

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

zichao zhou (✉ zhouzichao23@163.com)

Zhejiang Chinese Medical University <https://orcid.org/0000-0002-5891-4978>

Kaiyan Chen

Zhejiang Cancer Hospital

Na Li

Wenzhou Medical University

Mingying Xie

Zhejiang Chinese Medical University

Jiamin Sheng

Wenzhou Medical University

Yun Fan

Zhejiang Cancer Hospital

Zhiyu Huang

Zhejiang Cancer Hospital <https://orcid.org/0000-0002-8839-4088>

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Abstract

Background

Programmed cell death protein 1 (PD-1) blockade combined with radiotherapy may be a promising strategy to improve the prognosis of patients with advanced non-small-cell lung cancer (NSCLC). However, the optimum radiotherapy scheme, timing, and location have not been fully determined.

Methods

We conducted a retrospective study of 57 patients receiving PD-1/PD-ligand 1 (PD-L1) inhibitors with radiotherapy for metastatic NSCLC in Zhejiang Cancer Hospital between June 2017 and December 2019. 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 was 25.9 (95% CI: 18.4-33.4) months, and the median PFS was 10.3 (95% CI: 8.9-11.8) months. The in-field and out-of-field overall response rates were 45.2% and 32.1%, respectively. Multisite radiotherapy was associated with longer PFS than single-site radiotherapy (19.50 vs. 9.10 months, $P = 0.017$). Furthermore, immunotherapy with concurrent radiotherapy tended to have superior outcomes compared with immunotherapy with sequential radiotherapy (OS: NR vs. 20.87 months, $P = 0.079$; PFS: 11.4 vs. 9.0 months, $P = 0.153$), as did immunotherapy with stereotactic radiotherapy compared with traditional radiotherapy (OS: 30.6 vs. 25.9 months, $P = 0.840$; PFS: 11.1 vs. 9.9 months, $P = 0.803$). The incidence of treatment-related adverse events (AEs) was 61.4%, but only 5.3% of patients experienced grade 3 AEs.

Conclusions

The combination of immunotherapy and radiotherapy demonstrated favourable survival and good tolerability in Chinese patients with advanced NSCLC.

1. 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) currently are 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 tumour 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 outcome 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 tumour 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 tumour vaccination effect and abscopal effect. Radiotherapy enhances the systemic release of antigens from tumour 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 tumours into hot and inflamed tumours and improves anti-PD-1/PD-L1 immunotherapy (e.g., increases capillary permeability and promotes the expression of PD-L1 by tumour 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 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 in the Chinese population.

2. Materials And Methods

2.1. Patients

Among 728 advanced NSCLC patients treated with PD-1/PD-L1 inhibitors, we retrospectively identified 57 consecutive patients between June 2017 and December 2019 at Zhejiang Cancer Hospital. Patients who had wild-type EGFR and ALK tumours, 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). 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 cut-off was selected to analyse the synergistic effect of immunotherapy and radiotherapy. We also analysed subgroups based on treatment sequence, radiotherapy technology, and irradiated lesion number. According to the treatment sequence, patients were categorized into a group that received immunotherapy prior to or after radiotherapy (sequential arm) or a group that received immunotherapy concurrently with radiotherapy (concurrent arm). Clinical data were obtained from electronic medical records, and all patients provided written informed consent for the use of their tumour specimens. The study received approval from the institutional ethics boards of Zhejiang Cancer Hospital.

2.2 Procedures

We collected baseline data on age, sex, performance status, smoking status, histological features, previous lines of systemic therapy, PD-L1 expression, immunotherapy regimen, and so on. 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) on whose study mainly focused was respiratory gating technique.

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 Tumours (RECIST) version 1.1.

2.3 Statistical analysis

All statistical analyses were performed with SPSS (version 26.0) and GraphPad Prism (version 8.0). PFS and OS were estimated by the Kaplan–Meier method, and curves were compared with the log-rank test. Univariate and multivariate Cox analyses were performed to ascertain significant predictors of PFS and OS. All reported two-tailed P values were analysed, and $P \leq 0.05$ was considered statistically significant.

