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Real-world utilization of PD-1/PD-L1 inhibitors with palliative radiotherapy in patients with metastatic non-small cell lung cancer

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Abstract

Background: Programmed cell death protein 1 (PD-1) blockade plus radiotherapy may be a promising strategy to improve the prognosis of patients with metastatic non-small cell lung cancer (NSCLC). However, the optimum combined scheme, treatment time of radiotherapy, and irradiated lesion have not been fully determined.

Methods: A total of 321 metastatic NSCLC patients treated with immunotherapy were identified. Among them, 107 patients received PD-1/PD-ligand 1 (PD-L1) inhibitors with radiotherapy, while the remaining cases did not receive radiotherapy. Data on overall survival (OS), progression-free survival (PFS), treatment response and adverse events were collected. Comparisons based on type of radiation, timing of radiotherapy and number of irradiated lesions were performed.

Results: The median OS in PD-1/PD-L1 inhibitors plus radiotherapy was longer than in nonradiotherapy (22.8 vs. 16.6 months, $p = 0.022$). The median PFS showed a similar trend in this study (9.4 vs. 6.2 months, $p = 0.042$). Moreover, the combined strategy demonstrated a superior disease control rate and abscopal control rate versus without radiotherapy (both $p \leq 0.001$). Further multivariate analysis in the immunotherapy and radiotherapy groups revealed that age below 65 ($p = 0.004$), Eastern Cooperative Oncology Group performance scores of 0–1 ($p = 0.001$), oligometastasis ($p = 0.006$), concurrent combination ($p = 0.002$), and treated with SRT ($p = 0.013$) were associated with longer OS. There was a similar incidence of adverse events between the two groups (both $p \geq 0.05$).

Conclusions: The combination of PD-1/PD-L1 inhibitors plus palliative radiotherapy demonstrated favorable survival and good tolerability in metastatic NSCLC patients.

KEYWORDS
immunotherapy, non-small cell lung cancer, radiotherapy

INTRODUCTION

Immune checkpoint inhibitors targeting programmed cell death-1 (PD-1) and PD-ligand 1 (PD-L1) have emerged as effective anticancer therapies in the treatment of patients with metastatic non-small cell lung cancer (NSCLC).[1] PD-1/PD-L1 inhibitors (with or without chemotherapy) are currently a cornerstone of first-line treatment for metastatic NSCLC and attack cancer cells by reactivating and inducing proliferation of T cells stimulated by antigens in the tumor microenvironment.[2–4] KEYNOTE-024 demonstrated that the 5-year overall survival (OS) rate of advanced patients (with high PD-L1 expression) treated with immunotherapy was approximately double (31.9% vs. 16.3%) that in patients with chemotherapy.[5] However, only 17%–63% of NSCLC patients respond to immunotherapy-based approaches, necessitating the investigation of further options for nonresponders.[4,6–8]

To improve outcomes and local disease control for patients who are treated with immunotherapy, efforts have been aimed at combining immunotherapy with radiotherapy. Patients with oligometastatic NSCLC can achieve prolonged survival following metastasis-directed therapies like radiotherapy.[9] Radiation causes excessive release of oxygen free radicals to damage the DNA double helix molecular structure, inhibiting tumor proliferation and inducing apoptosis.[10] There is ample mechanistic evidence that radiotherapy can enhance the immune response.[11–14] Central to this notion are the in situ tumor vaccination effect and abscopal effect. Radiotherapy enhances the systemic release of antigens from tumor tissue, which are recognized by antigen-presenting cells (e.g., dendritic cells), which recruit and subsequently present these antigens to T lymphocytes (specifically cytotoxic CD8 T cells). Therefore, radiotherapy reprograms cold tumors into hot and inflamed tumors and improves anti-PD-1/PD-L1 immunotherapy (e.g., increases capillary permeability and promotes the expression of PD-L1 by tumor cells).

Several studies have preliminarily demonstrated that immunotherapy combined with radiotherapy improves patient prognosis compared to immunotherapy alone.[13–16] However, data are lacking regarding the optimum combined scheme, ideal type of radiation, timing of radiotherapy intervention and number of irradiated lesions. We conducted a real-world database analysis to evaluate the efficacy, safety and related factors of these combination strategies of PD-1/PD-L1 inhibitors plus radiotherapy compared with standard regimens without radiotherapy.

METHODS

Patients

Between June 2017 and December 2020, 321 metastatic NSCLC patients treated with PD-1/PD-L1 inhibitors at Zhejiang Cancer Hospital were enrolled in this retrospective study, of whom 107 patients were treated with PD-1/PD-L1 inhibitors plus radiotherapy and 214 patients received PD-1/PD-L1 inhibitors without radiotherapy. Patients who had wild-type EGFR and ALK tumors, regardless of what type of PD-1/PD-L1 inhibitor was used, met the inclusion criteria. Patients were eligible for the study if they had at least one unirradiated lesion (to monitor the out-of-field response).

