Thoracic Cancer

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Partial Stereotactic Ablative Radiotherapy Boost Before Conventional Radiotherapy (P-SABR) for Large (> 5 cm) Unresectable Stage III Nonsmall Cell Lung Cancer

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ABSTRACT

Objective: Stereotactic ablative radiotherapy (SABR) is renowned for its high local control (LC) rates. Nonetheless, for tumors that are either large in volume or in close proximity to critical organs at risk, the application of SABR to the entire tumor becomes impractical. This study aims to evaluate the efficacy and safety of partial SABR boost before conventional radiotherapy (P-SABR) for the treatment of large (> 5 cm) unresectable stage III nonsmall cell lung cancer (NSCLC).

Methods: From April 2014 to January 2024, 44 patients with > 5 cm unresectable T3-4N0-3M0 stage III NSCLC were analyzed. The median diameter was 9 cm (5.2–22.7 cm). The P-SABR plan is combined with a partial SABR boost part and a conventional fractionated radiotherapy (CFRT) part. In the partial SABR boost plan, the prescription dose for planning target volume (PTV) was 1.8–3 Gy per fraction over 3–4 fractions, and the artificially delineated gross tumor boost volume (GTVb) within GTV received a simultaneously integrated SABR dose (6 or 8 Gy per fraction). In the following CFRT plan, the median dose for the entire PTV was 54 Gy in 22 fractions. For the synthetic P-SABR plan, the median cumulative dose delivered to the PTV was 62.1 Gy, while the median cumulative dose to the GTVb was escalated to 78 Gy.

Results: The median follow-up time was 36 months (95% CI, 14.6–57.4 months). The LC rates at 1 and 2 years were 90.2% and 76.8%, respectively. The median OS was 47.0 months (95% CI, 16.8–77.2 months) and 15.0 months (95% CI, 6.0–24.0 months) for the chemoradiotherapy and radiotherapy groups, respectively. Univariate analysis showed that P-SABR combined with immunotherapy was associated with significantly longer OS (HR, 0.163; 95% CI, 0.038–0.704). Only one (2.3%) patient experienced grade 3 acute pneumonitis.

Conclusions: The P-SABR treatment has shown a high rate of LC and tolerable toxicity in patients with large unresectable stage III NSCLC.

1 | Introduction

Lung cancer is the leading cause of cancer death and approximately 35% of patients with nonsmall cell lung cancer (NSCLC) present with locally advanced nonmetastatic disease [1, 2]. The prognosis for patients with unresectable stage III NSCLC remains poor, especially those with large tumors (primary tumors greater than 5 cm in the greatest dimension). Due to the large

size, close relationship with surrounding organs at risk (OARs), and massive hypoxia, it is difficult to successfully treat this large lung cancer with the current treatment option: conventional fractionated radiotherapy (CFRT). The 2-year local control (LC) rate of CFRT concurrent with chemotherapy for unresectable stage III NSCLC is less than 70% [3, 4]. In addition, the LC rate and overall survival (OS) rate further decreases with the increasing tumor volume [5, 6].

With the remarkable technological developments, SABR has shown to be noninferior to surgery in operable stage I NSCLC [7, 8] and can achieve LC rates as high as 80% even in oligometastatic patients [9]. However, SABR is not indicated for stage III NSCLC, especially for large (> 5 cm) or node-positive lung cancer [10–12]. In most of these cases, the delivery of an ablative radiation dose to the entire tumor is demanding due to limitations in surrounding tissue tolerance. Recent studies have shown that the SABR boost following CFRT could increase the 2-year LC rate to 59%–76% in locally advanced NSCLC [13–15]. However, this combination treatment is indicated only for cases where the tumor may shrink to less than 5 cm after CFRT.

Thus, we intend to incorporate a partial SABR boost before conventional radiotherapy (P-SABR) in large, unresectable stage III NSCLC. This strategy offers several compelling benefits: (1) administering the SABR component prior to CFRT enables the SABR method to rapidly eliminate tumor cells, thus preventing the development of resistance to CFRT and reducing the rate of accelerated repopulation; (2) targeting the partial tumor with SABR rather than the entire mass, the untreated tumor regions can serve as "spacers" to protect critical OARs; (3) employing a single computed tomography (CT) simulation for treatment planning allows for a more assured evaluation of the radiation dose to critical structures. Previous research has shown that P-SABR is very promising in delivering the uttermost biologically effective dose (BED) within the tumor without increasing the risk of critical OAR damage [16]. We now present the results of P-SABR applied to this challenging clinical situation (large unresectable stage III NSCLC) in terms of tumor control and toxicity.

2 | Patients and Methods

2.1 | Target Population

This study was an Institutional Review Board-approved, retrospective analysis of patients with primary NSCLC who had been treated with P-SABR. Eligible patients had histologically or cytologically documented T3-4N0-3M0 stage III, unresectable NSCLC according to the American Joint Committee on Cancer staging manual, 8th edition. All patients were required to have primary tumors measuring > 5 cm in the greatest dimension via CT scans. Eligible patients were treated with platinum-based definitive concurrent chemoradiation. In addition, patients who refused or were intolerant to concurrent chemotherapy were also eligible. The inclusion criteria also included ≥ 18 years of age, Karnofsky Performance Status (KPS) ≥ 70, and an estimated life expectancy of 12 weeks or longer. Patients with previous exposure to local lung/mediastinal therapy, such as surgery, radiotherapy, or thermal ablation therapy, were excluded. Patients without at least one follow-up visit after treatment were excluded.

