploratory analysis to determine whether any feature was associated with PFS in the ICI plus RT group. As shown in Supplementary Table 2, we could not identify any clinical variables that were significantly associated with PFS in the univariate analysis; therefore, we did not perform multivariable analyses.

Safety

We conducted a safety evaluation of the ICI plus RT group (Table 3). The overall incidence of AEs was 97% (57 of 59), and most of the observed AEs were grade 1–2 (Table 3). Grade 3–5 treatment-related AEs occurred in nine patients (15%), and one patient died of severe pneumonia. These grade 3–4 AEs were pneumonia (four patients, 7%), bone marrow suppression (four patients, 7%), transaminitis (one patient, 2%), and headache and/or dizziness (one patient, 2%). Most AEs were clinically manageable, with no new toxicity signals.

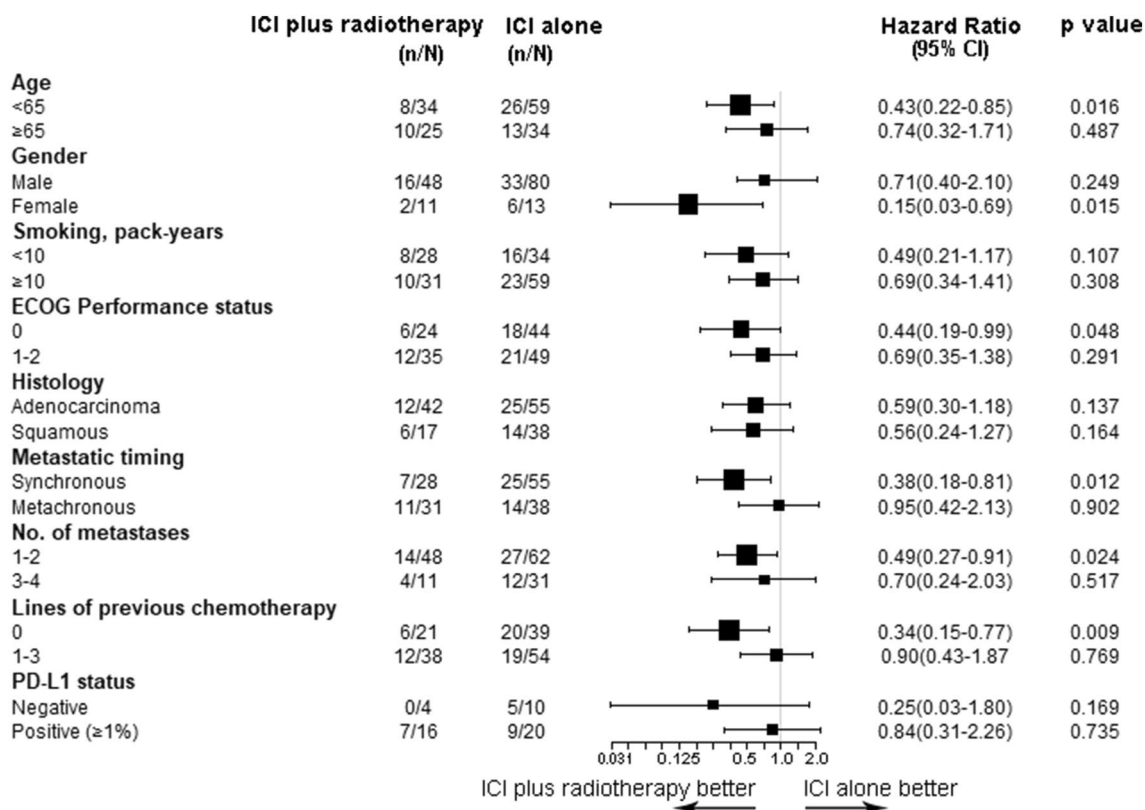


Fig. 5 Forest plot of subgroup analysis on progression-free survival

Table 3 Treatment-related adverse events with at least 10% incidence in study population

