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Original Research Article

# A real-world analysis of stereotactic body radiotherapy combined with immunotherapy in advanced or recurrent non-small cell lung cancer (NSCLC): A single-center experience

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ABSTRACT

*Background:* We aimed to assess the value of stereotactic body radiotherapy (SBRT) delivered under the situation of controlled or progressed disease during ICI therapy in advanced or recurrent NSCLC.

*Methods:* We retrospectively collected patients with advanced or recurrent NSCLC who received SBRT concurrently with ICI in our institution between January 2017 and December 2021. Patients were divided into two groups, including those for whom SBRT was delivered initially or to the residual tumors during the first- or later-line ICI treatment (Group 1), and those for whom SBRT was given to the progressed tumors irrespective of first- or later-line ICI treatment (Group 2).

*Results:* A total of 144 patients were included. With median follow-up duration of 25.6 (range: 3.6 to 56.2) months, median progression-free survival (PFS) was 13.7 (95 % CI: 10.4 to 17.1) months and median overall survival (OS) was 52.8 [95 % CI: 30.6 to not available (NA)] months. In Group 1 (n = 78), median PFS was 17.9 (95 % CI: 14.5 to 29.8) months while median OS was not reached and 5-year OS rate was 61.2 %. In Group 2 (n = 66), median PFS was 8.0 (95 % CI: 6.0 to 13.1) months and median OS was 30.6 (95 % CI: 21.5 to NA) months.

*Conclusions:* SBRT combined with ICI demonstrated favorable survival for advanced or recurrent NSCLC, delivered in a controlled-disease situation as well as to progressed diseases with salvage-intent. Future prospective studies are warranted to investigate the optimal SBRT dose regimen and appropriate combination strategy to synergize ICI.

## Introduction

Lung cancer is the leading cancer-related cause of death worldwide [1]. The utilization of immune checkpoint inhibitors (ICI) has emerged as the first-line standard treatment for recurrent or metastatic non-small-cell lung cancer (NSCLC) without driver gene mutation [2,3]. Nonetheless, response rates to immunotherapy alone, ranging from 20 % to 30 %, remain unsatisfactory [4] and combination with other strategies such as chemotherapy, antiangiogenic agents or radiotherapy are under investigation.

Several preclinical evidences indicated that stereotactic body radiotherapy (SBRT) might stimulate antitumor immunity by inducing tumor-cell death and the release of tumor-associated antigens (TAAs), promoting antigen presentation [5], as well as increasing T-cell infiltration to turn immunologically 'cold' tumors 'hot' [6]. The combination of SBRT with ICI has exhibited promising synergistic antitumor effect in advanced NSCLC. PEMBRO-RT study revealed a doubling of objective response rate (ORR) at 12 weeks when SBRT (24 Gy in 3 fractions) combined with ICI versus ICI alone (36 % vs. 18 %) and the improvement of median progression-free survival (PFS) and overall survival (OS) (6.6 vs. 1.9 months and 15.9 vs. 7.6 months, respectively) [7]. MDACC phase I/II trial reported a superior out-of-field ORR (38 % vs 10 %) and PFS (20.8 months vs 6.8 months) in pembrolizumab plus SBRT (50 Gy in 4 fractions) group versus pembrolizumab plus traditionally fractionated radiotherapy (45 Gy in 15 fractions) group [8]. Though the above two trials didn't have sufficient statistical power to detect clinically attainable improvements because of their limited sample sizes, a pooled analysis based on them confirmed that adding radiotherapy to ICI significantly increased responses and outcomes in metastatic NSCLC [9].

However, there is no higher-level evidence currently to direct the combination between SBRT and ICI treatment in order to obtain a more robust antitumor immune response in metastatic NSCLC. Moreover,

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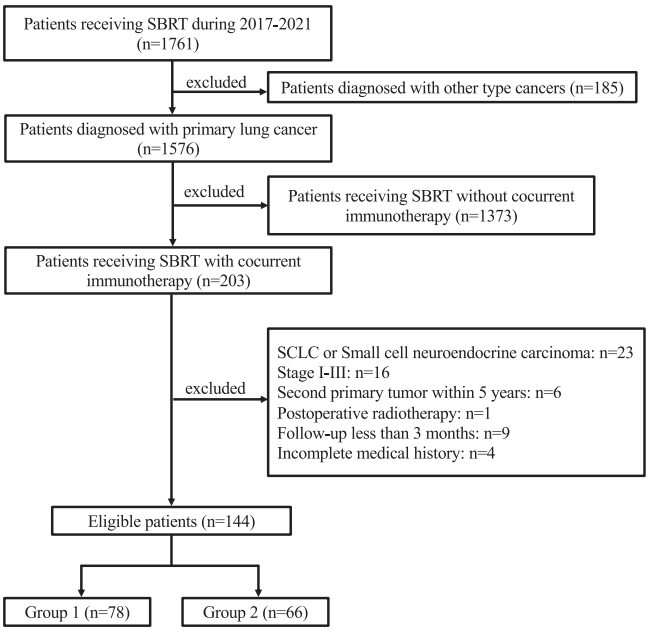


**Fig. 1.** Flow-chart of cohort selection. List of abbreviations: SBRT = stereotactic body radiotherapy; SCLC = small cell lung cancer.

problems regarding the optimal timing, dosing, or number of tumor sites of radiotherapy remain unclear and warrant further investigation. Hence, we evaluated the value of SBRT delivered under the situation of controlled or progressed disease during ICI therapy in advanced or recurrent NSCLC with our single-center, real-world data.