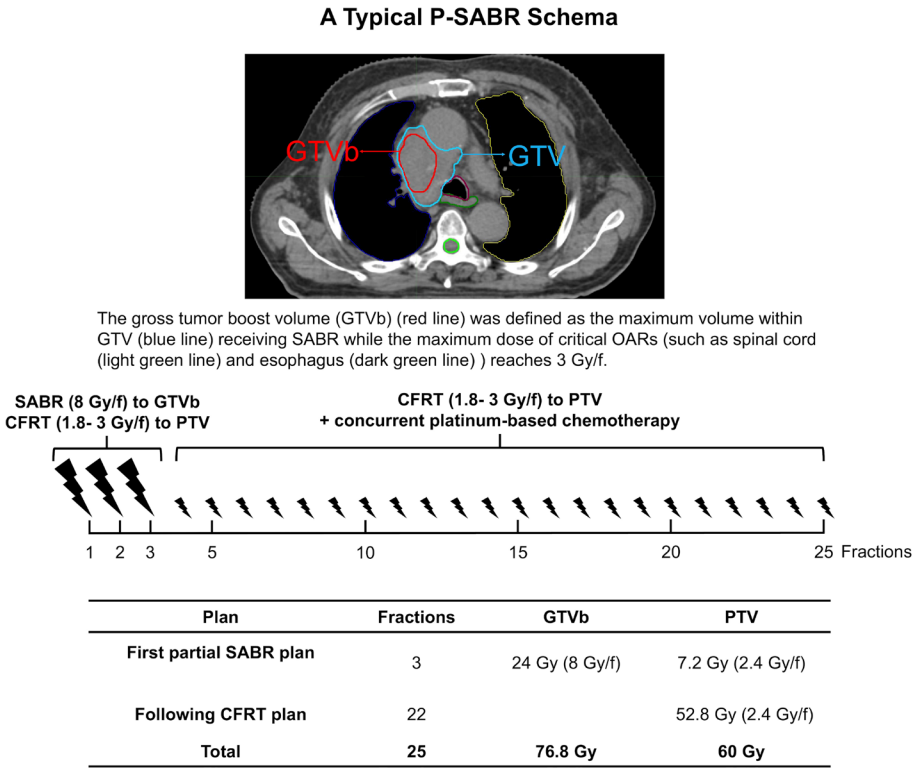
2.2 | Radiotherapy Technique

CT simulation was carried out with custom immobilization using BodyFix (Elekta AB, Stockholm, Sweden) and a four-dimensional (4D) CT scan. The internal gross tumor volume (iGTV) was delineated from the reconstructed maximum intensity projection and individual breathing phases of the 4D CT images. The clinical target volume (CTV) and the planning target volume (PTV) were contoured according to clinical practice. The CTV and even the PTV might be omitted in bulky tumors. In particular, the gross tumor boost volume (GTVb) was defined as the maximum volume within the gross tumor volume (GTV) receiving SABR while avoiding exceeding the tolerance of critical OARs (Figure 1). In clinical practice, the common delineation approach entails reducing the GTV by 10–15 mm in the direction away from critical OARs—including the (spinal cord, esophagus, heart, trachea, bronchi, chest wall, and brachial plexus)—to define the GTVb. No additional margin was applied for the clinical or planned target volume of GTVb. P-SABR plan combined with a partial SABR boost part and a CFRT part. In the SABR part of the P-SABR strategy, the prescription dose for PTV was 1.8–3 Gy per fraction, and GTVb received a simultaneous integrated boost up to 6 or 8 Gy per fraction in 3–4 fractions, and the maximum dose to critical OARs was less than 3 Gy per fraction. In the following CFRT part of the P-SABR strategy, the prescription dose for the entire PTV was 1.8–3 Gy per fraction. For the synthetic plan (combined partial SABR and CFRT parts), the total dose to the PTV was at least 60 Gy, and the prescribed dose covered at least 95% of the PTV (Figure 2). In particular, target uniformity is not required in the partial SABR plan, and we encourage higher doses to be delivered to the center of the tumor to form an "onion skin"-like dose distribution.

Concerning the dose constraints, in the first SABR part of P-SABR planning, the prescribed dose to the PTV ranged from 1.8 to 3 Gy per fraction, and the OAR dose had already been reduced to less than 3 Gy per fraction. This indicates that the OAR dose aligns with that of CFRT. Consequently, the two parts of P-SABR plan can be directly superimposed, and the total dose constraints for OARs can be set in accordance with the QUANTEC standards [17]. Treatment planning was conducted using Monaco with the Monte Carlo algorithm (Elekta) or Eclipse with Analytical Anisotropic Algorithm (Varian Medical Systems), and 6–12 coplanar 6 MV photon beams or two or more modulated arcs were used. Treatment regimens must be validated in the model before they can be applied to patients. P-SABR was delivered over consecutive days. Cone-beam CT was obtained to verify the position of the tumor target and critical OARs before each treatment. Treatment plans were promptly revised if the tumor shrunk or the patient's contour changed significantly.

2.3 | Follow-Up

The first assessment of the treatment response was performed 1 month after P-SABR, followed by repeated scans every 3 months for the first 2 years and every 6 months in the third year after treatment. Some patients with bulky tumors were treated for symptomatic relief, thus only ensuring the clinically necessary follow-up and limited number of follow-ups. Tumor response was defined based on the Response Evaluation Criteria in Solid Tumors



Plan	Fractions	GTVb	PTV
First partial SABR plan	3	24 Gy (8 Gy/f)	7.2 Gy (2.4 Gy/f)
Following CFRT plan	22		52.8 Gy (2.4 Gy/f)
Total	**25**	**76.8 Gy**	**60 Gy**

FIGURE 1 | A typical treatment schema for partial stereotactic ablative radiotherapy boost before conventional radiotherapy (P-SABR). CFRT, conventional fractionated radiotherapy; GTV, gross tumor volume; PTV, planning target volume; OARs, organs at risk; SABR, stereotactic ablative radiotherapy.

(RECIST) 1.1 criteria [18]. The durable response rate (DRR) was defined as the rate of complete response (CR) plus partial response (PR) lasting 6 months continuously and beginning within the first 12 months of P-SABR [19]. Local recurrence (LR) was defined as an enlarging lesion within the PTV. Local tumor response was defined as at least a 30% decrease in the diameter of the primary tumor treated with P-SABR. Regional recurrence (RR) was defined as disease recurrence within the unirradiated lung or nodal disease within lymph node stations N1, N2, or N3. Distant metastases (DMs) were defined as recurrent disease at any site other than within lung parenchyma or mediastinal lymph node stations. OS was calculated to the date of death from any cause. All endpoints were calculated from the radiotherapy start date. Toxicities were retrospectively reviewed according to the Common Terminology Criteria for Adverse Events (version 5.0). Acute toxicities occurred during treatment or within the first 3 months following the end of treatment. Late toxicities occurred after 3 months following the end of treatment.