	No. (%) of Patients (n = 59)		
	All grades	Grades 1–2	Grades 3–5
Any adverse event	57 (97)	48 (81)	9 (15)
Fatigue	32 (54)	32 (54)	0
Pain	20 (34)	20 (34)	0
Gastrointestinal response	20 (34)	20 (34)	0
Headache/Dizziness	17 (29)	16 (27)	1 (2)
Bone marrow suppression	12 (20)	8 (14)	4 (7)
Nausea	11 (19)	11 (19)	0
Pneumonia	11 (19)	7 (12)	4 (7)
Transaminitis	9 (15)	8 (14)	1 (2)
Cough	8 (14)	8 (14)	0
Dyspnea	6 (10)	6 (10)	0

Discussion

This study reported the efficacy and safety of combining single-site RT and ICIs in patients with oligometastatic NSCLC. Our study showed that the addition of single-site RT to immunotherapy could improve ORR and PFS with

acceptable AEs. Of note, this combination therapy enhances the occurrence of out-of-field (abscopal) response. The favorable clinical outcomes were also observed for patients with brain metastases. Subgroup analysis revealed that younger patients, patients with a better physical constitution, patients with fewer metastatic sites, and patients who received ICIs as first-line therapy benefited more from the combined approach.

Although no matched paired analysis was performed due to the relatively limited sample size, strict inclusion and exclusion criteria were followed to avoid potential bias. Our results showed that the clinical features were well balanced between the two groups. To further confirm this conclusion, we also performed a subgroup analysis (including brain metastases and primary tumors irradiation). Therefore, we believe our conclusion is interesting enough to warrant large-scale studies.

Oligometastasis with a small disease burden can be classified as an indolent state between the extensive and locally advanced stages. Despite having a relatively short follow-up time for oligometastatic NSCLC patients in the study, anti-PD-1 monotherapy achieved a median PFS of 8.9 months, with an ORR of 31.2%. This was significantly better than the results of the CheckMate 057 and KEYNOTE-001 studies in a second-line setting and was also

higher than the median PFS of 6.4 months (KEYNOTE-407) in a first-line setting (Borghaei et al. 2021; Herbst et al. 2016; Paz-Ares et al. 2020). This result suggests that a smaller tumor burden might be necessary for increasing the response to immunotherapy. Local therapy for oligometastatic NSCLC has been shown to improve clinical outcomes in multiple clinical trials (Gomez et al. 2016; Qiu et al. 2017; Weickhardt et al. 2012). RT as a primary local treatment provides local control of the irradiated lesion, and when administered in combination with immunotherapy, enhances antitumor response far outside of the radiation, which is known as the abscopal effect. This phenomenon crucially determines the anti-tumor efficiency of the local RT and ICI combination strategy (Ngwa et al. 2018). However, current strategies designed to test the efficacy of the combination strategy cannot optimally achieve abscopal effects through single-site irradiation in metastatic tumors (Kwon et al. 2014; McBride et al. 2021). In our study, we observed a significant response rate of 50.8% and an out-of-field response rate of 41.3%, which was higher than the ICI alone group (31.2%). Such a trial design is selected for oligometastatic patients with a small disease burden and equally immunogenic tumors that may fully activate the patient's immune system. In our subgroup analysis, patients with 1–2 vs. 3–4 metastatic sites benefited more from anti-PD-1 treatment plus RT, which further supports the view of a small disease burden in favor of immune responses. In contrast to oligometastatic disease, the heterogeneity of polymetastases means that tumor-associated antigens exposed to RT might not be present at other unirradiated locations, or, if they are present, they might only be recognized in subgroups of the tumor lesion and not in the entire cellular population, making immune clearance at these other unirradiated locations impossible or greatly limited (Easwaran et al. 2014; Heppner and Shekhar 2014; Sharabi et al. 2015; Spiotto et al. 2016).