## Methods

### *Patients*

Patients receiving SBRT in Shanghai Chest Hospital from January 2017 to December 2021 were selected based on the following criteria: (1) diagnosis of advanced (stage IV according to AJCC TNM staging 8th version) or recurrent NSCLC; (2) administration of SBRT to primary tumor or at least one metastatic lesion; (3) receiving at least one cycle anti-PD-1/PD-L1 agent within 4 weeks before or after SBRT; (4) complete medical history and imaging data; (5) follow-up duration of no less than 3 months. Patients who met the following criteria were excluded: pathologically confirmed small cell lung cancer or small cell neuroendocrine carcinoma, diagnosis of second primary tumor within 5 years, receiving postoperative prophylactic radiotherapy without solid lesions, or incomplete medical history (blinded in clinical trials). Clinical data acquisition from our electronic medical records has been approved by the Research Ethics Committee of our institution. In our study, to evaluate SBRT throughout a variety of dose–fractionation regimens, biologic effective dose (BED) assuming α/β of 10 ($BED_{10}$) was determined for all dose regimens.

### *Study design*

Patients were stratified into two groups to better analyze the role of SBRT in distinct clinical scenarios. Group 1 consisted of patients receiving SBRT initially or for residual tumors (single or multiple sites) during first- or later-line ICI treatment, aiming to maximize reduction of tumor burden and achieve radical treatment. Group 2 comprised patients receiving salvage SBRT for progressed tumors (single or multiple sites), regardless of first- or later-line ICI treatment. Therefore, the initial time of Group 1 was defined as the time of the first anti-tumor treatment at initial diagnosis or the beginning of the later-line ICI treatment. And

**Table 1**
Patient and treatment characteristics.

| Variable | All | | Group1 | | Group2 | |
|---|---|---|---|---|---|---|
| | (N = 144) | | (N = 78) | | (N = 66) | |
| **Age (years)** | | | | | | |
| Median (range) | 66 | (34–87) | 67 | (44–87) | 62.5 | (34–80) |
| **Gender** | | | | | | |
| Male | 118 | 82.7 % | 65 | 83.3 % | 53 | 80.3 % |
| Female | 26 | 17.3 % | 13 | 16.7 % | 13 | 19.7 % |
| **Smoking history** | | | | | | |
| No | 56 | 37.3 % | 32 | 41 % | 24 | 36.4 % |
| Yes | 88 | 62.7 % | 46 | 59 % | 42 | 63.6 % |
| **Family history** | | | | | | |
| No | 124 | 86.7 % | 69 | 88.5 % | 55 | 83.3 % |
| Yes | 20 | 13.3 % | 9 | 11.5 % | 11 | 16.7 % |
| **Pathology** | | | | | | |
| Non-squamous cell carcinoma | 111 | 77.8 % | 60 | 76.9 % | 51 | 77.3 % |
| Squamous cell carcinoma | 33 | 22.2 % | 18 | 23.1 % | 15 | 22.7 % |
| **Treatable driver mutations** | | | | | | |
| No | 111 | 56.7 % | 70 | 89.7 % | 41 | 62.1 % |
| Yes * | 11 | 7.3 % | – | – | 11 | 16.7 % |
| Unknown | 22 | 16.0 % | 8 | 10.3 % | 14 | 22.1 % |
| **Stage** | | | | | | |
| r-M & | 94 | 62.7 % | 28 | 35.9 % | 66 | 100 % |
| IVB | 26 | 17.3 % | 26 | 33.3 % | – | – |
| IVA | 24 | 16 % | 24 | 30.8 % | – | – |
| **PD-L1 status** | | | | | | |
| <1% | 29 | 20 % | 17 | 21.8 % | 12 | 18.2 % |
| 1–49 % | 25 | 16.6 % | 15 | 19.2 % | 10 | 15.1 % |
| 50–100 % | 38 | 26.7 % | 26 | 33.3 % | 12 | 18.2 % |
| Unknown | 52 | 36.7 % | 20 | 25.7 % | 32 | 48.5 % |
| **Metastasis sites** | | | | | | |
| Oligometastasis/ progression | 93 | 64.6 % | 54 | 69.2 % | 39 | 59.1 % |
| Multiple metastases/ progressions | 51 | 35.4 % | 24 | 30.8 % | 27 | 40.9 % |
| **Radiation to all tumor sites** | | | | | | |
| No | 103 | 71.5 % | 65 | 83.3 % | 38 | 57.6 % |
| Yes | 41 | 28.5 % | 13 | 16.7 % | 28 | 42.4 % |
| **SBRT sites** | | | | | | |
| Brain | 68 | | 44 | | 24 | |
| Lung | 69 | | 37 | | 32 | |
| Bone | 12 | | 6 | | 6 | |
| Adrenal glands | 9 | | 5 | | 4 | |
| Others # | 16 | | 5 | | 11 | |
| **BED10** | | | | | | |
| <60 Gy | 96 | 66.7 % | 54 | 69.2 % | 42 | 63.6 % |
| ≥60 Gy | 48 | 33.3 % | 24 | 30.8 % | 24 | 36.4 % |
| **Type of ICI** | | | | | | |
| PD-1 antibody | 135 | 93.7 % | 71 | 91 % | 64 | 97 % |
| PD-L1 antibody | 9 | 6.3 % | 7 | 9 % | 2 | 3 % |
| **Immunotherapy regimen** | | | | | | |
| ICI alone | 48 | 33.3 % | 21 | 26.9 % | 27 | 40.9 % |
| ICI + Combination | 96 | 66.7 % | 57 | 73.1 % | 39 | 59.1 % |