3. Results

3.1 Patient characteristics and Treatment

Among the 57 included patients, 80.7% (46 patients) were males, 71.9% (41 patients) were current or former smokers, 63.2% (36 patients) were younger than 65 years, 93.0% (53 patients) had ECOG scores of 1 or lower, and 68.4% (39 patients) had multiple metastases. According to histological examinations, 56.1% (32 patients) had adenocarcinoma, 38.6% (22 patients) had squamous cell carcinoma, and 5.3% (3 patients) had other pathologic types, like adenosquamous carcinoma. Regarding the immunotherapy regimen, 45.6% (26 patients) were treated with single immune agents, 31.6% (18 patients) received PD-1/PD-L1 inhibitors plus platinum-based chemotherapy, and 22.8% (13 patients) received PD-1/PD-L1 inhibitors plus nonplatinum regimens. A total of 38.6% (22 patients) received immunotherapy as first-line therapy, and 61.4% (35 patients) received immunotherapy as second- or subsequent-line therapy. Regarding the irradiation regimen, 24.6% (14 patients) received SRT, 75.4% (43 patients) received traditional radiotherapy, 82.5% (47 patients) were treated with single-site radiotherapy, and 17.5% (10 patients) received multisite radiotherapy. In addition, lung (N=16, 28.1%), bone (N=13, 22.8%), and brain (N=22, 38.6%) lesions were the most often to be irradiated. Regarding the treatment sequence of radiotherapy, 52.6% (30 patients) received PD-1/PD-L1 inhibitors and radiotherapy concurrently, and the rest received sequential PD-1/PD-L1 inhibitors and radiotherapy. The patient characteristics are summarized in Table 1.

Table 1
Baseline of patient and treatment characteristics.

Characteristic	All Patients <i>n</i> = 57	%
Age (years)		
<65	36	63.2
≥ 65	21	36.8
Gender		
Female	11	19.3
Male	46	80.7
ECOG performance score		
0-1	53	93
2	4	7
Histological features		
adenocarcinoma	32	56.1
squamous cell carcinoma	22	38.6
Other	3	5.3
Smoking status		
Current/former	41	71.9
Never smoker	16	28.1
PD-L1 status		
≥1%	8	14
<1%	8	14
Unknown	41	72
Metastasis sites		
solitary	39	68.4
multiple	18	31.6
Prior lines of systemic therapy		
0	22	38.6
≥1	35	61.4
Immunotherapy regimen		

Characteristic	All Patients <i>n</i> = 57	%
immune single agent	26	45.6
PD-1/PD-L1 inhibitor plus platinum-based chemotherapy	18	31.6
PD-1/PD-L1 inhibitor plus non-platinum regimens	13	22.8
Type of radiation		
Traditional RT ^{a)}	43	75.4
SRT ^{b)}	14	24.6
Treatment time of RT		
concurrent	30	52.6
sequential ^{c)}	27	47.4
No. of irradiated lesion		
single-site RT	47	82.5
multiple-site RT	10	17.5
Irradiated lesion		
Lung	16	28.1
Bone	13	22.8
Brain	22	38.6
Other	6	10.5
a) RT: radiotherapy.		
b) SRT: stereotactic radiotherapy.		
c) Include patients who received radiation less than 4 weeks before the first dose or after the last dose of immunotherapy.		

3.2 Evaluating patient outcomes

With a median follow-up time of 20.5 months (95% confidence interval (CI): 17.9-23.1), the median OS was 25.9 (95% CI: 18.4-33.4) months for all evaluable patients. We further analysed the relationship between different treatment parameters. Regarding the timing of radiotherapy intervention, 30 patients received a combination of immunotherapy with concurrent radiotherapy, which was associated with a trend towards a longer OS, although the difference was not significant (NR and 20.9 months, $P = 0.079$). Regarding the number of irradiated lesions, the median OS was 25.87 and NR months ($P = 0.293$) for patients who received single-site and multisite radiotherapy. When stratified by irradiation type, SRT

demonstrated longer OS than traditional radiotherapy, although no significant difference was reached (30.6 vs. 25.9, $P = 0.840$). Unfortunately, we did not determine independent prognostic factors affecting OS (Table 2).