2.4 | Statistical Analysis

We utilized the statistical software SPSS 29.0 for conducting our analyses. BED was calculated with MIM software (version 7.1.6) using the linear-quadratic equation (with an α/β ratio of 10 for NSCLC). The categorical variables were examined using the chi-squared test and the theoretical numbers under 10 were examined using Fisher's exact test. Continuous variables were compared using the Kruskal–Wallis rank sum test. The Kaplan–Meier method was used to estimate time-to-event outcomes with comparisons made with the log-rank test. The Cox proportional hazards model was used for univariate analysis. p values < 0.05 were considered to indicate statistical significance.

3 | Results

3.1 | Patients and Tumor Characteristics

From April 2014 to January 2024, 44 patients treated with P-SABR met the inclusion criteria for this study. The median follow-up was 36.0 months (95% CI, 14.6–57.4 months). The clinical characteristics of the patient population and tumors are displayed in Table 1. The vast majority of lesions were classified as T4 (75.0%), N3 (38.6%), or stage IIIC (38.6%). The median primary tumor size was 9.0 cm, with a range of 5.2–22.7 cm. The median volume of the GTV was 156.8 cm^3 (34.8–2041.4 cm^3), while the median ratio of the GTVb to GTV was 28.0% (10.3%–76.1%).

3.2 | Treatment Characteristics

Details of the treatment are shown in Table 2. Fifteen (34.1%) patients received chemotherapy or immunotherapy before P-SABR, seven of whom were assessed as progressive disease (PD). Twenty-three (52.3%) patients were treated concurrently with platinum-based chemotherapy, and 21 (47.7%) were treated with P-SABR alone. Among these 21 patients, 12 patients over the age of 75 refused chemotherapy, four patients with bulky primary tumors (> 10 cm) were unable to tolerate chemotherapy, two patients with poor pulmonary function were unable to tolerate chemotherapy, two patients were assessed PD after multiple

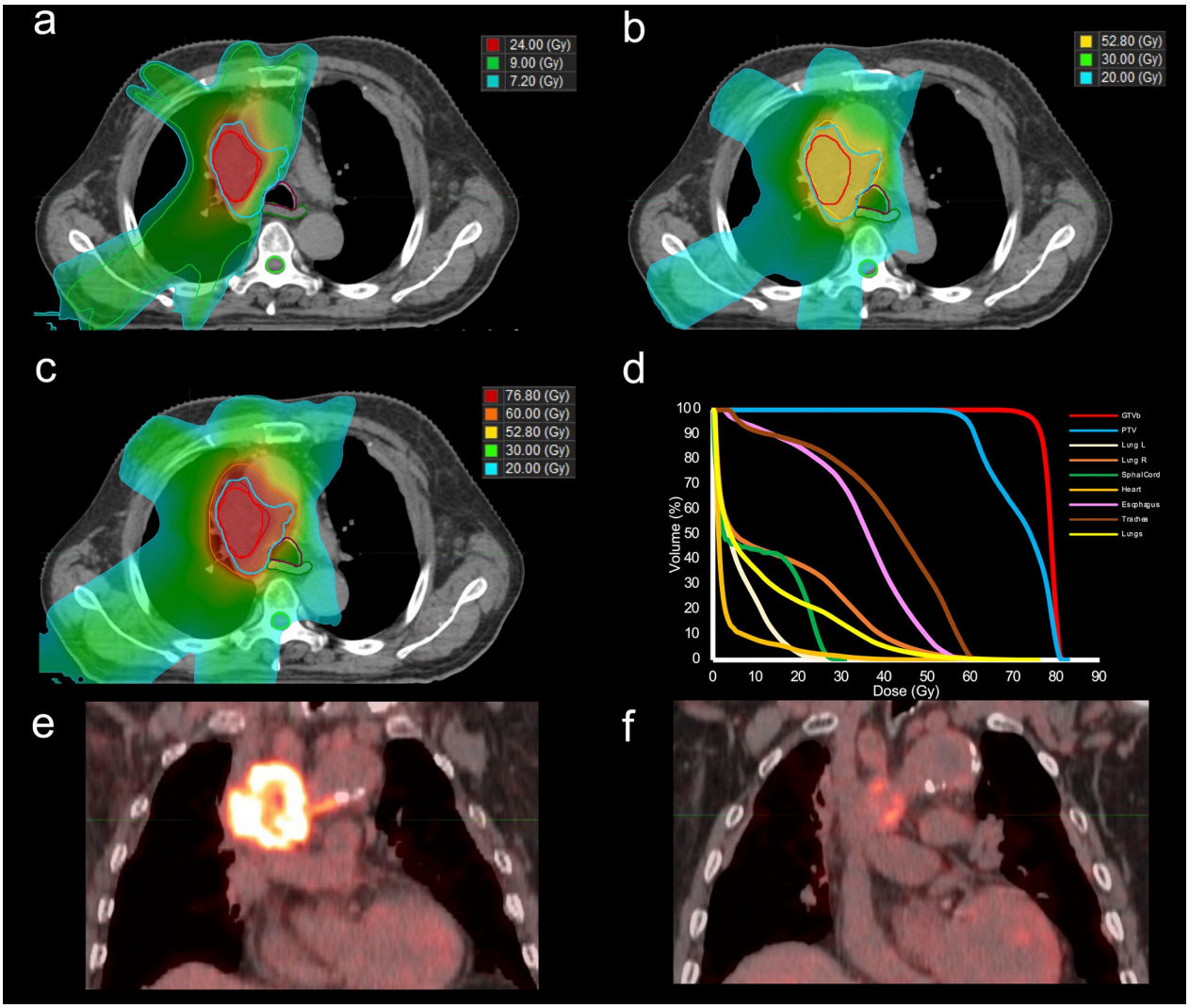


FIGURE 2 | A typical patient with cT4N3M0 NSCLC. The primary site and ipsilateral mediastinal metastatic lymph nodes were treated by P-SABR, while the supraclavicular lymph nodes were treated by CFRT (60 Gy in 25 fractions) concurrently. The greatest tumor diameter treated with P-SABR was 9.1 cm. (a) Contours of the GTV (blue line) and the gross tumor boost volume (GTVb) (red line). In the partial SABR plan, a dose of 24 Gy in 3 fractions was delivered to the GTVb, while the prescription dose for the GTV was 7.2 Gy in three fractions. The maximum dose to the spinal cord and esophagus was 3 Gy per fraction. (b) In the subsequent conventional radiotherapy plan for P-SABR, a dose of 52.8 Gy in 22 fractions was delivered to the GTV. (c) In total, the cumulative doses of GTV and GTVb were 60 and 76.8 Gy, respectively. (d) Dose and volume histogram (DVH) of the synthetic P-SABR plans. (e) Patient's pretreatment PET/CT scan. (f) PET/CT scan performed 13 months after treatment, which showed partial response and relief of the superior vena cava compression.

cycles of neoadjuvant chemotherapy and refused chemotherapy, and one patient strongly refused chemotherapy. In particular, 11 (25.0%) patients have been treated with immunotherapy (PD-L1 or PD-1 antibody) since 2020, and six patients were treated with adjuvant immunotherapy (all with PD-L1 antibodies).