(*continued on next page*)

**Table 1** (*continued*)

| Variable | All | | Group1 | | Group2 | |
|---|---|---|---|---|---|---|
| | (N = 144) | | (N = 78) | | (N = 66) | |
| **Prior lines of systemic treatment** | | | | | | |
| 0 | 75 | 52.1 % | 75 | 96.2 % | – | – |
| 1 | 38 | 26.4 % | 3 | 3.8 % | 35 | 53 % |
| ≥2 | 31 | 21.5 % | – | – | 31 | 47 % |

Abbreviations: BED10, biologically effective dose assuming α/β of 10; ICI, immune checkpoint inhibitors. Notes: *"Yes" means patients with treatable driver mutations including 21L858R, 19del and ALK; &"r-M", tumor recurred and metastasized after receiving radical treatment including surgery or concurrent chemoradiotherapy; #"Others" includes the metastases of liver, lymph nodes and chest wall.

the initial time of Group 2 was defined as the time of the first anti-tumor treatment given to the progressed tumor which was treated with salvage SBRT. Oligometastasis is defined as 1 to 5 metastatic lesions, according to ESTRO − ASTRO consensus [10]. Development of treatment-related adverse effects, including pneumonitis, was determined using all available records and adverse events were graded using the Common Terminology Criteria for Adverse Events Version 5.0.

### *Statistical analysis*

Continuous variables were summarized by descriptive statistics such as means, standard deviations, medians, and ranges. Categorical variables were tabulated by frequency and percentage. PFS was defined as the initial time to the first disease progression or death from any cause. OS was defined as the interval from initiation of two groups to death from any cause. Kaplan–Meier method was used to estimate PFS, OS. Univariable and multivariable Cox proportional hazard models were applied to determine significant prognostic factors. All statistical analyses were performed in R version 4.2.3, with the "survival", "survminer", packages (https://www.r-project.org).

## Results

### *Patients*

Of the 1761 patients who received SBRT in Shanghai Chest Hospital during January 2017 and December 2021, 144 eligible patients were included (Fig. 1), 78 in Group 1 and 66 in Group 2. The baseline characteristics of the patients in two different groups are shown in Table 1.

In Group 1, 96.2 % patients received SBRT during first-line systemic treatment, 16.7 % receiving irradiation to all tumor sites while 83.3 % receiving partial irradiation. And in Group 2, 47.0 % patients had received more than two lines of systemic treatment, 45.5 % receiving frontline ICI-based treatment, 59.1 % oligoprogression status, and 42.4 % received irradiation to all progression sites.

### *Survival outcomes*

The median follow-up time was 25.6 months (range: 3.6–56.2 months). Median PFS was 13.7 months (95 % CI: 10.4–17.1 months) and median OS was 52.8 months (95 % CI: 30.6 months − NA). In Group 1, median PFS was 17.9 months (95 % CI: 14.5–29.8 months) while median OS was not reached and 5-year OS rate was 61.2 %. In Group 2, median PFS was 8.0 months (95 % CI: 6.0–13.1 months) and median OS was 30.6 months (95 % CI: 21.5 months-NA). Kaplan-Meier survival curves for PFS and OS are shown in Fig. 2.

### *Univariate and multivariate analysis for PFS and OS*

As shown in Table 2, in Group 1, multiple metastases were associated with poor PFS (HR, 3.59; 95 % CI, 1.89–6.83; $p < 0.001$), so as the squamous cell carcinoma (HR, 1.92; 95 % CI, 0.96–3.81; $p = 0.064$) with a borderline significance. Comparing to treating only part of metastatic lesions, total irradiation of metastatic lesions was associated with superior PFS (HR, 0.44; 95 % CI, 0.18–1.11; $p = 0.083$), and higher radiation doses ($BED_{10} \geq 60$ Gy) showed a favorable trend to improve the