Table 2

Univariate and multivariate cox regression analyses estimating the associations of different clinical factors with patients' overall survival.

	Crude HR	95%CI	P-value	Adjust HR	95%CI	P-value
Age (years)						
<65	1 (ref)			1 (ref)		
≥65	2.1	0.9-5.0	0.098	1.9	0.8-4.8	0.144
Gender						
Female	1 (ref)					
Male	0.6	0.2-1.7	0.339			
ECOG performance score						
0-1	1 (ref)					
2	2.0	0.5-8.7	0.356			
Histological features						
adenocarcinoma	1 (ref)					
squamous cell carcinoma	0.6	0.2-1.7	0.360			
Other	1.2	0.6-2.6	0.592			
Smoking status						
Current/former	1 (ref)					
Never smoker	0.9	0.3-2.3	0.812			
PD-L1 status						
<1%	1 (ref)					
≥1%	3.1	0.3-29.8	0.335			

a) RT: radiotherapy.

b) SRT: stereotactic radiotherapy.

c) Include patients who received radiation less than 4 weeks before the first dose or after the last dose of immunotherapy.

	Crude HR	95%CI	P-value	Adjust HR	95%CI	P-value
Metastasis sites						
multiple	1 (ref)			1 (ref)		
solitary	0.3	0.1-0.9	0.072	0.4	0.1-1.3	0.112
Prior lines of systemic therapy						
0	1 (ref)					
≥1	1.1	0.4-2.6	0.868			
Immunotherapy regimen						
immune single agent	1 (ref)					
PD-1/PD-L1 inhibitor plus platinum-based chemotherapy	1.1	0.4-3.0	0.910			
PD-1/PD-L1 inhibitor plus non-platinum regimens	0.9	0.5-1.6	0.755			
Irradiated schema						
Traditional RT ^{a)}	1 (ref)					
SRT ^{b)}	0.9	0.3-2.5	0.840			
Treatment time of RT						
sequential ^{c)}	1 (ref)			1 (ref)		
concurrent	0.5	0.2-1.1	0.079	0.9	0.3-2.6	0.885
No. of irradiated lesion						
single-site RT	1 (ref)					
multiple-site RT	0.5	0.2-1.5	0.293			
Irradiated lesion						

a) RT: radiotherapy.

b) SRT: stereotactic radiotherapy.

c) Include patients who received radiation less than 4 weeks before the first dose or after the last dose of immunotherapy.

	Crude HR	95%CI	P-value	Adjust HR	95%CI	P-value
Lung	1 (ref)					
Bone	10.0	1.2-79.8	0.030			
Brain	9.8	1.2-79.1	0.031			
Other	3.4	0.3-38.3	0.323			
a) RT: radiotherapy.						
b) SRT: stereotactic radiotherapy.						
c) Include patients who received radiation less than 4 weeks before the first dose or after the last dose of immunotherapy.						

Kaplan–Meier analysis showed that the median PFS was 10.3 (95% CI: 8.9-11.8) months in the entire population. Regarding the treatment sequence of radiotherapy, the group that received immunotherapy administered concurrently with radiotherapy showed a tendency to have longer PFS, but the difference was not statistically significant (11.4 vs. 9.0 months, P = 0.153). Regarding the number of irradiated lesions, the multisite group showed significantly superior median PFS (19.50 vs. 9.10 months, P = 0.017). The SRT group demonstrated longer PFS than the traditional radiotherapy group, although no significant difference was reached (11.1 vs. 9.9 months, P = 0.803), potentially (Table 3).