In the PD-1/PD-L1 inhibitors plus radiotherapy group, patients were given radiotherapy starting 4 weeks before the first dose of immunotherapy and ending 4 weeks after the last dose of immunotherapy. Consistent with a previous study,[16,17] a 4-week cutoff was selected to analyze the synergistic effect of immunotherapy and radiotherapy. We also analyzed subgroups in the PD-1/PD-L1 inhibitors plus radiotherapy group based on metastasis sites, treatment sequence, radiotherapy technology, and irradiated lesion number. According to the treatment sequence, patients were categorized into a sequential group (patients started immunotherapy before or after radiotherapy) or a concurrent group (patients received immunotherapy concurrently with radiotherapy). Clinical data were obtained from electronic medical records, and all patients provided written informed consent for the use of their tumor specimens. The study received approval from the institutional ethics boards of Zhejiang Cancer Hospital.

Procedures

We collected baseline data on age, sex, Eastern Cooperative Oncology Group performance score (ECOG PS), smoking status, histological features, previous lines of systemic therapy, PD-L1 expression, immunotherapy regimen, etc. Efficacy was evaluated by imaging every 6 weeks during treatment. Radiation techniques included conventional radiotherapy modalities (three-dimensional conformal radiation therapy [3D-CRT] and intensity-modulated radiation therapy [IMRT] with accurate radiation beam intensity distribution) and stereotactic radiotherapy (SRT) mainly characterized by the respiratory gating technique.

In the combined treatment group, OS was calculated from the beginning of combination treatment (the first dose of immunotherapy or immunotherapy) to the date of death from any cause. PFS was calculated from the beginning of combination treatment to the date of progression or death from any cause. Overall response rate (ORR) and disease control rate (DCR) assessments were based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1; in-field ORR (ifRR) and in-field DCR (ifCR) were defined in irradiated lesions only, whereas abscopal response rates (ARR) and abscopal disease control rate (ACR) were assessed in unirradiated lesions.

Additionally, the OS and PFS in the nonradiotherapy group were calculated from the first dose of PD-1/PD-L1 inhibitor to the date of death from any cause and the date of progression or death, respectively.

Enrolled patients underwent laboratory assessments (including hematology, blood chemistry, and liver and kidney function tests) before each treatment cycle, and imaging was repeated every two weeks. Toxicities were graded per the Common Terminology Criteria for Adverse Events, version 5.0.

Statistical analysis

All statistical analyses were performed with SPSS (version 26.0) and GraphPad Prism (version 8.0). OS and PFS were estimated by the Kaplan–Meier method and compared between groups by use of the log-rank test. Hazard ratios were estimated by use of Cox proportional hazards regression, with 95% CIs calculated by use of log

(−log) and the Efron method for ties. Univariate and multivariate Cox analyses were performed to ascertain significant predictors of OS and PFS. To eliminate possible confounding factors, the variables of univariate analysis with $p \leq 0.2$ were included in multivariate Cox regression analysis. All reported two-tailed p-values were analyzed, and $p \leq 0.05$ was considered statistically significant.

TABLE 1 Patient baseline and treatment characteristics

Characteristic	Total ($N = 321$)	PD-1/PD-L1 inhibitor plus radiotherapy ($N = 107$)	PD-1/PD-L1 inhibitor without radiotherapy ($N = 214$)	p-value
Age (years)				0.872
<65	193 (60.1%)	65 (60.7%)	128 (59.8%)	
≥ 65	128 (39.9%)	42 (39.3%)	86 (40.2%)	
Gender				0.682
Female	58 (18.1%)	18 (16.8%)	40 (18.7%)	
Male	263 (81.9%)	89 (83.2%)	174 (81.3%)	
ECOG PS				0.151
0–1	300 (93.5%)	97 (90.7%)	203 (94.9%)	
2	21 (6.5%)	10 (9.3%)	11 (5.1%)	
Histological features				0.197
Adenocarcinoma	165 (51.4%)	58 (54.2%)	107 (50.0%)	
Squamous cell carcinoma	138 (43.0%)	38 (35.5%)	100 (46.7%)	
Other	18 (5.6%)	11 (10.3%)	7 (3.3%)	
Smoking status				0.589
Current/former	238 (74.1%)	77 (72.0%)	161 (75.2%)	
Never smoker	83 (25.9%)	30 (28.0%)	53 (24.8%)	
PD-L1 status				0.796
≥1%	84 (26.2%)	30 (28.0%)	54 (25.2%)	
<1%	19 (5.9%)	6 (5.6%)	13 (6.1%)	
Unknown	218 (67.9%)	71 (66.4%)	147 (68.7%)	
Metastasis sites				0.905
Multiple metastasis	186 (57.9%)	63 (58.9%)	123 (57.5%)	
Oligometastasis	135 (42.1%)	44 (41.1%)	91 (42.5%)	
Prior lines of systemic therapy				0.555
0	167 (52.0%)	53 (49.5%)	114 (53.3%)	
≥1	154 (48.0%)	54 (50.5%)	100 (46.7%)	
Immunotherapy regimen				0.582
Immune single agent	99 (30.8%)	32 (29.9%)	67 (31.3%)	
PD-1/PD-L1 inhibitor plus platinum-based chemotherapy	139 (43.3%)	50 (46.7%)	89 (41.6%)	
PD-1/PD-L1 inhibitor plus nonplatinum regimens	83 (25.9%)	25 (23.4%)	58 (27.1%)	
Type of radiation				-
Traditional RT	–	73 (68.2%)	–	
SRT	–	34 (31.8%)	–	
Treatment time of RT				–
Concurrent	–	58 (54.2%)	–	
Sequential[a]	–	49 (45.8%)	–	
No. of irradiated lesions				–
Single site RT	–	87 (81.3%)	–	
Multiple site RT	–	20 (18.7%)	–	

Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performance scores; RT, radiotherapy; SRT, stereotactic radiotherapy.
[a]Includes patients who received radiation less than 4 weeks before the first dose or after the last dose of immunotherapy.

RESULTS

Patient characteristics and treatment

Table 1 shows the clinical characteristics of the 321 patients enrolled in the study. The median age of patients was 62 years old, with a range of 34 to 78 years. A total of 60.1% of patients ($n = 193$) were younger than 65 years. The majority of patients were male ($n = 263$, 81.9%), had been smokers ($n = 238$, 74.1%), with an ECOG PS of 0–1 ($n = 300$, 93.5%). In addition, 42.1% of patients ($n = 135$) could be categorized as having oligometastasis. Histological examination revealed that the screened patients consisted of 165 (51.4%) adenocarcinoma samples and 138 (43.0%) squamous cell carcinoma samples, whereas 18 (5.6%) patients were diagnosed with other pathological types. Among the 103 samples tested, 84 cases had PD-1 expression ≥1%. In the group treated with radiotherapy, about half of the patients received first-line therapy ($n = 53$, 49.5%), the same as the group

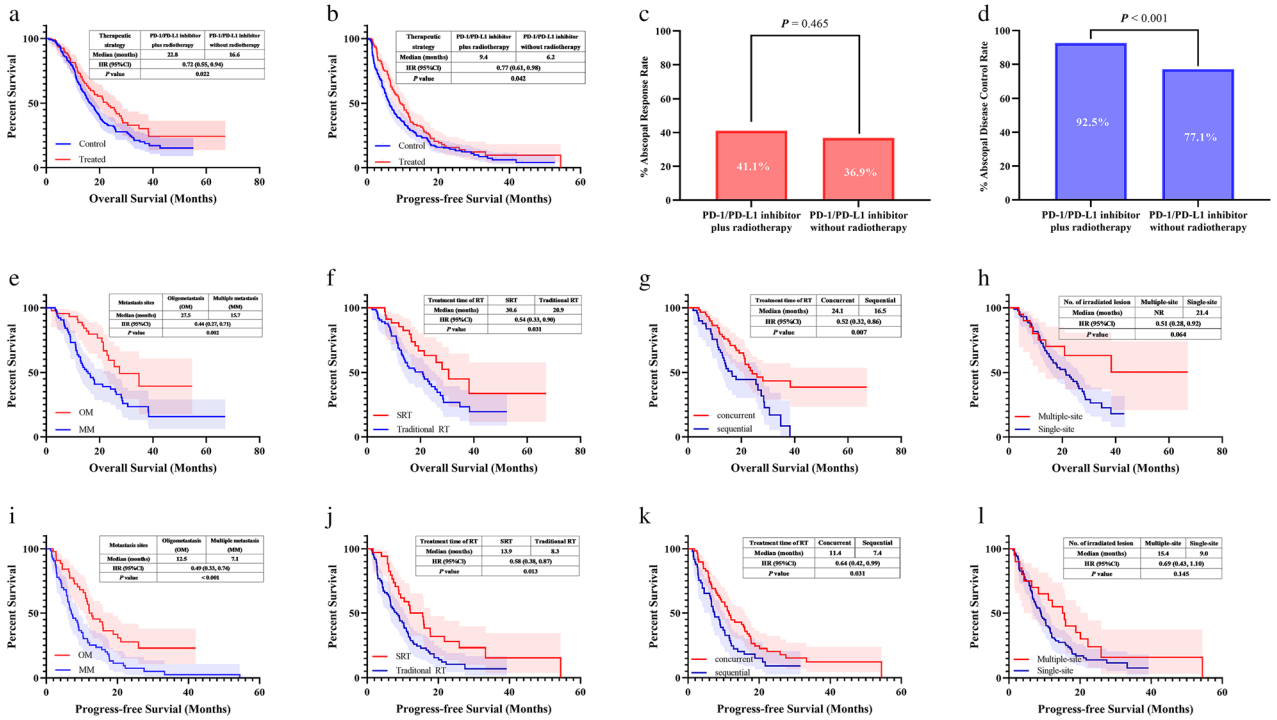

FIGURE 1 Kaplan–Meier curves and bar graph illustrating the overall survival (OS), progression-free survival (PFS), abscopal response rates (ARR), and abscopal disease control rates (ACR) of 321 patients with metastatic non-small cell lung cancer (NSCLC), stratified according to the treatment received. (a,b) Patients who treated with PD-1/PD-L1 inhibitors plus radiotherapy showed superior OS and PFS (OS: 22.8 vs. 16.6 months, $p = 0.022$; PFS: 9.4 vs. 6.2 months, $p = 0.042$). (c,d) Patients receiving PD-1/PD-L1 inhibitors plus radiotherapy showed higher ACR (92.5% vs. 77.1%, $p \leq 0.001$), while no statistical difference in ARR (41.1% vs. 36.9%, $p = 0.465$). (e–l) In PD-1/PD-L1 inhibitors plus radiotherapy group, longer OS and PFS were noted in patients who were diagnosed as oligometastasis (OM) compared with multiple metastasis (MM) (OS: 27.5 vs. 15.7 months, $p = 0.002$; PFS: 12.5 vs. 7.1 months, $p \leq 0.001$), treated with SRT (OS: 30.6 vs. 20.9 months, $p = 0.031$; PFS: 13.9 vs. 8.3 months, $p = 0.013$), and adopted concurrent modality (OS: 24.1 vs. 16.5 months, $p = 0.007$; PFS: 11.4 vs. 7.4 months, $p = 0.031$). Patients treated with multiple-site radiotherapy showed a trend to have improved OS and PFS (OS: NR vs. 21.4 months, $p = 0.064$; PFS: 15.4 vs. 9.0 months, $p = 0.145$)

TABLE 2 Overall survival, progression-free survival, and response to treatment

	PD-1/PD-L1 inhibitor plus radiotherapy ($N = 107$)	PD-1/PD-L1 inhibitor without radiotherapy ($N = 214$)	*HR* (95% CI)	*p*-value
Median OS (month, 95% Cl)	22.8 (17.3–28.3)	16.6 (14.4–18.8)	0.72 (0.55–0.94)	0.022
Median PFS (month, 95% Cl)	9.4 (7.8–11.0)	6.2 (5.2–7.3)	0.77 (0.61–0.98)	0.042
ORR (%)	47.7% (51/107)	36.9% (79/214)	0.83 (0.67–1.02)	0.064
DCR (%)	93.5% (100/107)	77.1% (165/214)	0.29 (0.13–0.61)	< 0.001
ARR (%)	41.1% (44/107)	36.9% (79/214)	0.93 (0.77–1.13)	0.465
ACR (%)	92.5% (99/107)	77.1% (165/214)	0.33 (0.16–0.66)	< 0.001

Abbreviations: ACR, abscopal control rate; ARR, abscopal response rate; DCR, disease control rate; fRR, in-field response rate; ifCR, in-field control rate; iORR, overall response rate.

treated without radiotherapy ($n = 114$, 53.3%). Moreover, regarding the immunotherapy regimen, 29.9% (32 patients) were treated with single immune agents, 46.7% (50 patients) received PD-1/PD-L1 inhibitors plus platinum-based chemotherapy, and 23.4% (25 patients) received PD-1/PD-L1 inhibitors plus nonplatinum regimens. There were no significant differences in the baseline of patient and treatment characteristics between the two groups.

In the PD-1/PD-L1 inhibitors plus radiotherapy group, 31.8% ($n = 34$) of 107 patients were treated with SRT, and 58 (54.2%) patients received concurrent immunotherapy and radiotherapy. A total of 18.7% ($n = 20$) of patients experienced multiple-site radiotherapy.