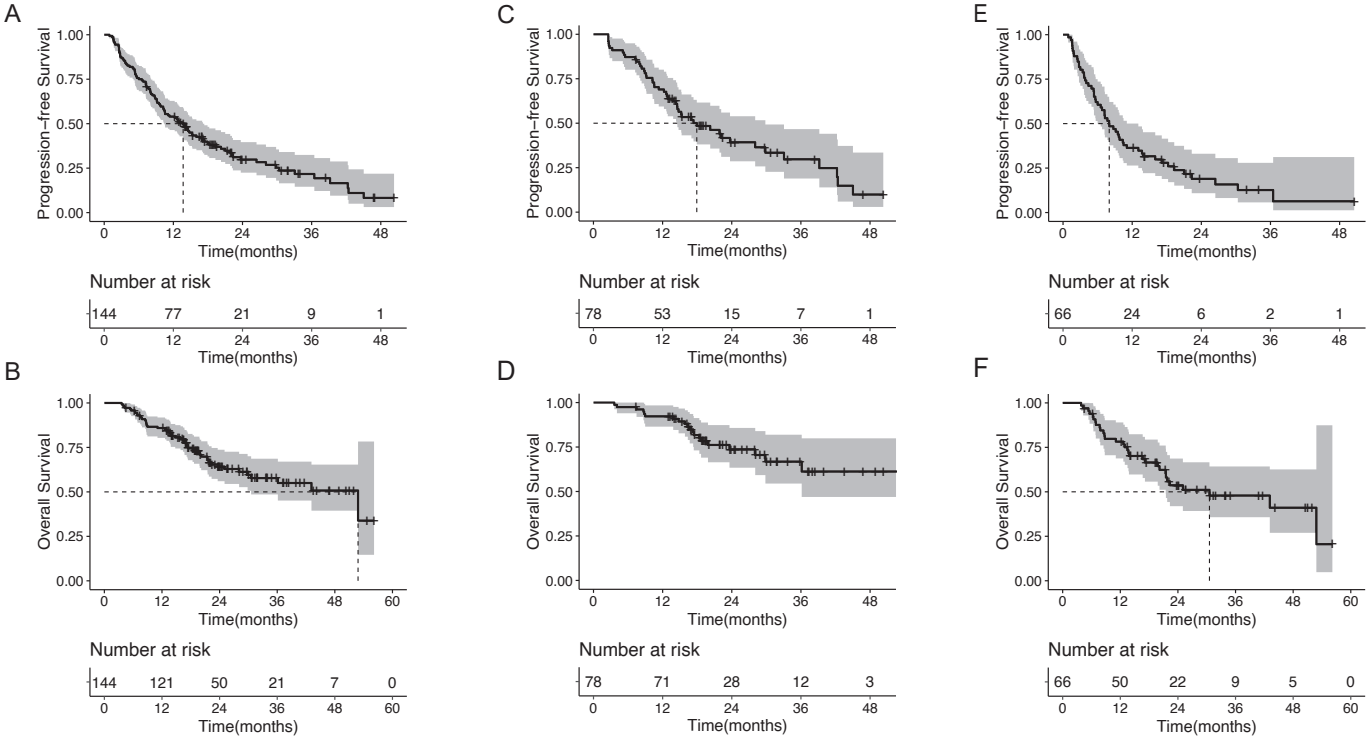


**Fig. 2.** Kaplan–Meier estimates of the progression-free survival (PFS) and overall survival (OS) of the entire cohort (A and B), Group 1 (C and D) and Group 2 (E and F). The shaded areas showed the 95% confidence interval.

**Table 2**
Univariable and multivariable analysis of patient characteristics with PFS and OS in Group1.

| Variable | N/(%) | mPFS | | | | | mOS | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Univariate analysis | | Multivariate analysis | | | Univariate analysis | | Multivariate analysis | |
| | | (Months) | HR (95 %CI) | P-value | HR (95 %CI) | P-value | (Months) | HR (95 %CI) | P-value | HR (95 %CI) | P-value |
| **Age** | | | | 0.180 | | | | | 0.351 | | |
| ≤67 years | 44 (56.4) | 23.7(14.6-NA) | 1 | | | | Not Reach | 1 | | | |
| >67 years | 34 (43.6) | 14.8(12.7-NA) | 1.47 (0.84–2.60) | | | | Not Reach | 1.52 (0.63–3.66) | | | |
| **Gender** | | | | 0.756 | | | | | 0.397 | | |
| Male | 65 (83.3) | 20.3 (13.8–39.2) | 1 | | | | Not Reach | 1 | | | |
| Female | 13 (16.7) | 17.9(14.3-NA) | 1.12 (0.54–2.32) | | | | 36.1(23.6-NA) | 1.55 (0.56–4.29) | | | |
| **Smoking history** | | | | 0.776 | | | | | 0.368 | | |
| No | 32 (41.0) | 17.9(14.3-NA) | 1 | | | | 36.1(28.1-NA) | 1 | | | |
| Yes | 46 (59.0) | 17.4(11.3-NA) | 0.92 (0.52–1.64) | | | | Not Reach | 0.67 (0.28–1.61) | | | |
| **Family history** | | | | 0.854 | | | | | 0.690 | | |
| No | 69 (88.5) | 17.9 (14.3–29.8) | 1 | | | | Not Reach | 1 | | | |
| Yes | 9 (11.5) | 17.4(8.1-NA) | 1.08 (0.46–2.56) | | | | Not Reach | 0.74 (0.17–3.21) | | | |
| **Pathology** | | | | **0.009** | | **0.064** | | | **0.013** | | **0.013** |
| No-squamous cell carcinoma | 60 (76.9) | 22.2 (15.3–42.3) | 1 | | 1 | | Not Reach | 1 | | 1 | |
| Squamous cell carcinoma | 18 (23.1) | 9.7(8.0-NA) | 2.33 (1.23–4.40) | | 1.92 (0.96–3.81) | | Not Reach | 3.18 (1.27–7.93) | | 3.39 (1.29–8.89) | |
| **Treatable driver mutations** | | | | 0.466 | | | | | 0.702 | | |
| No | 70 (89.7) | 17.9 (14.5–33.1) | 1 | | | | Not Reach | 1 | | | |
| Unknown | 8 (10.3) | 13.1(9.1-NA) | 1.42 (0.56–3.62) | | | | Not Reach | 1.34 (0.30–5.88) | | | |
| **Stage** | | | | 0.218 | | | | | 0.306 | | |
| r-M & | 28 (35.9) | 21.9(10.5-NA) | 1 | | | | Not Reach | 1 | | | |
| IVB | 26 (33.3) | 14.6(12.2-NA) | 1.47 (0.75–2.89) | 0.263 | | | 36.1(29.8-NA) | 1.40 (0.52–3.78) | 0.503 | | |
| IVA | 24 (30.8) | 23.7(13.8-NA) | 0.78 (0.38–1.59) | 0.488 | | | Not Reach | 0.58 (0.17–1.97) | 0.379 | | |
| **PD-L1 status** | | | | 0.481 | | | | | 0.519 | | |
| <1% | 17 (21.8) | 22.2(12.2-NA) | 1 | | | | 36.1(23.6-NA) | 1 | | | |
| 1–49 % | 15 (19.2) | 14.6(10.5-NA) | 1.61 (0.68–3.81) | 0.279 | | | Not Reach | 0.34 (0.07–1.63) | 0.177 | | |
| 50–100 % | 26 (33.3) | 33.1(13.8-NA) | 0.87 (0.39–1.93) | 0.735 | | | Not Reach | 0.59 (0.20–1.75) | 0.340 | | |
| Unknown | 20 (25.7) | 17.9(10.2-NA) | 1.28 (0.56–2.91) | 0.562 | | | Not Reach | 0.67 (0.21–2.12) | 0.498 | | |
| **Metastasis sites** | | | | **0.000** | | **0.000** | | | **0.001** | | **0.004** |
| Oligometastasis | 54 (69.2) | 29.8 (20.3–45.0) | 1 | | 1 | | Not Reach | 1 | | 1 | |
| Multiple metastases | 24 (30.8) | 10.2 (7.5–14.6) | 4.30 (2.35–7.87) | | 3.59 (1.89–6.83) | | 19.9(17.3-NA) | 4.75 (1.93–11.73) | | 3.92 (1.54–9.98) | |
| **Radiation to all tumor sites** | | | | 0.121 | | 0.083 | | | **0.030** | | **0.003** |
| No | 65 (83.3) | 15.3 (12.9–28.1) | 1 | | 1 | | Not Reach | 1 | | 1 | |