Table 3

Univariate and multivariate cox regression analyses estimating the associations of different clinical factors with patients' progress-free survival.

	Crude HR	95%CI	P-value	Adjust HR	95%CI	P-value
Age (years)						
<65	1 (ref)					
≥65	1.0	0.6-1.8	0.984			
Gender						
Female	1 (ref)					
Male	0.7	0.3-1.4	0.312			
ECOG performance score						
0-1	1 (ref)					
2	1.1	0.4-3.2	0.827			
Histological features						
adenocarcinoma	1 (ref)					
squamous cell carcinoma	0.9	0.5-1.5	0.590			
Other	1.0	0.6-1.9	0.898			
Smoking status						
Current/former	1 (ref)					
Never smoker	0.8	0.4-1.4	0.395			
PD-L1 status						
<1%	1 (ref)					
≥1%	1.2	0.4-3.7	0.710			

a) RT: radiotherapy.

b) SRT: stereotactic radiotherapy.

c) Include patients who received radiation less than 4 weeks before the first dose or after the last dose of immunotherapy.

	Crude HR	95%CI	P-value	Adjust HR	95%CI	P-value
Metastasis sites						
multiple	1 (ref)					
solitary	0.7	0.4-1.2	0.238			
No. of prior therapies						
1	1 (ref)					
≥2	1.1	0.6-1.9	0.846			
Immunotherapy regimen						
immune single agent	1 (ref)			1 (ref)		
PD-1/PD-L1 inhibitor plus platinum-based chemotherapy	1.7	0.8-3.4	0.147			
PD-1/PD-L1 inhibitor plus non-platinum regimens	1.5	1.1-2.2	0.024	1.5	0.7-3.1	0.249
Irradiated schema						
Traditional RT ^{a)}	1 (ref)					
SRT ^{b)}	0.9	0.5-1.8	0.803			
Treatment time of RT						
sequential ^{c)}	1 (ref)					
concurrent	0.7	0.4-1.2	0.153			
No. of irradiated lesion						
single-site RT	1 (ref)			1 (ref)		
multiple-site RT	0.5	0.3-0.8	0.017	0.4	0.2-1.0	0.048
Irradiated lesion						

a) RT: radiotherapy.

b) SRT: stereotactic radiotherapy.

c) Include patients who received radiation less than 4 weeks before the first dose or after the last dose of immunotherapy.

	Crude HR	95%CI	P-value	Adjust HR	95%CI	P-value
Lung	1 (ref)					
Bone	1.4	0.6-3.1	0.402			
Brain	2.2	1.0-4.7	0.041			
Other	0.3	0.1-1.2	0.087			
a) RT: radiotherapy.						
b) SRT: stereotactic radiotherapy.						
c) Include patients who received radiation less than 4 weeks before the first dose or after the last dose of immunotherapy.						

The best in-field and out-of-field ORRs were 45.2% and 32.1% (P = 0.208), respectively, and the DCRs were 97.6% and 94.3% (P = 0.627). ORR and DCR (whether local or distant) were not significantly correlated with the type of radiation, timing of radiotherapy or number of irradiated lesions.

3.3 Treatment toxicity

The treatment-related AEs are displayed in Table 4. The incidence of treatment-related AEs was 61.4% (n=35). Pneumonitis (22.8%), rash (17.5%) and hepatic insufficiency (15.8%) occurred most commonly. Only 3 patients (5.3%) experienced grade 3 events: pneumonitis (n=1), rash (n=1) and hepatic insufficiency (n=1).

Table 4
Treatment-related adverse events in 57 patients evaluable for toxicity of combined immunotherapy with radiotherapy therapy.