TABLE 3 Univariate and multivariate Cox regression analyses estimating the associations of different clinical factors with patients' overall survival in PD-1/PD-L1 inhibitors plus radiotherapy group

	Crude HR	95% CI	*p*-value	Adjust HR	95% CI	*p*-value
Age (years)						
<65	1 (ref)			1 (ref)		
≥65	1.68	1.03–2.74	0.039	2.20	1.29–3.74	0.004
Gender						
Female	1 (ref)					
Male	0.79	0.42–1.48	0.454			
ECOG PS						
0–1	1 (ref)			1 (ref)		
2	2.49	1.23–5.04	0.012	3.39	1.63–7.06	0.001
Histological features						
Adenocarcinoma	1 (ref)					
Squamous cell carcinoma	1.02	0.60–1.74	0.994			
Other	1.26	0.86–1.86	0.242			
Smoking status						
Never smoker	1 (ref)					
Current/former	1.31	0.75–2.29	0.339			
PD-L1 status						
<1%	1 (ref)					
≥1%	0.98	0.35–2.68	0.961			
Metastasis sites						
Multiple metastasis	1 (ref)			1 (ref)		
Oligometastasis	0.44	0.27–0.71	0.002	0.46	0.27–0.80	0.006
Prior lines of systemic therapy						
0	1 (ref)					
≥1	1.29	0.79–2.13	0.312			
Immunotherapy regimen						
Immune single agent	1 (ref)					
PD-1/PD-L1 inhibitor plus platinum-based chemotherapy	0.86	0.47–1.57	0.632			
PD-1/PD-L1 inhibitor plus nonplatinum regimens	1.13	0.83–1.55	0.446			
Irradiated schema						
Traditional RT	1 (ref)			1 (ref)		
SRT	0.54	0.33–0.90	0.031	0.48	0.27–0.86	0.013
Treatment time of RT						
sequential[a]	1 (ref)			1 (ref)		
Concurrent	0.52	0.32–0.86	0.007	0.43	0.25–0.74	0.002
No. of irradiated lesion						
Single site RT	1 (ref)			1 (ref)		
Multiple site RT	0.51	0.28–0.92	0.064	0.51	0.23–1.10	0.087

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance scores. RT, radiotherapy; SRT, stereotactic radiotherapy.
[a]Includes patients who received radiation less than 4 weeks before the first dose or after the last dose of immunotherapy.

Evaluating patient outcomes

A total of 98 (30.5%) patients (42 [39.3%] patients from the group with radiotherapy and 56 [26.2%] patients treated without radiotherapy) were alive at the time of this analysis, and the median follow-up time for all patients was 28.0 months (95% confidence interval [CI]: 24.0–32.0). The median OS was significantly longer in the PD-1/PD-L1 inhibitors plus radiotherapy group (22.8 months, 95% CI: 17.3–28.3) compared with those treated without radiotherapy (16.6 months, 95% CI: 14.4–18.8; hazard ratio [HR] 0.72, 95% Cl 0.55–0.94; $p = 0.022$; Figure 1a). In subgroup analyses (Figures 1e–h), the combination of immunotherapy and radiotherapy appeared to be more beneficial in

TABLE 4 Univariate and multivariate Cox regression analyses estimating the associations of different clinical factors with patient progression-free survival in PD-1/PD-L1 inhibitors plus radiotherapy group

	Crude HR	95% CI	*p*-value	Adjust HR	95% CI	*p*-value
Age (years)						
<65	1 (ref)					
≥65	1.16	0.76–1.76	0.496			
Gender						
Female	1 (ref)					
Male	0.93	0.52–1.64	0.794			
ECOG PS						
0–1	1 (ref)			1 (ref)		
2	1.67	0.83–3.33	0.149	1.88	0.77–4.62	0.169
Histological features						
Adenocarcinoma	1 (ref)					
Squamous cell carcinoma	1.01	0.65–1.59	0.937			
Other	1.09	0.76–1.55	0.651			
Smoking status						
Never smoker	1 (ref)					
Current/former	1.18	0.74–1.90	0.486			
PD-L1 status						
<1%	1 (ref)					
≥1%	1.67	0.63–4.40	0.301			
Metastasis sites						
Multiple metastasis	1 (ref)			1 (ref)		
Oligometastasis	0.49	0.33–0.74	0.001	0.50	0.27–0.95	0.033
No. of prior therapies						
1	1 (ref)			1 (ref)		
≥2	1.45	0.96–2.19	0.081	1.57	0.74–3.34	0.240
Immunotherapy regimen						
immune single agent	1 (ref)			1 (ref)		
PD-1/PD-L1 inhibitor plus platinum-based chemotherapy	1.07	0.65–1.77	0.791			
PD-1/PD-L1 inhibitor plus nonplatinum regimens	1.28	0.96–1.70	0.090	1.31	0.97–1.77	0.074
Irradiated schema						
Traditional RT	1 (ref)			1 (ref)		
SRT	0.58	0.38–0.87	0.013	0.57	0.30–1.09	0.087
Treatment time of RT						
Sequential[a]	1 (ref)			1 (ref)		
Concurrent	0.64	0.42–0.99	0.031	0.51	0.28–0.93	0.029
No. of irradiated lesion						
Single site RT	1 (ref)			1 (ref)		
Multiple site RT	0.69	0.43–1.10	0.145	0.66	0.30–1.43	0.290

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance scores; RT, radiotherapy; SRT, stereotactic radiotherapy.
[a]Includes patients who received radiation less than 4 weeks before the first dose or after the last dose of immunotherapy.