3.3 | Radiotherapy Characteristics

Table 3 shows the radiotherapy parameters for P-SABR. In the first part of the P-SABR, which was SABR, the median single dose for PTV was 2.4 Gy per fraction, and the most common simultaneously integrated SABR scheme for GTVb changed from 6 Gy per fraction for four fractions in the early years to 8 Gy per fraction for three fractions after 2019. In the following part of P-SABR, which was the CFRT, the median CFRT dose for PTV was 54.0 Gy (range, 42.0–62.4 Gy) with 2.4 Gy per fraction (1.8–3 Gy per fraction) in 22 fractions (16–30 fractions). In the total P-SABR plan, the median cumulative dose and BED_{10} of the PTV were 62.1 Gy (range 50.0–72.0 Gy) and 78.0 Gy (range 60.0–89.6 Gy), respectively. Furthermore, the total cumulative median dose and BED_{10} for the GTVb were escalated to 78.0 Gy (range 68.0–86.4 Gy) and 108.6 Gy (range 94.3–120.0 Gy), respectively. Twenty (45.5%) patients were treated concurrently with CFRT (60–70 Gy for 25 fractions to 33 fractions) for lymph node metastasis.

3.4 | LC Rates

The 1- and 2-year LC rates for P-SABR were 90.2% and 76.8%, respectively (Figure 3a). The estimated 1-, and 2-year LC rates were 93.3% and 77.0% for the chemoradiotherapy group,

TABLE 1 | Patient and tumor characteristics.

Characteristic	CRT ($n=23$)	RT ($n=21$)	p value
Age, median (range) (years)	66 (47–86)	77 (51–85)	0.068[a]
Sex			
Female	2 (8.7)	1 (4.8)	0.605
Male	21 (91.3)	20 (95.2)	
Histology (%)			
Squamous cell carcinoma	15 (65.2)	16 (76.2)	0.725
Adenocarcinoma	5 (21.7)	3 (14.3)	
Other	3 (13.0)	2 (9.5)	
KPS (%)			
≤90	19 (86.4)	17 (85.0)	0.900
>90	3 (13.6)	3 (15.0)	
T stage (%)			
T3	7 (30.4)	4 (19.0)	0.384
T4	16 (69.6)	17 (81.0)	
N stage (%)			
N0	3 (13.0)	5 (23.8)	0.614
N1	2 (8.7)	1 (4.8)	
N2	10 (43.5)	6 (28.6)	
N3	8 (34.8)	9 (42.9)	
Stage (%)			
IIIA	5 (21.7)	6 (28.6)	0.588
IIIB	10 (43.5)	6 (28.6)	
IIIC	8 (34.8)	9 (42.9)	
Primary tumor size, median (range) (cm)	8.5 (5.2–17.0)	9.8 (6.4–22.7)	0.118[a]
Volume of GTV, median (range) (cm^3)	117.9 (34.8–812.6)	201.0 (71.7–2041.4)	**0.035**[a]
Volume of GTVb, median (range) (cm^3)	34.5 (7.1–226.6)	83.3 (10.5–571.8)	**0.016**[a]
Ratio of GTVb to GTV, median (range) (%)	24.8 (10.8–65.4)	31.1 (10.3–76.1)	0.099[a]

Note: Bolded text indicates $p < 0.05$.
Abbreviations: CRT, chemoradiotherapy; GTVb, gross tumor boost volume; KPS, Karnofsky Performance Status; RT, radiotherapy.
[a]Kruskal–Wallis rank sum test was used to compare continuous variables.

and 80.0% and 80.0% for the radiotherapy group, respectively ($p=0.980$). A typical case of tumor response to P-SABR is shown in Figure 2. Since only four patients experienced LR, we cannot determine the risk factors for LC; thus, we analyzed the complex factors affecting the local tumor response to radiotherapy. The 1- and 2-year local tumor response rates were 66.9% and 51.4%, respectively. (Figure 3a) The 1-, and 2-year local tumor response rates were 66.7% and 66.7% in the high-BED subgroup ($B_{100}>57\%$), and 65.0% and 32.5% in the low-BED subgroup ($B_{100}\leq 57\%$), respectively (Figure 3b; $p=0.230$). The 1-year local tumor response rate was 25.5% for the primary tumors larger than 169 cm^3 and 84.9% for smaller tumors (Figure 3c; $p<0.001$). Univariate analysis revealed that an increase of 10 cm^3 in primary tumor volume raised the risk of local tumor progression by 1.9% (HR = 1.019; 95% CI, 1.007–1.031; $p=0.002$), and an increase of 1 cm in primary tumor size increased the risk of local tumor progression by 24.4% (HR = 1.244; 95% CI, 1.068–1.451; $p=0.005$).

3.5 | Overall Survival

The median OS was 26.0 months (95% CI, 6.0–46.0 months), and the 1- and 2-year OS rates were 67.1% and 52.7%, respectively. The median OS was 47.0 months (95% CI, 16.8–77.2 months) and 15.0 months (95% CI, 6.0–24.0 months) for the chemoradiotherapy group and radiotherapy group, respectively ($p=0.344$). (Figure 3d) The estimated 1- and 2-year OS rates were 67.4% and 62.6% for the chemoradiotherapy group and 68.2%, and 39.8% for the radiotherapy group, respectively. The median PFS was

TABLE 2 | Treatment characteristics.