Treatment-related AEs	All patient (N = 57)		
	Any grade	Grade 1-2	Grade 3
All AEs	35 (61.4%)	32 (56.1%)	3 (5.3%)
Pneumonitis	13 (22.8%)	12 (21.1%)	1 (1.7%)
Rash	10 (17.5%)	9 (15.8%)	1 (1.7%)
Hepatic Insufficiency	9 (15.8%)	8 (14.0%)	1 (1.8%)
Endocrinopathies	3 (5.3%)	3 (5.3%)	0 (0%)
Thyroid dysfunction	3 (5.3%)	3 (5.3%)	0 (0%)
renal insufficiency	2 (3.5%)	2 (3.5%)	0 (0%)
Other	3 (5.3%)	3 (5.3%)	0 (0%)

We also evaluated the associations between AE incidence and radiotherapy parameters. The rates of treatment-related AEs were similar between the concurrent and sequential radiotherapy groups, the multisite and single-site radiation groups, and the groups with different radiation types ($P > 0.05$). Pneumonitis is a major concern in lung cancer, and the incidence of pneumonitis was similar for patients receiving immunotherapy with thoracic radiotherapy and patients treated without thoracic radiotherapy (31.6% vs. 18.4%, $P = 0.435$).

4. Discussion

In the present study, we described the efficacy and safety of immunotherapy combined with radiotherapy in 57 NSCLC patients. Among the evaluable patients, the median OS was 25.9 months, and the median PFS was 10.3 months. The in-field and out-of-field overall response rates were 45.2% and 32.1%, respectively; the disease control rates were 97.6% and 94.3%. Furthermore, the combination of immunotherapy with radiotherapy was well tolerated and was not associated with an increase in the rate of pneumonitis.

Immunotherapy combined with radiotherapy showed longer OS and PFS in our study than in previous studies in which patients received immunotherapy alone, with an OS of 11.8-22.0 months and a PFS of 4.0-9.0 months (18, 19), indicating that combination therapy could be a good strategy in metastatic NSCLC patients. There is growing evidence to suggest that a focus on combining immunotherapy with radiotherapy is warranted. 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(20). 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, 21). Although there were no significant differences in response rates and outcomes when the above two studies were analysed individually, a pooled analysis combining the data from these two randomized trials reported that immunotherapy combined with radiotherapy significantly increased the abscopal response rate and control rate (41.7% vs. 19.7%, $P = 0.004$; 65.3% vs. 43.4%, $P = 0.007$, respectively), with 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 abscopal response rates was 41%(22). Collectively, in line with the findings of our study, the addition of radiotherapy to immunotherapy showed great promise for advanced NSCLC.

To further study the ideal radiotherapy timing, number of lesions to be irradiated, and schedule of combined treatment, subgroup analyses were performed. Patients receiving immunotherapy with concurrent radiotherapy showed a trend to have improved PFS and OS compared to those who were given sequential radiotherapy, although the difference did not reach statistical significance. Although several studies attribute outcome benefits to the abscopal effect(23, 24), the exact mechanisms of the concurrent combination are not known and need to be confirmed by future studies with larger sample sizes. In the subgroup analysis of the number of irradiated lesions, multisite radiotherapy was associated with longer PFS than single-site radiotherapy, which was an independent prognostic factor for PFS. However, similar to previous studies(21), the median OS was significantly different. This result may suggest that multisite radiotherapy could prolong systemic lesion control and lead to better prognosis by activating systemic immunity; however, there are many factors affecting OS, such as posterior treatment mode.

A previous study of radiotherapy schemes demonstrated that hypofractionated radiation therapy (HFRT) has a therapeutic advantage compared with conventional fractionated radiation therapy(25). A preclinical study proved that HFRT treatment of the primary tumour could reduce the recruitment of myeloid-derived suppressor cells into tumours and decrease the expression of PD-L1 on those cells, which unleashed the cytotoxicity of CD8+ T cells(26). Although low-dose radiation therapy (LDRT) has an inferior tumour-killing effect, LDRT is conducive to T cell recruitment and reprograms macrophages in the tumour microenvironment(27). 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) ($P < 0.001$) (28). However, our study found a similar PFS and OS in the SRT and conventional radiotherapy groups. Several factors might be related to the results. First, the relatively small sample size was a limitation for the detection of potentially significant differences. Second, 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.