TABLE 5 Treatment-related adverse events (AEs) in patients evaluable for toxicity of receiving PD-1/PD-L1 inhibitors with or without radiotherapy

Treatment-related AEs	Any grade n (%)			Grade 3+ n (%)		
	PD-1/PD-L1 inhibitor plus radiotherapy ($N = 107$, %)	PD-1/PD-L1 inhibitor without radiotherapy ($N = 214$, %)	*p*-value	PD-1/PD-L1 inhibitor plus radiotherapy ($N = 107$, %)	PD-1/PD-L1 inhibitor without radiotherapy ($N = 214$, %)	*p*-value
All AEs	80 (74.8)	153 (71.5)	0.596	8 (7.5)	15 (7.0)	1.000
Hepatic insufficiency	38 (35.5)	82 (38.3)	0.714	4 (3.7)	3 (1.4)	0.224
Pneumonitis	26 (24.3)	39 (18.2)	0.202	2 (1.9)	6 (2.8)	0.723
Renal insufficiency	22 (20.5)	27 (12.6)	0.071	1 (0.9)	1 (0.5)	1.000
Thyroiditis/ hypothyroidism	12 (11.2)	27 (12.6)	0.857	0 (0)	0 (0)	1.000
Rash/pruritus	11 (10.2)	14 (6.5)	0.271	1 (0.9)	4 (1.8)	0.668
Hematological toxicity	9 (8.4)	15 (7.0)	0.657	2 (1.9)	2 (0.9)	0.603
CCEP	3 (2.8)	8 (3.7)	0.757	0 (0)	0 (0)	1.000
Colitis/diarrhea	1 (0.9)	5 (2.3)	0.668	0 (0)	1 (0.5)	1.000
Myocarditis	0 (0)	2 (0.9)	0.554	0 (0)	0 (0)	1.000
Pancreatic insufficiency	0 (0)	1 (0.5)	1.000	0 (0)	1 (0.5)	1.000

Abbreviation: CCEP, cutaneous capillary endothelial proliferation.

patients who were younger than 65 years ($p = 0.039$), with an ECOG PS of 0–1 ($p = 0.012$), categorized as oligometastasis ($p = 0.002$), treated with SRT ($p = 0.031$), and received concurrent immunotherapy and radiotherapy ($p = 0.007$). Multivariable analysis of prognostic factors showed that age younger than 65 years, ECOG PS of 0–1, diagnosed as oligometastasis, concurrent combination, and treated with SRT were significantly associated with longer OS ($p \leq 0.05$, Table 3).

Kaplan–Meier analysis showed that the median PFS was longer in patients with immunotherapy plus radiotherapy (9.4 months) compared to those with immunotherapy alone (6.2 months, HR = 0.77, 95% CI: 0.61–0.98; $p = 0.042$; Figure 1b). In subgroup analyses of PFS (Figure 1i–l), the combination of immunotherapy and radiotherapy seemed to be more effective in patients who received SRT ($p = 0.013$), concurrent radiotherapy ($p = 0.031$), and oligometastastic patients ($p = 0.001$). Meanwhile, the diagnosis of oligometastases and the concurrent sequence of immunotherapy with radiotherapy were also independently associated with longer PFS (Table 4, $p \leq 0.05$).

Table 2 shows data for the best overall response to treatment. Best ORR and ARR were higher with the PD-1/PD-L1 inhibitor-related regimen plus radiotherapy compared with the regimen without radiotherapy, but the differences were not statistically significant (ORR: 47.7% vs. 36.9%, $p = 0.064$; ARR: 41.1% vs. 36.9%, $p = 0.465$). However, the best DCR and ACR were significantly higher in the combined radiotherapy group (DCR: 93.5% vs. 77.1%, $p<0.001$; ACR: 92.5% vs. 77.1%, $p \leq 0.001$). In addition, the ifRR and ifCR were 58.0 and 98.8%. Further subgroup analysis of ORR and DCR (whether local or distant) in the group with radiotherapy were not significantly correlated with the type of radiation, timing of radiotherapy or number of irradiated lesions.