Characteristic	CRT ($n=23$)	RT ($n=21$)	p value
Previous treatment (%)			0.352
None	14 (60.9)	15 (71.4)	
Chemotherapy	9 (39.1)	5 (23.8)	
Chemotherapy and immunotherapy	0 (0.0)	1 (4.8)	
Response to previous systemic treatment (%)			0.538
PR or SD	20 (87.0)	16 (80.0)	
PD	3 (13.0)	4 (20.0)	
Adjuvant treatment (%)			0.075
None	9 (45.0)	11 (84.6)	
Chemotherapy	6 (30.0)	1 (7.7)	
Immunotherapy	5 (25.0)	1 (7.7)	
Immunotherapy (%)			0.039
None	14 (60.9)	19 (90.5)	
Neoadjuvant	0 (0.0)	1 (4.8)	
Adjuvant	5 (21.7)	1 (4.8)	
Salvage	4 (17.4)	0 (0.0)	
P-SABR finished (%)			0.947
Yes	22 (95.7)	20 (95.2)	
No	1 (4.3)	1 (4.8)	
CFRT for lymph node metastasis (%)			0.123
No	10 (43.5)	14 (66.7)	
Yes	13 (56.5)	7 (33.3)	

Abbreviations: CFRT, conventional fractionated radiotherapy; CRT, chemoradiotherapy; PD, progressive disease; PR, partial response; RT, radiotherapy; SD, stable disease.

TABLE 3 | Radiotherapy characteristics for P-SABR.

Characteristic	CRT ($n=23$)	RT ($n=21$)	p value
SABR regimen (%)			0.181
18 Gy in 3 fractions	1 (4.3)	0 (0.0)	
24 Gy in 4 fractions	5 (21.7)	10 (47.6)	
24 Gy in 3 fractions	16 (69.6)	9 (42.9)	
32 Gy in 4 fractions	1 (4.3)	2 (9.5)	
CFRT dose of PTV per fraction (Gy) (%)			**0.016**
≤2	5 (21.7)	12 (57.1)	
>2	18 (78.3)	9 (42.9)	
Number of PTV CFRT fractions (%)			0.384
<22	7 (30.4)	4 (19.0)	
≥22	16 (69.6)	17 (81.0)	
Total CFRT dose of PTV (Gy) (%)			0.989
<54	11 (47.8)	10 (47.6)	
≥54	12 (52.2)	11 (52.4)	
Total prescribed dose of GTVb (Gy) (%)			0.515
<78	11 (47.8)	8 (38.1)	
≥78	12 (52.2)	13 (61.9)	
Cumulative BED_{10} of GTVb (Gy) (%)			0.276
<108.7	14 (60.9)	16 (76.2)	
≥108.7	9 (39.1)	5 (23.8)	
Total prescribed dose of PTV (Gy) (%)			0.763
<64	11 (47.8)	11 (52.4)	
≥64	12 (52.2)	10 (47.6)	
Cumulative BED_{10} of PTV (Gy) (%)			**0.012**
≤82	13 (56.5)	19 (90.5)	
>82	10 (43.5)	2 (9.5)	
B_{100} (%)			0.887
≤57	10 (45.5)	10 (47.6)	
>57	12 (54.5)	11 (52.4)	

Note: Bolded text indicates $p < 0.05$.
Abbreviations: B_{100}, calculated by the tumor volume receiving a BED > 100 Gy to the volume of GTV; BED, biologically effective dose ($\alpha/\beta=10$); CFRT, conventional fractionated radiotherapy; CRT, chemoradiotherapy; GTVb, gross tumor boost volume; RT, radiotherapy [16].

12.0 months (95% CI, 6.3–17.7 months), and the 1- and 2-year PFS rates were 47.3% and 25.3%, respectively. In particular, all six patients who were treated with adjuvant PD-L1 antibody after P-SABR were still alive at the time of analysis. Univariate analysis showed that P-SABR combined with immunotherapy was associated with significantly longer OS (HR, 0.163; 95% CI, 0.038–0.704). The 1- and 2-year OS rates were 100% and 90.0% in the P-SABR with immunotherapy subgroup and 55.1% and 38.5% in the P-SABR subgroup, respectively (Figure 3e; $p=0.005$). A corresponding swimmer plot was generated to plot the OS and the duration of tumor response in the chemoradiotherapy subgroup (Figure 4). The DRR was 88.9% with immunotherapy and 50.0% without immunotherapy in the chemoradiotherapy group ($p=0.056$).

3.6 | Patterns of Failure

Twenty-six (59.1%) patients experienced disease recurrence. The initial recurrence manifested as LR in 4 (9.1%) patients, RR in 8 (18.2%), and DMs in 11 (25.0%). Three (6.8%) patients had simultaneous RR and DM. For the 11 patients who had initial DM, the most common site was the brain (45.5%), and the other sites were the bone, liver, and adrenal gland. The 1- and 2-year RR rates were 25.4% and 39.0% for the chemoradiotherapy group