Undeniably, more biological and clinical evidence supports the use of comprehensive RT delivered to multiple lesions combined with immunotherapy. Irradiating multiple sites helps to increase the likelihood of exposure to both shared and exclusive tumor-associated antigens and promptly reduce tumor burden (Brooks and Chang 2019). A randomized clinical trial from MADCC assessing the effect of combining pembrolizumab with stereotactic body RT showed an out-of-field response rate of 38%, which was much higher than that of PD-1 monotherapy (Welsh et al. 2020). Overall, using multisite irradiation combined with immunotherapy could be beneficial to achieve better therapeutic outcomes. However, this approach is not being widely tested in clinical trials, most likely owing to the lack of official guidelines or fear of AEs.

RT is a local treatment that acts on both the tumor and the surrounding non-malignant tissues; therefore, the likelihood of a successful immunogenic event is also influenced by the

tumor microenvironment, the surrounding tissue or organ, and the nodal characteristics of the irradiated site. For example, irradiation of liver metastases in NSCLC patients has resulted in stronger activation of antitumor immunity than the irradiation of pulmonary metastases (Tang et al. 2017). For liver metastases, our sample size is inadequate for accurate analysis. Additionally, the results of our subgroup analyses showed that patients who derived benefit had good prognostic factors, including young age, good body condition, and have received immunotherapy as first-line treatment. Certainly, these optimizations of the ICI combination with RT still need to be validated in prospective clinical trials.

Nevertheless, our study had several limitations. First, this was a retrospective, single-institution analysis with a small sample size, which may introduce selection bias. For example, the percentage of patients with brain metastases in this study was higher than that reported in other studies. Another weakness of our study is the heterogeneity of treatment, including administering different PD-1 pathway inhibitors and different RT regimens; this represents a significant confounding factor. Third, because of the relatively short follow-up period, the survival analysis is limited to PFS, and the conclusion should be interpreted with caution. Moreover, the PD-L1 status of most patients in our study was unknown, making comprehensive subgroup analysis difficult. Nonetheless, we still analyzed the available data, despite being limited.

Conclusion

In conclusion, our results support that combining single-site RT with PD-1 inhibitors increased responses significantly and improved clinical outcomes in oligometastatic NSCLC patients. This treatment approach warrants further prospective investigation in a randomized clinical trial.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s00432-021-03849-3>.

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Availability of data and material The datasets used in this study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest The authors have no conflict of interest or potential financial disclosures.

Ethics approval This study have obtained appropriate institutional review board approval and have followed the principles outlined in the Declaration of Helsinki for all human investigations. As a retrospective study, formal consent is not required.