(*continued on next page*)

**Table 2** (*continued*)

| Variable | N/(%) | mPFS | | | | | mOS | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Univariate analysis | | Multivariate analysis | | | Univariate analysis | | Multivariate analysis | |
| | | (Months) | HR (95 %CI) | P-value | HR (95 %CI) | P-value | (Months) | HR (95 %CI) | P-value | HR (95 %CI) | P-value |
| Yes | 13 (16.7) | 39.2(17.4-NA) | 0.53 (0.23–1.26) | | 0.44 (0.18–1.11) | | Not Reach | 0.00(0.00-Inf) | | 0.00(0.00-Inf) | |
| **BED10** | | | | 0.358 | | 0.319 | | | 0.578 | | 0.357 |
| <60 Gy | 54 (69.2) | 17.0 (13.8–33.1) | 1 | | 1 | | Not Reach | 1 | | 1 | |
| ≥60 Gy | 24 (30.8) | 21.9(14.3-NA) | 0.74 (0.39–1.40) | | 0.71 (0.36–1.39) | | Not Reach | 0.75 (0.27–2.07) | | 0.75 (0.27–2.07) | |
| **Type of ICI** | | | | 0.068 | | | | | 0.104 | | |
| PD-1 antibody | 71 (91.0) | 20.3 (14.8–39.2) | 1 | | | | Not Reach | 1 | | | |
| PD-L1 antibody | 7(9.0) | 10.6(8.0-NA) | 2.25 (0.94–5.35) | | | | 26.7(17.4-NA) | 2.50 (0.83–7.55) | | | |
| **Immunotherapy regimen** | | | | 0.924 | | | | | 0.425 | | |
| ICI alone | 21 (26.9) | 17.4(11.3-NA) | 1 | | | | Not Reach | 1 | | | |
| ICI + Combination | 57 (73.1) | 17.9 (14.3–42.3) | 0.97 (0.51–1.83) | | | | Not Reach | 0.69 (0.27–1.73) | | | |
| **Prior lines of systemic treatment** | | | | 0.996 | | | | | 0.998 | | |
| 0 | 75 (96.2) | 17.0 (14.3–28.1) | 1 | | | | Not Reach | 1 | | | |
| 1 | 3(3.8) | Not Reach | 0.00(0.00-Inf) | | | | Not Reach | 0.00(0.00-Inf) | | | |

Abbreviations: BED10, biologically effective dose assuming α/β of 10; HR, hazard ratio; CI, confidence interval; NA, not available; Inf, infinity. Notes: & "r-M", tumor recurred and metastasized after receiving radical treatment including surgery or concurrent chemoradiotherapy.

PFS (HR, 0.71; 95 % CI, 0.36–1.39; p = 0.319). Multiple metastases (HR, 3.92; 95 % CI, 1.54–9.98; p = 0.004) and squamous cell carcinoma (HR, 3.39; 95 % CI, 1.29–8.89; p = 0.013) were also found significantly associated with inferior OS, while total irradiation of metastatic sites maintained apparent benefit for OS (p = 0.003).

However, in Group 2 with more complicated history of prior systemic treatment, no significant factor was found associated with PFS (Table 3). Multiple progression contributed to poorer OS though barely failed to attain statistical significance (HR, 3.26; 95 % CI, 0.94–11.28; p = 0.062). Higher radiation doses ($BED_{10} \geq 60$ Gy) brought numerically longer OS versus lower radiation doses ($BED_{10} < 60$ Gy) (43.1 vs 21.5 months) but the difference did not appear to be sufficiently significant (HR, 0.47; 95 % CI, 0.21–1.07; p = 0.071).

### *Treatment-related adverse events*

Concerning toxicity, 23 (29.5 %) patients in Group 1 reported treatment-related adverse events (TRAEs), with 10 (12.8 %) of them classified as Grade ≥ 3 TRAEs, including 6 (7.7 %) cases of pneumonitis, 3 (2.6 %) cases of hematological toxicity, and 1(1.3 %) case of immunological colitis. While in Group 2, 18 (27.3 %) patients developed TRAEs, with 8 (12.1 %) of them classified as Grade ≥ 3, including 6 (9.1 %) cases of pneumonitis and 2 (6.1 %) cases of hematological toxicity (Table 4).