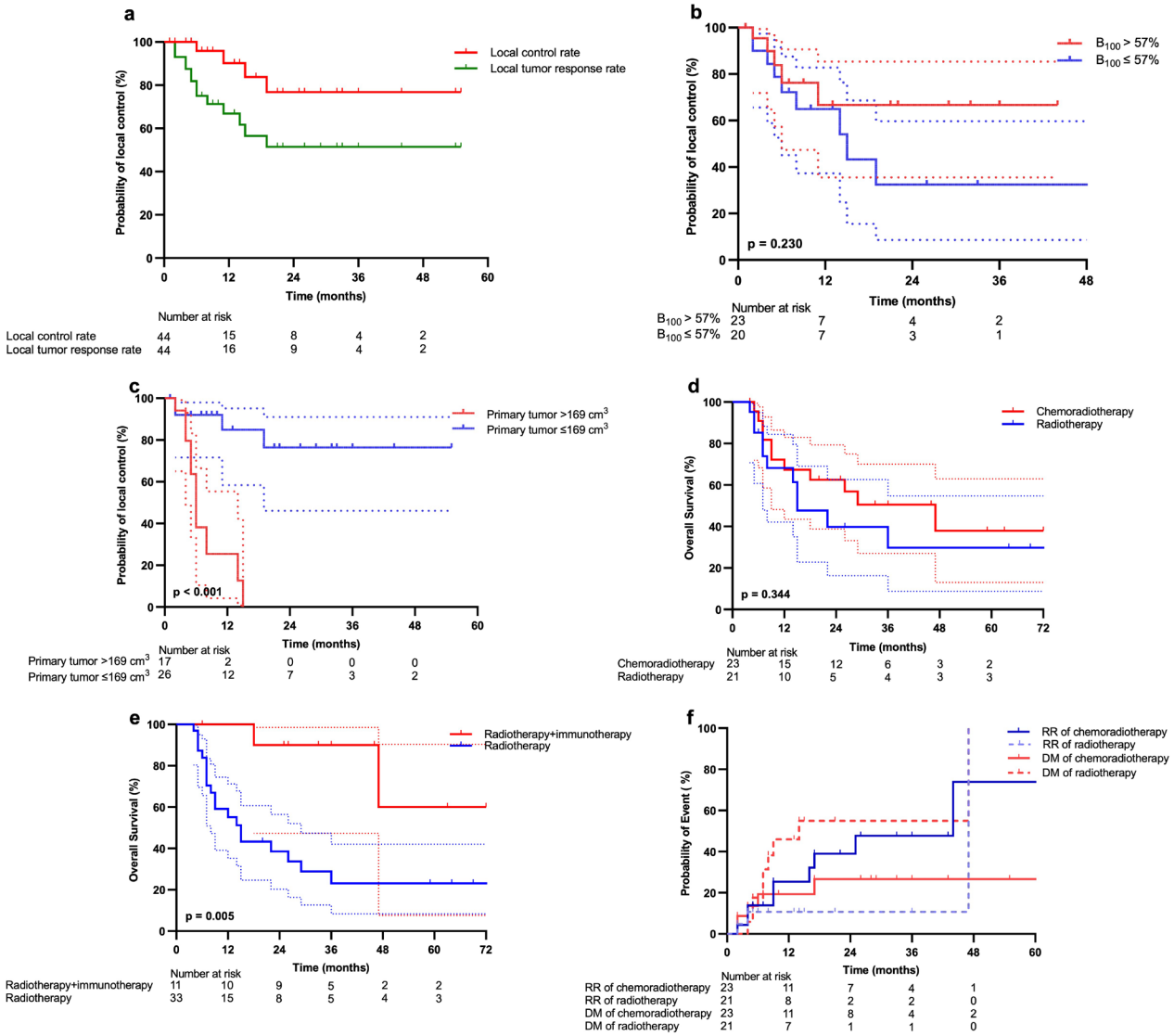


FIGURE 3 | (a) Local control rate and local tumor response rate for primary tumors from patients who underwent P-SABR therapy; (b) local tumor response rate for the high BED group ($B_{100} > 57\%$) and the low BED group ($B_{100} \leq 57\%$); (c) local tumor response rate for large primary tumor volume ($> 169\,cm^3$) and small primary tumor volume ($\leq 169\,cm^3$); (d) overall survival (OS) for the chemoradiotherapy group and radiotherapy group; (e) OS outcomes for the group receiving radiotherapy alone and the group receiving a combination of radiotherapy and immunotherapy; (f) patterns of failure for the chemoradiotherapy group and radiotherapy group. B_{100}, calculated by the tumor volume receiving a BED > 100 Gy to the volume of GTV; DM, distant metastasis; RR, regional recurrence.

and 10.7% and 10.7% for the radiotherapy group, respectively ($p = 0.358$). The 1- and 2-year DM rates were 19.3% and 26.6% in the chemoradiotherapy group and 46.0% and 55.0% in the radiotherapy group, respectively ($p = 0.086$) (Figure 3f).

3.7 | Toxicity

Acute toxic effects were evaluated in 44 patients, and late effects were evaluated in 33 patients (Table 4). Only two patients were unable to complete the P-SABR due to worsening medical comorbidities, resulting in a completion rate of 95.5%. P-SABR was well tolerated. In the radiotherapy group, 2 (4.5%) patients had grade 2 acute pneumonitis, 1 (3.0%) had grade 2 late pneumonitis, and no grade 3 or higher adverse events were reported. In the chemoradiotherapy group, only 1 (2.3%) patient experienced grade 3 acute pneumonitis 7 weeks after radiotherapy, with no grade 4–5 nonhematologic toxic effects. This patient had a 7.6-cm peripheral tumor with mediastinal and bilateral hilar lymph node metastasis. Thus, he received P-SABR and CFRT for the primary lesion and lymph nodes concurrent with docetaxel and carboplatin for 4 cycles. The bilateral lungs V_{20} (volume of bilateral lungs receiving doses > 20%) was as high as 31.5%. Luckily, the pneumonitis was relieved after steroid administration.

4 | Discussion

It is well-known that larger tumor volumes are associated with worse LC and OS. Our research supported these findings by demonstrating that both larger primary tumor volumes ($p = 0.002$) and larger primary tumor sizes ($p = 0.005$) were negative prognostic factors for local tumor response. Our study focused on patients with large, unresectable stage III NSCLC, whose median primary

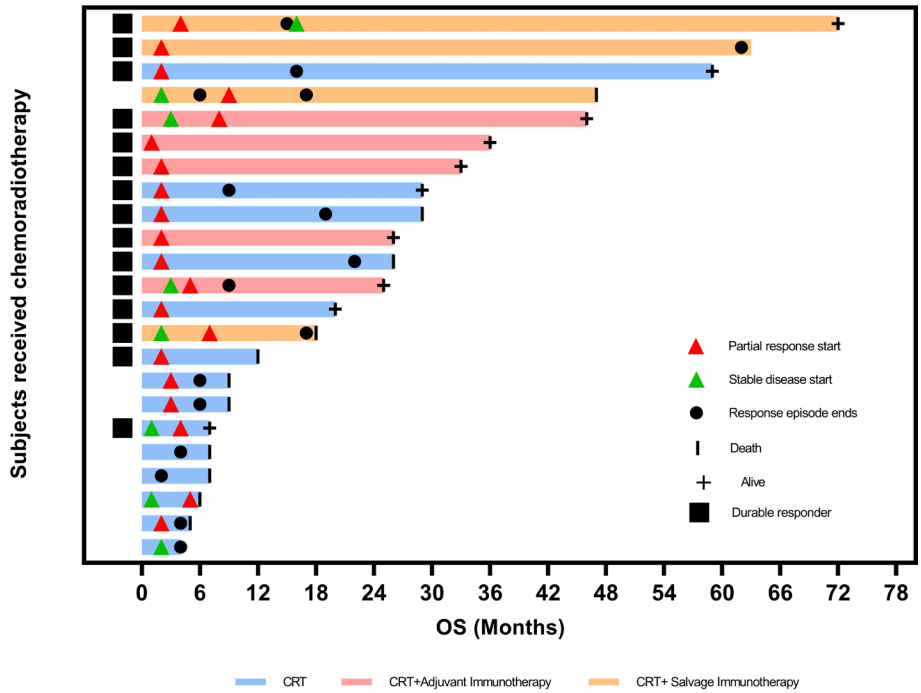


FIGURE 4 | Swimmer plots showing overall survival (OS) and duration of tumor response in the chemoradiotherapy subgroup.