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References

- Bauml JM, Mick R, Ciunci C, Aggarwal C, Davis C, Evans T, Langer CJ (2019) Pembrolizumab after completion of locally ablative therapy for oligometastatic non-small cell lung cancer: a phase 2 trial. *JAMA Oncol*. <https://doi.org/10.1001/jamaoncol.2019.1449>
- Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, Brahmer JR (2015) Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *N Engl J Med* 373(17):1627–1639. <https://doi.org/10.1056/NEJMoa1507643>
- Borghaei H, Gettinger S, Vokes EE, Chow LQM, Burgio MA, de Castro Carpeno J, Brahmer J (2021) Five-year outcomes from the randomized, phase III trials checkmate 017 and 057: nivolumab versus docetaxel in previously treated non-small-cell lung cancer. *J Clin Oncol* 39(7):723–733. <https://doi.org/10.1200/JCO.20.01605>
- Brooks ED, Chang JY (2019) Time to abandon single-site irradiation for inducing abscopal effects. *Nat Rev Clin Oncol* 16(2):123–135. <https://doi.org/10.1038/s41571-018-0119-7>
- Deng L, Liang H, Burnette B, Beckett M, Darga T, Weichselbaum RR, Fu YX (2014) Irradiation and anti-PD-L1 treatment synergistically promote antitumor immunity in mice. *J Clin Invest* 124(2):687–695. <https://doi.org/10.1172/JCI67313>
- Easwaran H, Tsai HC, Baylin SB (2014) Cancer epigenetics: tumor heterogeneity, plasticity of stem-like states, and drug resistance. *Mol Cell* 54(5):716–727. <https://doi.org/10.1016/j.molcel.2014.05.015>
- Formenti SC, Demaria S (2013) Combining radiotherapy and cancer immunotherapy: a paradigm shift. *J Natl Cancer Inst* 105(4):256–265. <https://doi.org/10.1093/jnci/djs629>
- Formenti SC, Rudqvist NP, Golden E, Cooper B, Wennerberg E, Luuillier C, Demaria S (2018) Radiotherapy induces responses of lung cancer to CTLA-4 blockade. *Nat Med* 24(12):1845–1851. <https://doi.org/10.1038/s41591-018-0232-2>
- Gandhi L, Rodriguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, Investigators, K (2018) Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N Engl J Med* 378(22):2078–2092. <https://doi.org/10.1056/NEJMoa1801005>
- Gomez DR, Blumenschein GR Jr, Lee JJ, Hernandez M, Ye R, Camidge DR, Heymach JV (2016) Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: a multicentre, randomised, controlled, phase 2 study. *Lancet Oncol* 17(12):1672–1682. [https://doi.org/10.1016/S1470-2045\(16\)30532-0](https://doi.org/10.1016/S1470-2045(16)30532-0)
- Heppner GH, Shekhar M (2014) Tumor heterogeneity is fundamental to the tumor ecosystem. *Oncology (williston Park)* 28(9):780–781
- Herbst RS, Baas P, Kim DW, Felip E, Perez-Gracia JL, Han JY, Garon EB (2016) Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet* 387(10027):1540–1550. [https://doi.org/10.1016/S0140-6736\(15\)01281-7](https://doi.org/10.1016/S0140-6736(15)01281-7)
- Khalife M, Shahid K, Dabney RS, Phan AT (2019) Stereotactic body radiation therapy and immunotherapy. *Clin Adv Hematol Oncol* 17(9):518–523
- Kwon ED, Drake CG, Scher HI, Fizazi K, Bossi A, van den Eertwegh AJ, CA Investigators (2014) Ipilimumab versus placebo after radiotherapy in patients with metastatic castration-resistant prostate cancer that had progressed after docetaxel chemotherapy (CA184-043): a multicentre, randomised, double-blind, phase 3 trial. *Lancet Oncol* 15(7):700–712. [https://doi.org/10.1016/S1470-2045\(14\)70189-5](https://doi.org/10.1016/S1470-2045(14)70189-5)
- McBride S, Sherman E, Tsai CJ, Baxi S, Aghalar J, Eng J, Lee N (2021) Randomized phase ii trial of nivolumab with stereotactic body radiotherapy versus nivolumab alone in metastatic head and neck squamous cell carcinoma. *J Clin Oncol* 39(1):30–37. <https://doi.org/10.1200/JCO.20.00290>
- Mok TSK, Wu YL, Kudaba I, Kowalski DM, Cho BC, Turna HZ, Investigators, K (2019) 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(10183):1819–1830. [https://doi.org/10.1016/S0140-6736\(18\)32409-7](https://doi.org/10.1016/S0140-6736(18)32409-7)
- Ngwa W, Irabor OC, Schoenfeld JD, Hesser J, Demaria S, Formenti SC (2018) Using immunotherapy to boost the abscopal effect. *Nat Rev Cancer* 18(5):313–322. <https://doi.org/10.1038/nrc.2018.6>
- Pariikh RB, Cronin AM, Kozono DE, Oxnard GR, Mak RH, Jackman DM, Chen AB (2014) Definitive primary therapy in patients presenting with oligometastatic non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 89(4):880–887. <https://doi.org/10.1016/j.ijrobp.2014.04.007>
- Paz-Ares L, Vicente D, Tafreshi A, Robinson A, Soto Parra H, Mazieres J, Halmos B (2020) A randomized, placebo-controlled trial of pembrolizumab plus chemotherapy in patients with metastatic squamous NSCLC: protocol-specified final analysis of KEYNOTE-407. *J Thorac Oncol* 15(10):1657–1669. <https://doi.org/10.1016/j.jtho.2020.06.015>
- Qiu B, Liang Y, Li Q, Liu G, Wang F, Chen Z, Liu H (2017) Local therapy for oligoprogressive disease in patients with advanced stage non-small-cell lung cancer harboring epidermal growth factor receptor mutation. *Clin Lung Cancer* 18(6):e369–e373. <https://doi.org/10.1016/j.clcc.2017.04.002>
- Reck M, Rodriguez-Abreu D, Robinson AG, Hui R, Csoszi T, Fulop A, Investigators K (2016) Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. *N Engl J Med* 375(19):1823–1833. <https://doi.org/10.1056/NEJMoa1606774>