## Discussion

To our knowledge, this is the first real-world analysis to investigate the effect of combination of SBRT and immunotherapy for advanced or recurrent NSCLC, indicating SBRT plus immunotherapy as a potential and efficient strategy in these patients.

Several phase III randomized studies established immunotherapy plus chemotherapy as standard treatment in advanced or recurrent NSCLC without driver gene mutation, with mPFS of 7.0–9.8 months and mOS of 18.6–24.2 months for nonsquamous NSCLC [11–14] and mPFS of 5.5–8.0 months and mOS of 14.2–26.1 months for squamous NSCLC [15–18]. Patients in the above trials were not allowed to receive local radiotherapy during the first-line treatment until disease progression. Since the secondary analysis of the KEYNOTE-001 trial suggested that previous radiotherapy resulted in longer PFS and OS in patients with advanced NSCLC with pembrolizumab treatment than that seen in patients who did not have previous radiotherapy (4.0 vs 2.1 months and 10.7 vs 5.3 months) [19], showing that combination of ICI and radiotherapy produced synergistic antitumor activity or transferred non-responders into responders. Since phase II trials [20–22] indicated that the consolidative radiation after first-line systemic therapy prolonged the PFS of metastatic NSCLC in the era of chemotherapy, whether consolidative radiation might stimulate maximal response of immunotherapy-based systemic treatment has been drawing increasing attention from researchers. To address this concern, Group 1 in our cohort, collecting patients who received SBRT initially or consolidatively in combination with ICI, reported a promising long-term survival (mPFS, 17.9 months and 5-year-rate OS, 61.2 %). Even Group 2, which contained patients facing disease progression and thus receiving salvage SBRT plus ICI, exhibited a fair PFS of 8.0 months and OS of 30.6 months, comparing to the survival reported by PEMBRO-RT study (mPFS, 6.6 months and OS, 15.9 months) [7].

In Group 1 for which SBRT was delivered for somewhat 'curative' purpose, baseline tumor burden appeared to influence the prognosis even if most metastatic lesions were well controlled by ICI based systemic regimen. Better prognosis was observed on patients with oligometastases, a clinical state between locally confined and systemic

**Table 3**
Univariable and multivariable analysis of patient characteristics with PFS and OS in Group2.

| Variable | N/(%) | mPFS | | | | | mOS | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Univariate analysis | | Multivariate analysis | | | Univariate analysis | | Multivariate analysis | |
| | | | HR (95 %CI) | P-value | HR (95 %CI) | *P*-value | (Months) | HR (95 %CI) | *P*-value | HR (95 %CI) | *P*-value |
| **Age** | | | | 0.268 | | | | | 0.421 | | |
| ≤62 years | 33 (50.0) | 7.2 (5.3–17.1) | 1 | | | | Not reach | 1 | | | |
| >62 years | 33 (50.0) | 9.5 (6.0–22.3) | 0.74 (0.43–1.27) | | | | 25.0(19.8-NA) | 1.34 (0.66–2.72) | | | |
| **Sex** | | | | **0.016** | | 0.219 | | | 0.400 | | |
| Male | 53 (80.3) | 9.5 (7.3–16.0) | 1 | | 1 | | 43.1(21.5-NA) | 1 | | | |
| Female | 13 (19.7) | 6.0(2.8-NA) | 2.20 (1.16–4.17) | | 1.73 (0.72–4.15) | | 21.5(7.8-NA) | 1.42 (0.63–3.21) | | | |
| **Smoking history** | | | | **0.023** | | 0.374 | | | 0.647 | | |
| No | 24 (36.4) | 5.8 (4.0–9.7) | 1 | | 1 | | 43.1(21.5-NA) | 1 | | | |
| Yes | 42 (63.6) | 10.1 (8.0–19.3) | 0.53 (0.31–0.92) | | 0.73 (0.36–1.46) | | 22.3(19.8-NA) | 1.19 (0.56–2.52) | | | |
| **Family history** | | | | 0.904 | | | | | 0.657 | | |
| No | 55 (83.3) | 8.0 (5.7–13.7) | 1 | | | | 22.3(20.2-NA) | 1 | | | |
| Yes | 11 (16.7) | 9.1(6.0-NA) | 0.96 (0.47–1.97) | | | | 30.6(25.0-NA) | 0.80 (0.31–2.11) | | | |
| **Pathology** | | | | 0.182 | | | | | 0.698 | | |
| Non-squamous cell carcinoma | 51 (77.3) | 7.3 (5.7–11.1) | 1 | | | | 30.6(20.2-NA) | 1 | | | |
| Squamous cell carcinoma | 15 (22.7) | 10.5(5.3-NA) | 0.63 (0.32–1.24) | | | | 43.1(19.8-NA) | 0.85 (0.38–1.92) | | | |
| **Treatable driver mutations** | | | | 0.342 | | | | | 0.477 | | |
| No | 41 (62.1) | 6.8 (4.0–9.8) | 1 | | | | 25.0(20.2-NA) | 1 | | | |
| Yes* | 11 (16.7) | 9.7(7.2-NA) | 0.66 (0.31–1.38) | 0.269 | | | 52.8(17.1-NA) | 0.61 (0.22–1.68) | 0.342 | | |
| Unknown | 14 (21.2) | 12.2(8.0-NA) | 0.67 (0.34–1.33) | 0.248 | | | Not Reach | 0.64 (0.25–1.63) | 0.353 | | |
| **PD-L1 status** | | | | 0.445 | | | | | 0.577 | | |
| <1% | 12 (18.2) | 7.6(5.4-NA) | 1 | | | | 25.0(8.7-NA) | 1 | | | |
| 1–49 % | 10 (15.1) | 4.7(2.5-NA) | 1.50 (0.61–3.65) | 0.377 | | | 21.8(7.7-NA) | 1.14 (0.37–3.46) | 0.823 | | |
| 50–100 % | 12 (18.2) | 17.1(4.0-NA) | 0.71 (0.29–1.74) | 0.456 | | | 20.2(13.8-NA) | 0.89 (0.30–2.67) | 0.841 | | |
| Unknown | 32 (48.5) | 8.4 (6.0–16.0) | 0.84 (0.41–1.72) | 0.635 | | | Not Reach | 0.61 (0.24–1.56) | 0.305 | | |
| **Metastasis sites** | | | | 0.160 | | 0.528 | | | **0.008** | | 0.062 |
| Oligoprogression | 39 (59.1) | 9.7 (7.3–18.2) | 1 | | 1 | | Not Reach | 1 | | 1 | |
| Multiple progressions | 27 (40.9) | 5.6 (3.8–13.1) | 1.47 (0.86–2.53) | | 1.30 (0.58–2.92) | | 19.8(8.5-NA) | 2.66 (1.30–5.45) | | 3.26 (0.94–11.28) | |
| **Radiation to all tumor sites** | | | | 0.103 | | 0.519 | | | 0.054 | | 0.886 |
| No | 38 (57.6) | 6.1 (3.7–13.1) | 1 | | 1 | | 21.8(12.9-NA) | 1 | | 1 | |
| Yes | 28 (42.4) | 10.0 (8.0–21.0) | 0.63 (0.37–1.10) | | 0.77 (0.35–1.70) | | Not Reach | 0.48 (0.22–1.01) | | 1.10 (0.30–4.02) | |
| **BED10** | | | | 0.326 | | 0.475 | | | 0.191 | | 0.071 |
| <60 Gy | 42 (63.6) | 7.9 (5.6–13.9) | 1 | | 1 | | 21.5(17.1-NA) | 1 | | 1 | |