There is growing evidence of the encouraging safety profile of immunotherapy combined with radiotherapy. Our study showed no increase in toxicity and a rate of treatment-related AEs of 61.4%, consistent with the range of 50–70% previously reported(29, 30). The incidence of grade 3 AEs was 5.3%. 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, and the incidence of pneumonitis was not increased for patients receiving immunotherapy with thoracic radiotherapy. Additionally, patients receiving immunotherapy with concurrent radiotherapy or multisite radiotherapy did not have an increased risk of severe or unexpected toxicities.

This study is limited by its small sample size and 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. Further large-volume, randomized trials are needed to address these unresolved questions.

5. Conclusion

Immunotherapy combined with radiotherapy demonstrated favourable survival without increased toxicity in the treatment of patients with advanced NSCLC. Notably, multisite radiotherapy was associated with longer PFS. Patients receiving immunotherapy with concurrent radiotherapy and immunotherapy with SRT showed a tendency to have improved prognosis. The radiotherapy dose and scheme, as well as the timing of radiotherapy intervention, remain to be further studied.

Declarations

Ethics approval and consent to participate

Clinical data were obtained from electronic medical records, and all patients provided written informed consent for the use of their tumour specimens. The study received approval from the institutional ethics boards of Zhejiang Cancer Hospital.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due to privacy or ethical restrictions but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Z.Z conducted the analysis and interpretation of data, performed the literature search and wrote the manuscript. K.C revised the entire manuscript and guaranteed its integrity. Z.H and YF provided the conception and conceived the framework of the manuscript. NL, M.X and J.S made contributions to acquisition of data. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

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Figures

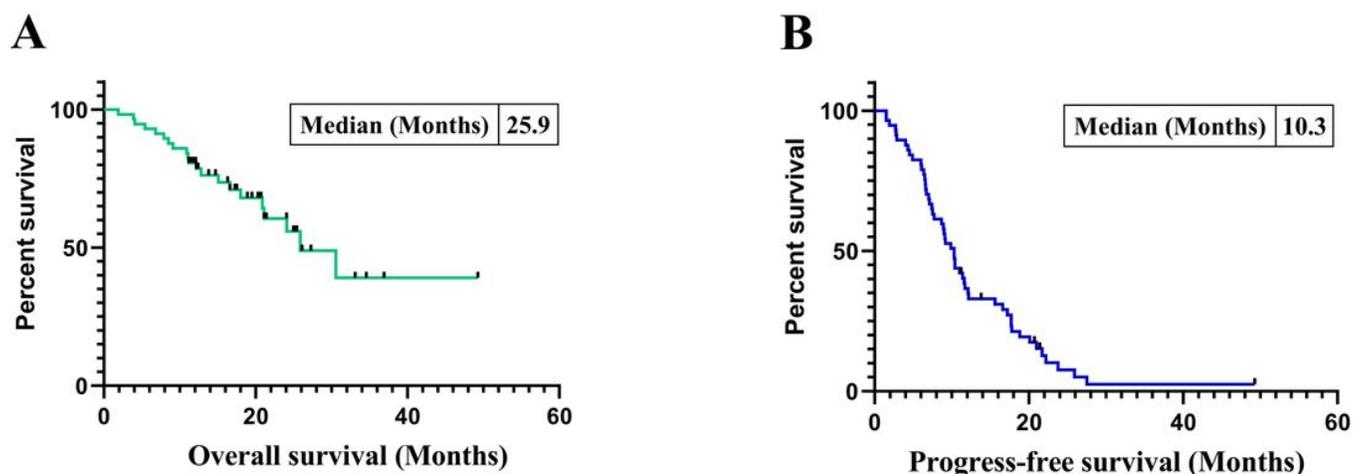


Figure 1

Kaplan–Meier curves of overall survival (OS) and progression-free survival (PFS) in 57 advanced non-small-cell lung cancer (NSCLC) patients receiving immunotherapy with radiotherapy. (A) NSCLC patients treated with immunotherapy combined with radiotherapy showed a median OS of 25.9 months. (B) The median PFS in the entire population was 10.3 months.