Treatment toxicity

The treatment-related adverse events (AEs) are shown in Table 5. A total of 233 (72.6%) of 321 patients had an AE at least possibly related to therapy (80 [74.8%] in the PD-1/PD-L1 inhibitors plus radiotherapy group; 153 [71.5%] in the group treated without radiotherapy; $p = 0.596$). Hepatic insufficiency (38 [35.5%] patients with radiotherapy vs. 82 [38.3%] patients without radiotherapy; $p = 0.714$), pneumonitis (26 [24.3%] vs. 39 [18.2%]; $p = 0.202$), and renal insufficiency (17 [15.9%] vs. 27 [12.6%]; $p = 0.071$) occurred most commonly.

Overall, 23 (7.2%) patients experienced grade 3 or worse AEs (8 [7.5%] in the group with radiotherapy and 15 [7.0%] in the group without radiotherapy; $p = 1.000$). The most common grade 3 or worse AEs were pneumonitis (2 [1.9%] in the group with radiotherapy; 6 [2.8%] in the group without radiotherapy; $p = 0.723$), hepatic insufficiency (4 [3.7%] in the group with radiotherapy; 3 [1.4%] in the group without radiotherapy; $p = 0.224$), and rash (1 [0.9%] in the group with radiotherapy; 4 [1.8%] in the group without radiotherapy; $p = 0.668$). No patients died from serious treatment-related AEs in the study.

DISCUSSION

In the present study, we describe the efficacy and safety of immunotherapy based on PD-1/PD-L1 inhibitors

combined with or without radiotherapy in 321 NSCLC patients. We found that the addition of palliative radiotherapy to immunotherapy induced significantly longer OS (22.8 months vs. 16.6 months, $p = 0.022$) and PFS (9.4 months vs. 6.2 months, $p = 0.042$). Moreover, DCR and ACR assessing response was significantly increased in the combination treatment arm (both $p \leq 0.001$). Additionally, the combination of immunotherapy with radiotherapy was well tolerated and was not associated with an increase in the rate of pneumonitis.

To our knowledge, this is the first controlled study with a large sample size to compare the treatment efficacy of immunotherapy plus radiotherapy and immunotherapy alone, indicating combination therapy could be an effective strategy in metastatic NSCLC patients. A secondary analysis of the phase I KEYNOTE-001 study assessed 98 patients and suggested that patients who received pembrolizumab and had previously received radiotherapy history had longer PFS (4.4 months vs. 2.1 months, $p = 0.019$) and OS (10.7 months vs. 5.3 months, $p = 0.026$) than those who did not receive radiotherapy.[18] In the PEMBRO-RT (phase 2, $n = 76$) and MDACC (phase 1/2, $n = 72$) trials, patients with metastatic NSCLC were divided into a pembrolizumab with radiotherapy group and a pembrolizumab alone group.[14,19] Although there were no significant differences in response rates and outcomes when the above two studies were analyzed individually, a pooled analysis combining the data from these two randomized trials reported that the additional radiotherapy significantly increased response rates of unirradiated lesions (ARR: 41.7% vs. 19.7%, $p = 0.004$; ACR: 65.3% vs. 43.4%, $p = 0.007$), which also led to significantly higher PFS (9.0 vs. 4.4 months, $p = 0.045$) and OS (19.2 vs. 8.7 months, $p < 0.001$).[15] Moreover, a systematic review including 18 articles (6 prospective studies) described 1736 patients treated with an ICI-SABR combination; the OS and PFS were 12.4 and 4.6 months, respectively, and ARR was 41%.[20] Collectively, in line with the findings of our study, the addition of radiotherapy to immunotherapy showed great promise for metastatic NSCLC.

To further study the ideal benefit population, subgroup analyses on radiotherapy timing, number of lesions to be irradiated, and schedule of combined treatment were performed. We found that age of patients, ECOG PS, metastasis sites, irradiated schema, and treatment time of radiotherapy were independent prognostic factors for OS in patients who received immunotherapy and radiotherapy, while gender, histological features, smoking status, PD-L1 status, prior lines of systemic therapy, and immunotherapy regimen showed no impact on survival. Additionally, patients who received radiotherapy at multiple sites showed a trend to have improved OS compared to those who received radiotherapy at a single site, although the difference did not reach statistical significance. We also found that metastasis sites and treatment time of radiotherapy were also independent prognostic factors for PFS.

The combination modalities used in previous prospective studies can all be classified as concurrent radiotherapy.[13] The present study did discover that concurrent radiotherapy resulted in significantly longer OS than sequential radiotherapy ($p = 0.007$), and that sequential radiotherapy appeared to fail to prolong OS compared with the nonradiotherapy group. Therefore, the strategy with radiotherapy concurrently may be the key to reaping the survival benefits of this combination modality.