TABLE 4 | Acute and late adverse events postradiotherapy at any of the follow-up time points.

	Acute ($n=44$)						Late ($n=33$)	
	Grade 2		Grade 3		Grade 4		Grade 2	
Adverse events	RT ($n=21$)	CRT ($n=23$)	RT ($n=21$)	CRT ($n=23$)	RT ($n=21$)	CRT ($n=23$)	RT ($n=16$)	CRT ($n=17$)
Pneumonitis (%)	2 (4.5)	1 (2.3)	0	1 (2.3)	0	0	1 (3.0)	1 (3.0)
Esophagitis (%)	1 (2.3)	1 (2.3)	0	0	0	0	0	0
Leucopenia (%)	2 (4.5)	7 (15.9)	0	2 (4.5)	0	1 (2.3)	0	0
Anemia (%)	3 (6.8)	2 (4.5)	0	2 (4.5)	0	0	0	0
Thrombocytopenia (%)	1 (2.3)	0	0	0	0	0	0	0
Dermatitis (%)	1 (2.3)	0	0	0	0	0	0	0
Pericardial effusion (%)	0	0	0	0	0	0	1 (3.0)	0
Any (%)	10 (22.7)	11 (25.0)	0	5 (11.4)	0	1 (2.3)	2 (6.1)	1 (3.0)

Note: Adverse events were graded with CTCAE version 5.0. Acute adverse events are those arising within 90 days of completion of radiotherapy. Late adverse events are those that arise after 90 days of completion of radiotherapy.
Abbreviations: CRT, chemoradiotherapy; RT, radiotherapy.

tumor size was 9.0 cm (ranging from 5.2 to 22.7 cm). We found that these patients had high LC rates of 90.2% and 76.8% at 1 and 2 years, respectively, with tolerable side effects when treated with a partial SABR boost before conventional radiotherapy (P-SABR).

It is currently standard practice to administer doses of 60–70 Gy of conventional radiotherapy for locally advanced NSCLC, resulting in a 2-year LC rate ranging from 54% to 70% [4, 20–24] (Table S1). A combination of partial SABR boost before conventional radiotherapy (P-SABR) has shown promising results, with a 2-year LC rate of 76.8%. This success is most likely due to the ability of P-SABR to deliver more BED within the tumor without increasing the dose for critical OARs when compared to that of CFRT [16]. An increased BED can lead to better local tumor control and OS [25]. In our study of P-SABR, while the accumulated median dose of PTV remained at 62.1 Gy, the total cumulative median dose and BED of GTVb within the tumor increased to 78 and 108.6 Gy, respectively. Although this study did not find a statistically significant difference in local effective rates between the high-BED group ($B_{100} > 57\%$) and low-BED group ($B_{100} \leq 57\%$), the Kaplan–Meier curve indicated that the high-BED group had a greater trend toward local effective

rates. (Figure 3b) Notably, previous randomized controlled trials on CFRT for stage III NSCLC excluded N3 patients and had a low percentage of T4 stage (0%–48.8%) patients. In contrast, our study included a high percentage of T4 stage (75.0%) and N3 (38.6%) patients. Therefore, our study supports the notion that P-SABR may be more effective than CFRT for achieving greater LC in more advanced NSCLC patients.

The PACIFIC study proved that durvalumab, when used after chemoradiotherapy in stage III NSCLC, can significantly prolong OS [26]. This study also revealed that P-SABR combined with immunotherapy can significantly improve OS, with a hazard ratio of 0.163 (95% CI, 0.038–0.704). The chemoradiotherapy group with immunotherapy had a higher DRR, and all six patients who received adjuvant PD-L1 antibodies survived. However, it is important to note that the PACIFIC study used a conventional fractionation scheme with a dose of 60–66 Gy to reach the PTV. In contrast, in the present P-SABR study, the median dose to the PTV was 62.1 Gy, but the median accumulated dose to the GTVb was increased to 78.0 Gy, which is expected to further improve patient outcomes. In our study's chemoradiotherapy group, 21.7% received adjuvant immunotherapy, 17.4% received salvage immunotherapy, and 60.9% did not receive immunotherapy. Interestingly, the median OS was still 47.0 months, similar to the 47.5 months in the immunotherapy group of the PACIFIC study. It is important to note that the patients in the PACIFIC study had relatively early-stage tumors, with 52.9% at stage IIIA and 44.5% at stage IIIB. In comparison, the patients in this study had relatively late-stage tumors, with 21.7% at stage IIIA, 43.5% at stage IIB, and 34.8% at stage IIIC. Therefore, future clinical studies are needed to investigate the efficacy of P-SABR synchronous chemotherapy and sequential immunotherapy for treating large stage III NSCLC tumors.