(*continued on next page*)

**Table 3** (*continued*)

| Variable | N/(%) | mPFS | | | | | mOS | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Univariate analysis | | Multivariate analysis | | | Univariate analysis | | Multivariate analysis | |
| | | | HR (95 %CI) | P-value | HR (95 %CI) | *P*-value | (Months) | HR (95 %CI) | *P*-value | HR (95 %CI) | *P*-value |
| ≥60 Gy | 24 (36.4) | 9.8 (5.7–30.3) | 0.75 (0.42–1.34) | | 0.79 (0.42–1.50) | | 43.1(30.6-NA) | 0.59 (0.27–1.30) | | 0.47 (0.21–1.07) | |
| **Type of ICI** | | | | 0.281 | | | | | 0.937 | | |
| PD-1 antibody | 64 (97.0) | 8.4 (6.5–13.1) | 1 | | | | 30.6(21.5-NA) | 1 | | | |
| PD-L1 antibody | 2(3.0) | 6.1(4.9-NA) | 2.20 (0.52–9.27) | | | | 12.6(12.6-NA) | 1.08 (0.15–7.98) | | | |
| **Immunotherapy regimen** | | | | 0.306 | | | | | 0.403 | | |
| ICI alone | 27 (40.9) | 8.7 (4.9–30.3) | 1 | | | | 43.1(21.5-NA) | 1 | | | |
| ICI + Combination | 39 (59.1) | 7.3 (6.0–13.9) | 1.35 (0.76–2.40) | | | | 25.0(17.1-NA) | 1.37 (0.66–2.83) | | | |
| **Prior lines of systemic treatment** | | | | 0.276 | | | | | 0.981 | | |
| 1 | 35 (53.0) | 10.4 (5.4–22.3) | 1 | | | | 25.0(21.5-NA) | 1 | | | |
| ≥2 | 31 (47.0) | 7.2 (5.6–11.1) | 1.35 (0.79–2.31) | | | | 30.6(17.1-NA) | 0.99 (0.48–2.04) | | | |

Abbreviations: BED10, biologically effective dose assuming α/β of 10; HR, hazard ratio; CI, confidence interval; NA, not available. Notes: *"Yes" means patients with treatable driver mutations including 21L858R, 19del and ALK.

**Table 4**
Treatment-related adverse events (TRAEs) Data.

| TRAEs | Any grade n (%) | | | | Grade ≥ 3n (%) | | | |
|---|---|---|---|---|---|---|---|---|
| | Group1 (N = 78, %) | | Group2 (N = 66, %) | | Group1 (N = 78, %) | | Group2 (N = 66, %) | |
| All TRAEs | 23 | 29.5 % | 18 | 27.3 % | 10 | 12.8 % | 8 | 12.1 % |
| Pneumonitis | 19 | 7.9 % | 13 | 19.7 % | 6 | 7.7 % | 6 | 9.1 % |
| Hematological toxicity | 3 | 2.6 % | 4 | 6.1 % | 3 | 2.6 % | 2 | 6.1 % |
| Immunological Colitis | 1 | 1.3 % | 0 | 0 | 1 | 1.3 % | 0 | 0 |
| Myocarditis | 0 | 0 | 1 | 1.5 % | 0 | 0 | 0 | 0 |