A previous study of radiotherapy schemes demonstrated that hypofractionated radiation therapy (HFRT) has a therapeutic advantage compared with conventional fractionated radiation therapy.[21] A preclinical study proved that HFRT treatment of the primary tumor could reduce the recruitment of myeloid-derived suppressor cells into tumors and decrease the expression of PD-L1 on those cells, which unleashed the cytotoxicity of CD8+ T cells.[22] Although low-dose radiation therapy (LDRT) has an inferior tumor-killing effect, LDRT is conducive to T cell recruitment and reprograms macrophages in the tumor microenvironment.[23] Thus, studies to determine which radiotherapy mode can achieve the best combination effect are warranted. In the pooled analysis of the PEMBRO-RT and MDACC trials, the PFS in the SBRT group was significantly longer than that in the traditional radiotherapy group (21.1 vs. 6.8 months, $p = 0.03$).[14] In a retrospective analysis, patients receiving immunotherapy with SRT ($n = 228$) showed a superior OS compared with those receiving a traditional radiation scheme ($n = 2235$) ($p < 0.001$).[24] Similarly to previous studies, we discovered that patients who received SRT had a longer OS than those who received traditional radiotherapy; however, there was no significant difference in PFS. Several factors might be related to the results. For example, among enrolled patients treated with SRT, 16 (47.1%) patients received gamma knife for brain lesions and 18 (52.9%) with stereotactic body radiotherapy (SBRT) for body lesions. Further examination of the differences in PFS revealed that patients with SBRT had a longer PFS than patients who received brain radiotherapy (17.7 months vs. 9.2 months, HR 0.53, 95% CI: 0.24–1.15; $p = 0.082$). Although the benefit of PFS can still be obtained in combination with brain radiotherapy, this is significantly limited, which may be caused by the blood–brain barrier and the highly immune suppressive environment of the nervous system,[25–29] which inhibits the activating effect of radiotherapy on immunity. In addition, the lack of PD-L1 assay standardization and limited stratification due to the difficulty in obtaining samples from retrospective studies might have affected the results.

Although the exact mechanisms of the synergy effect between PD-1/PD-L1 inhibitors and radiotherapy are not known, several studies attribute outcome benefits to the abscopal effect.[30,31] Based on several analyses of randomized trial results, the review by Brooks and Chang advocated exploring comprehensive irradiation of multiple/all lesions in order to enhance the likelihood of abscopal effect which led to obtain meaningful clinical outcomes.[32] The above

conclusion was not confirmed in our study. Several factors can potentially explain why the patients treated with multiple site radiotherapy did not experience statistically longer OS or PFS than subjects having received therapy with single site radiotherapy. First, 12 (60%) patients were alive at the time of this analysis in the multiple site radiotherapy group, and median OS had not been reached statistically; additional follow-up time may reveal a difference in OS between multiple site radiotherapy and single site radiotherapy cohorts. Second, previous studies used the SRT technique for multiple site radiotherapy; in this study, only five (25%) patients in this subgroup used SRT, and the rest used traditional radiotherapy, which may have reduced the abscopal effect of multiple-site radiotherapy. Furthermore, we conducted exploratory analyses to assess the effect of multiple-site radiotherapy using the SRT technique on OS and PFS. There were statistically significant differences in OS ($p = 0.009$), although still not in PFS ($p = 0.102$).

There is growing evidence of the encouraging safety profile of immunotherapy combined with radiotherapy. In our study, there was no increased rate of overall treatment-related AEs in the combined treatment group compared with the nonradiotherapy group ($p = 0.596$). Also, the incidence of grade 3 or higher AEs was similar between the two groups ($p = 1.000$). Therefore, administration of immunotherapy combined with radiotherapy does not increase the incidence of AEs in the real world. Pneumonitis is a major concern in lung cancer, the occurrence rate of pneumonitis was not increased for patients treated with radiotherapy; on the contrary, compared to two (1.9%) patients with grade 3 pneumonitis in the group with the addition of radiotherapy, there were six (2.8%) patients with grade 3 pneumonitis in the group treated without radiotherapy ($p = 0.723$). Overall, the safety profile of this combination radiotherapy group is acceptable and manageable.

This study was limited by its retrospective nature. Furthermore, the relationship between PD-L1 expression and outcomes in our combined cohort could not be determined due to the lack of sufficient tissue samples. Additionally, many questions remain about the effect of different radiotherapy doses and fractionation schedules on the magnitude of the immune-boosting effect.

In conclusion, in the treatment of patients with metastatic NSCLC, PD-1/PD-L1 inhibitors combined with radiotherapy demonstrated favorable survival with acceptable and manageable toxicity when compared to immunotherapy based on PD-1/PD-L1 inhibitors without radiotherapy. Additionally, the patients who are younger than 65 years old, have ECOG PS of 0–1, and are oligometastatic may have a superior OS. Moreover, we advocated patients receiving the PD-1/PD-L1 inhibitors with concurrent radiotherapy, and using the SRT technique, all of which are associated with a better prognosis. Further large volume, randomized trials are needed to address these unresolved questions.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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