- Samuel E, Lie G, Balasubramanian A, Hiong A, So Y, Voskoboinik M, Parakh S (2020) Impact of radiotherapy on the efficacy and toxicity of anti-pd-1 inhibitors in metastatic NSCLC. *Clin Lung Cancer*. <https://doi.org/10.1016/j.clcc.2020.06.001>
- Sezen D, Patel RR, Tang C, Onstad M, Nagarajan P, Patel SP, Lin LL (2021) Immunotherapy combined with high- and low-dose radiation to all sites leads to complete clearance of disease in a patient with metastatic vaginal melanoma. *Gynecol Oncol*. <https://doi.org/10.1016/j.ygyno.2021.03.017>
- Sharabi AB, Lim M, DeWeese TL, Drake CG (2015) Radiation and checkpoint blockade immunotherapy: radiosensitisation and potential mechanisms of synergy. *Lancet Oncol* 16(13):e498–509. [https://doi.org/10.1016/S1470-2045\(15\)00007-8](https://doi.org/10.1016/S1470-2045(15)00007-8)
- Spiotto M, Fu YX, Weichselbaum RR (2016) The intersection of radiotherapy and immunotherapy: mechanisms and clinical implications. *Sci Immunol*. <https://doi.org/10.1126/sciimmunol.aag1266>
- Tang C, Welsh JW, de Groot P, Massarelli E, Chang JY, Hess KR, Hong DS (2017) Ipilimumab with stereotactic ablative radiation therapy: phase i results and immunologic correlates from peripheral T cells. *Clin Cancer Res* 23(6):1388–1396. <https://doi.org/10.1158/1078-0432.CCR-16-1432>
- Theelen W, Peulen HMU, Lalezari F, van der Noort V, de Vries JF, Aerts J, Baas P (2019) 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*. <https://doi.org/10.1001/jamaoncol.2019.1478>
- Theelen WS, de Jong MC, Baas P (2020) Synergizing systemic responses by combining immunotherapy with radiotherapy in metastatic non-small cell lung cancer: The potential of the abscopal effect. *Lung Cancer* 142:106–113. <https://doi.org/10.1016/j.lungcan.2020.02.015>
- Verbrugge I, Hagekyriakou J, Sharp LL, Galli M, West A, McLaughlin NM, Haynes NM (2012) Radiotherapy increases the permissiveness of established mammary tumors to rejection by immunomodulatory antibodies. *Cancer Res* 72(13):3163–3174. <https://doi.org/10.1158/0008-5472.CAN-12-0210>
- Weickhardt AJ, Scheier B, Burke JM, Gan G, Lu X, Bunn PA Jr, DR Camidge (2012) Local ablative therapy of oligoprogressive disease prolongs disease control by tyrosine kinase inhibitors in oncogene-addicted non-small-cell lung cancer. *J Thorac Oncol* 7(12):1807–1814. <https://doi.org/10.1097/JTO.0b013e3182745948>
- Welsh J, Menon H, Chen D, Verma V, Tang C, Altan M, Heymach JV (2020) Pembrolizumab with or without radiation therapy for metastatic non-small cell lung cancer: a randomized phase I/II trial. *J Immunother Cancer*. <https://doi.org/10.1136/jitc-2020-001001>
- Zhuang H (2020) Abscopal effect of stereotactic radiotherapy combined with anti-PD-1/PD-L1 immunotherapy: Mechanisms, clinical efficacy, and issues. *Cancer Commun (Lond)* 40(12):649–654. <https://doi.org/10.1002/cac2.12111>

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