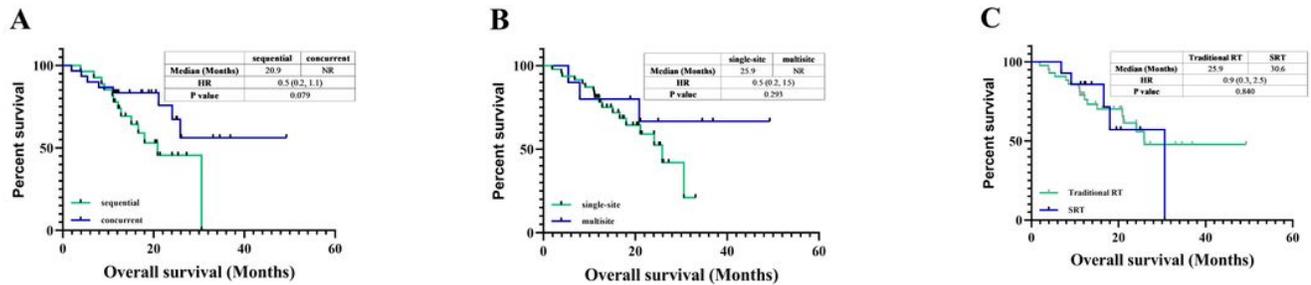


Figure 2

Kaplan–Meier curves of overall survival (OS) in 57 advanced non-small-cell lung cancer (NSCLC) patients receiving immunotherapy with radiotherapy stratified by radiotherapy schedule. (A) Patients receiving immune checkpoint inhibitors concurrently with radiotherapy had improved OS compared with individuals receiving sequential treatment (median OS: not reached versus 20.9 months, $P = 0.079$). (B, C) The number of irradiated lesions and radiotherapy scheme (single-site versus multisite; traditional radiotherapy versus stereotactic radiotherapy) were not remarkably correlated with OS (both $P > 0.05$).

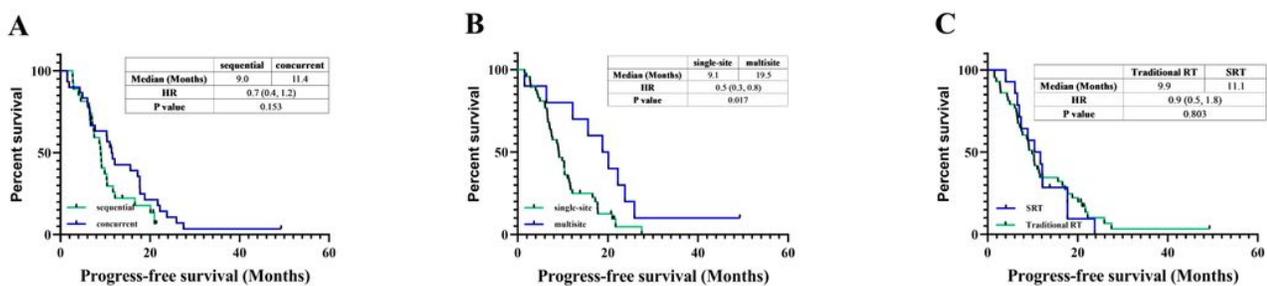


Figure 3

Kaplan–Meier curves of progression-free survival (PFS) in 57 advanced non-small-cell lung cancer (NSCLC) patients receiving immunotherapy with radiotherapy stratified by radiotherapy schedule. (A, C) Timing of radiotherapy and radiation type were not significantly correlated with PFS in advanced NSCLC (both $P > 0.05$). (B) Patients who received multisite radiation had significantly longer PFS than those who received single-site radiation (median PFS: 19.50 versus 9.10 months, $P = 0.017$).