metastasized disease, which was reported to be potentially curative from positive local treatment like SBRT [10]. And according to another retrospective analysis of our institution, primary lesion (59.1 %) was found to be the most common progression site after first-line immunotherapy [23], which also provides a rationale for local consolidative treatment. Besides that, irradiation of all disease sites contributed to superior PFS and OS comparing to irradiation of limited sites, supporting the idea that irradiating multiple/all lesions increases the chance of successfully priming an antitumor immune response. As observed by Brooks et al [24], having all lesions irradiated increases the likelihood of a successful TAA priming event as well as shared TAA, and has the potential to prime immune cells to recognize a wider range of TAAs due to tumor heterogeneity. However, irradiation of multiple/all disease sites would be more likely to be provided to patients with oligometastases to radical purpose, and thus it becomes difficult to ascertain the number of irradiation sites as a prognostic factor independent of oligometastases in a retrospective study. While in Group 2 for whom received salvage SBRT to the progressed tumors, it seemed that there was barely significant factor correlated with treatment outcomes. The most possible reason could be attributed to the fact that nearly half the patients in this group had undergone more than two lines of systemic treatment and considerable heterogeneity was inevitable. It seemed that the advantage of multiple/all lesions irradiation to prime the immunity could hardly make sense in a more complicated, salvage setting.

The optimal dose fractionation of SBRT to combine with ICI in order to induce maximal antitumor effect remains unclear, though $BED_{10} \geq 100$ Gy is usually recommended to ablate early-stage NSCLC. Different from ablative radiation (>10 Gy per fraction) which may induce immunogenic cell death associated with release of TAAs and death-associated molecular patterns (DAMPs), non-ablative moderately dosed radiation (≤10 Gy per fraction) can up-regulate MHC-1, promote recruitment and activation of dendritic cells, and probably be more effective in priming CD8 + T cells that mediate abscopal effects in the context of ICI [25,26]. As demonstrated by PEMBRO-RT study, 8 Gy × 3 regimen preceding ICI potentially enhanced tumor response in metastatic NCSLC [27]. In our results, radiation regimens with $BED_{10} \geq 60$ Gy, for instance, 10 Gy × 3 regimen, showed a pronounced trend to improve the outcomes comparing to those with lower $BED_{10}$ in both Group 1 and 2. Notably, irradiation of different sites might require different doses, and the tolerance of the specific organ should be also considered. Evidence also suggests that the combination of hypofractionated radiation (10 Gy × 3) and low-dose radiation (≤2Gy per fraction for up to 10 Gy in total) in the presence of ICI might be a promising strategy to obtain an appreciable response and even enhance abscopal effect [28,29]. However, future clinical trials are still required to investigate the optimal SBRT or combination strategy to synergize ICI.

In terms of the choice of ICI type, PD-1 antibody was considered as a better option to combine with SBRT according to our results, but too limited sample of PD-L1 antibody group is insufficient to draw a definite conclusion, and little evidence has been obtained for PD-L1 antibody plus SBRT by far, mainly in early-stage NSCLC [30,31]. As to biomarker for immune response, PEMBRO-RT study reported patients with PD-L1-negative NSCLC attained a significant benefit of SBRT with respect to PFS and OS [7], while we found no significant associations between PD-L1 expression and PFS or OS, possibly due to small size enrollment or considerable proportion of unknown PD-L1 expression.

There are several limitations to our current study. As a retrospective study, our single-arm cohort with limited sample sizes, diverse tumor

locations and volumes, as well as diverse radiation doses and fractionations, may introduce bias, although the entire cohort were divided into two groups to decrease inherent heterogeneity as much as possible. From our data, some questions regarding how to combine SBRT with ICI appropriately remain inconclusive, such as the optimal combination sequence, radiation dose regimen, the specific organ to prime the immunity and so on. Nevertheless, the present study may offer valuable insights for the design of future prospective study investigating SBRT combing ICI in advanced or recurrent NSCLC, that radiation regimens with $BED_{10} \geq 60$ Gy and with multiple/all lesions irradiated might be more efficient to synergize ICI. The salvage-intent SBRT during later-line systemic treatment exhibited less powerful than a consolidative- or curative-intent SBRT, but remained to promise benefit comparing to systemic treatment alone. Additionally, sufficient collection of potential biomarkers should be considered in the future study to identify patients who are prone to benefit from the combination of SBRT and ICI.

## Conclusion

In conclusion, SBRT, in both consolidative and salvage situation, combined with ICI demonstrated favorable survival for advanced or recurrent NSCLC. Intermediate-dose SBRT regimen with multiple/all lesions irradiated showed association with superior outcomes, but future prospective studies are warranted to investigate the optimal SBRT or combination strategy to synergize ICI.

## CRediT authorship contribution statement

**Dan Yao:** Conceptualization, Methodology, Software, Validation, Investigation, Formal analysis, Data curation, Writing – original draft. **Xueru Zhu:** Validation, Resources, Methodology. **Jindong Guo:** Resources, Investigation. **Xiaohuan Dong:** Investigation, Software. **Ya Zeng:** Investigation, Software. **Xiaolong Fu:** Conceptualization, Methodology, Resources, Supervision, Funding acquisition. **Wen Yu:** Conceptualization, Methodology, Writing – review & editing, Resources, Project administration, Supervision.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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### *Ethical approval statement*

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Ethics Committee of Shanghai Chest Hospital board of No.: KS22176 and patients/participants provided their written informed consent to participate in this study.

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