The LC rate for the P-SABR in this study is consistent with those in other studies that have investigated SABR boost in combination with CFRT. The 1y-LC for P-SABR was 90.2%, which is compared to the 76%–83% range seen in studies where SABR boost followed CFRT [13–15], and matches the 100% reported in a study where SABR boost preceded CFRT [27]. Moreover, P-SABR demonstrates superior tolerability. In a prospective study of CFRT followed by SABR boost concurrent with chemotherapy for stage IIB–III NSCLC, the incidence of acute and late grade ≥ 2 radiation pneumonitis was 17.1% and 9.4%, respectively. In addition, two patients experienced fatal hemoptysis, classified as grade 5 toxicity [13]. In another prospective study focusing on primary tumor SABR boost before concurrent chemoradiation for locally advanced NSCLC, the rates of acute and late grade ≥ 2 radiation pneumonitis were 19.0% and 14.3%, respectively, and for acute and late grade ≥ 2 esophagitis, the rates were 57.1% and 9.5%, respectively. Furthermore, one patient developed grade 4 radiation pneumonitis [27]. In contrast, with the chemoradiotherapy arm of P-SABR, the rates of acute and late grade ≥ 2 radiation pneumonitis were significantly lower at 4.5% and 3.0%, respectively, and the rates of acute and late grade ≥ 2 esophagitis were 2.3% and 0%, respectively, with no grade 4–5 nonhematologic toxic effects. The mitigated adverse effect of the P-SABR on large tumors might be due to the following reasons. In the P-SABR study, we delivered the SABR dose to the GTVb instead of the GTV, which allowed us to decrease the maximal dose (*D*max) of critical OARs to less than 3 Gy per fraction. In contrast, other SABR studies delivered SABR to the whole tumor area, which inevitably resulted in high doses to adjacent OARs. This may be why P-SABR could treat bulky tumors with tolerable side effects. In addition, SABR boost to the whole tumor was indicated for residual disease less than 5 cm, and the median length of the primary tumor in those studies was only 5–5.7 cm. However, the tumor size does not affect the application of partial SABR boost before CFRT, which is the so-called P-SABR. In particular, P-SABR is particularly indicated for bulky tumors, for which the median size of the primary tumor was 9.0 cm (ranging from 5.2 to 22.7 cm).

In large NSCLC, P-SABR has the potential to achieve comparable LC and OS outcomes to those of SABR but with superior safety. According to the current guidelines, SABR is not recommended for tumors larger than 5 cm due to their unacceptable side effects [12]. Therefore, we compared the results of P-SABR with those of several attempts at SABR for large NSCLC. The SABR study demonstrated a 2y-LC of 71%–75% and a 2y-OS of 34%–57.6% [28–33], which are comparable to our P-SABR results of 2y-LC of 76.8% and 2y-OS of 52.7%. SABR treatment of large tumors is associated with a high incidence of Grade 2 or higher late pneumonitis, with a rate of up to 10%–19.3% [28, 29], while P-SABR treatment was associated with a rate of only 3.0%. In addition, it is essential to note that SABR studies involved only patients who were nodal-negative and had tumors with a median diameter of no more than 6 cm. In contrast, our P-SABR study had a nodal-positive rate of up to 81.8%, and the median tumor diameter was 9 cm. Interestingly, even with a GTVb to GTV ratio of only 28.0%, a partial SABR boost to GTVb can achieve similar effectiveness as that of the whole-GTV SABR. Preclinical research has shown that partial SABR for the hypoxic segment of the tumor can enhance the tumor's nontargeted effects by harnessing the local bystander and the distant abscopal effects [34]. Additionally, SABR, particularly 24 Gy in three fractions, which is the main SABR regimen of P-SABR, is known to boost antitumor immunity [35]. Therefore, we intend to further investigate the underlying mechanism of P-SABR and immunity.

To optimize the implementation of P-SABR, several points need to be considered. The definition of the gross tumor boost volume (GTVb) is to maximize the SABR target area within the GTV while ensuring that the maximum dose (*D*max) to critical OARs does not exceed 3 Gy per fraction. Current clinical experience involves shrinking the GTV by 10–15 mm away from the direction of the critical OARs to create GTVb. Recently, we have been exploring the use of artificial intelligence to contour GTVb more accurately [36, 37]. Moreover, there are no established dose limits for combining SABR with CFRT. Therefore, we recommend that the maximum dose of critical OARs should not exceed 3 Gy per fraction during the first course of partial SABR treatment. Since the subsequent course also employs CFRT, the cumulative dose for OARs can adhere to the standard CFRT constraints. Our follow-up results have validated the safety of this approach, with a P-SABR completion rate of 95.5% and no incidence of grade 3 or higher adverse events.

Several limitations of this study merit discussion. First, it was a retrospective study with a small number of enrolled participants that may have been subject to selection bias. The results of our study thus necessitate verification through prospective research.

Second, the standard treatment for stage III NSCLC is simultaneous radiotherapy and chemotherapy [2]. However, only 52.3% of patients in this study underwent concurrent chemoradiotherapy. The analysis revealed that some patients either refused or could not tolerate chemotherapy due to various clinical issues such as advanced age, large tumor size, and poor pulmonary function. An analysis of the SEER database showed that out of 20 986 patients with unresectable III NSCLC, only 63.3% received chemoradiotherapy, 19.0% were treated with radiotherapy alone, and 17.7% were treated with chemotherapy alone [38]. This finding indicates that not all patients can receive concurrent chemoradiotherapy in real clinical practice. Fortunately, the 2-year LC rate after radiotherapy alone was as high as 80.0%. Third, although the LC rate of P-SABR is high, DM remains the primary pattern of failure. Currently, the guidelines recommend immune maintenance after chemoradiotherapy. However, the number of patients treated with immunotherapy included in this study was small. Luckily, all four patients survived, and univariate analysis showed that combining immunotherapy with P-SABR improved OS. Therefore, we plan to further explore the impact of immunotherapy on the efficacy of P-SABR. In addition, while this study was retrospective in nature, we have an ongoing prospective project on the use of P-SABR for treating large NSCLC. Furthermore, we are interested in exploring the use of P-SABR at other disease sites.

In conclusion, P-SABR is a feasible treatment option for large unresectable stage III NSCLC. It has exhibited a high LC rate and acceptable adverse reactions. Further exploration is necessary to determine the effectiveness of immunotherapy in enhancing OS in this population.

Author Contributions

Yun Bai contributed to the acquisition, analysis, and interpretation of the data and drafted the manuscript. Xianshu Gao and Shangbin Qin contributed to the design of the study, revised the draft, and led the research direction. Xi Cao, Feng Lyu, Xin Qi, and Mingwei Ma contributed to revising the paper and providing clinical input. Jiayan Chen, Siwei Liu, and Yan Gao contributed to the analysis of the treatment plan, imaging acquisition, and support. Hongzhen Li, Xiaomei Li, and Xiaoying Li participated in the study design and drafted the manuscript. Siwei Liu, Xueying Ren, and Lei Huang contributed to the statistical analysis. All the authors read and approved the final manuscript.

Ethics Statement

The study was approved by the Peking University First Hospital National Unit of Clinical Trial Ethics Committees (protocol number 2017/57). No patient consent was required since this was a retrospective study, and the data were collected during standard care. All medical data were deidentified.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

All the data generated or analyzed during this study are included in this published article. Additional information is available from the corresponding author upon reasonable request.

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Supporting Information

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