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Safety and efficacy of stereotactic body proton therapy for high-risk lung tumors

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ABSTRACT

Purpose: Stereotactic body proton therapy (SBPT) is an emerging treatment strategy for lung tumors that aims to combine the excellent local control benefits of ultra-hypofractionation with the physical advantages of protons, which reduce the integral dose to organs at risk (OARs) compared to photons. To date, however, very little data delivering SBPT in 5 or fewer fractions to lung tumors have been reported. Given that photon stereotactic body radiation therapy can struggle to deliver ablative doses to high-risk tumors (i.e., central/ultra-central location, prior in-field radiation, tumor size >5 cm, or the presence of severe pulmonary comorbidities) while adhering to OAR dose constraints, we hypothesized that SBPT would be an effective alternative for patients with high-risk tumors.

Methods and Materials: Twenty-seven high-risk patients with 29 lung tumors treated with SBPT at the New York Proton Center between December 2019 and November 2022 were retrospectively identified. Patients were divided into three major subgroups: early-stage non-small cell lung cancer (NSCLC), locally recurrent NSCLC, and metastatic cancer from lung cancer or other histologies. Patient characteristics were reported using descriptive statistics, actuarial methods were used to quantify disease control rates, and toxicities were scored using CTCAE v 5.0.

Results: The most common high-risk indications for SBPT were central/ultra-central tumor location (69.0%), severe COPD (48.1%), reirradiation (44.4%), significant pulmonary fibrosis (22.2%), and large tumor size > 5 cm (18.5%). In total, 96.6% of tumors were fully covered by the prescription dose without compromising target coverage. Three-year actuarial rates of local control for early-stage NSCLC, locally recurrent NSCLC, and metastatic patients were 89%, 100%, and 43%, respectively. Three-year actuarial rates of regional control were 89%, 67%, and 86%. Three-year actuarial rates

of distant metastasis-free survival were 79%, 100%, and 0%. Two patients (7.4%), both of whom had clinically significant baseline interstitial lung disease and pre-treatment continuous oxygen demand, experienced grade ≥2 pulmonary toxicity (1 grade 3, 1 grade 5). There were no acute or late grade ≥2 toxicities related to esophagitis, cardiac injury, airway injury, pulmonary fibrosis, bronchopulmonary hemorrhage or brachial plexopathy.

Conclusions: In the largest study of proton SBRT reported to date, SBPT has a favorable toxicity profile while being an effective approach for treating most high-risk tumors without requiring dose de-escalation or compromising tumor coverage and warrants further investigation.

Keywords: Proton therapy, pencil beam scanning, stereotactic body radiation therapy, stereotactic ablative radiotherapy, lung cancer, thoracic malignancies

INTRODUCTION

Stereotactic body radiation therapy (SBRT) is the standard treatment approach for patients with inoperable early-stage non-small cell lung cancer,[1].m, node-negative limited stage small cell lung cancer,[2] and intrathoracic oligometastatic or oligoprogressive disease.[3] When able to safely deliver ablative doses to biologically effective doses [BED] ≥100 Gy,[4] photon SBRT enhances local control in non-small cell lung cancer (NSCLC)[5,6] and conveniently spares patients much of the time toxicity and physical morbidity associated with prolonged conventionally fractionated radiotherapy courses.[7] The feasibility and effectiveness of photon SBRT, however, hinges on its ability to visualize tumors with 3D on-board imaging and adhere to organs-at-risk (OAR) dose constraints while still delivering ablative doses of ultra-hypofractionated radiotherapy (i.e., doses ≥5 Gy per fraction). Photon SBRT can meet these objectives for most smaller, peripheral tumors, but it can struggle to achieve both objectives in certain clinical scenarios: (i) central or ultra-central tumors;[8–14] (ii) reirradiation;[15] (iii) large tumors (e.g., >5 cm);[16–19] and (iv) treating patients with severe pulmonary comorbidities.[20–22]¨

Proton therapy has physical and dosimetric advantages compared with photon therapy. While there is an exponential decrease in photon dose deposition as a function of depth, protons deposit increasing dose as they slow down to reach a finite depth in tissue. As a result, protons have a dosimetric profile consisting of a low integral dose, maximal dose deposition at the target with Bragg peaks, and negligible exit dose beyond the target. These proton properties limit the irradiation dose received by OARs adjacent to thoracic target volumes,[23–25] which may allow for reduced toxicity and better preservation of quality of life compared to photons.[26,27]

Stereotactic body proton therapy (SBPT) is an emerging treatment strategy in NSCLC, which uses ultra-hypofractionation to maximize local control while concurrently leveraging the physical advantages of protons that may allow for safer treatment of high-risk tumors without the need to dose de-escalate SBRT or compromise tumor coverage. This study describes the use of SBPT for patients with high-risk lung tumors to assess the safety and effectiveness of this treatment approach for patients at high risk for developing severe pulmonary and central OAR toxicities.

METHODS

Data source

After institutional review board approval, data were retrospectively obtained from a database tracking all patients treated with thoracic proton SBPT at the New York Proton Center (NYPC). NYPC is a partnership between Memorial Sloan Kettering Cancer Center (MSKCC), Mount Sinai Health System, and the Montefiore Health System. NYPC treats over 1,300 patients per year, approximately 10% of whom are treated for lung cancer and other thoracic malignancies.

Patient selection

Consecutive MSKCC patients who had lung tumors treated with SBPT at NYPC between December 2019 and November 2022 were identified in NYPC's database. All patients received intensity-modulated SBPT. The following criteria were necessary for an intensity-modulated proton therapy treatment course to be classified as SBPT: (i) radiation doses ≥5 CGyE per fraction; (ii) less than or equal to 8 total fractions; and (iii) daily volumetric image guidance.[28] In order to be included in this analysis, patients were required to have at least

one post-treatment follow-up visit for toxicity assessment, at least one post-treatment imaging study for tumor response assessment, and at least one high-risk feature such as central or ultra-central tumor location, prior in-field radiation, tumor size >5 cm, or history of interstitial lung disease. Central lung tumors were defined as being within 2 cm of the proximal bronchial tree. Ultra-central lung tumors were defined as the presence of clinical target volume overlap of the trachea, proximal bronchial tree, esophagus, great vessels, and/or heart.

Variables

Data collected included patient characteristics (e.g., age, sex, race, smoking history, comorbidities, etc.), tumor features (e.g., histology, size, location, etc.), SBPT specifications (e.g., total dose, number of fractions, treatment schedule), CTCAE v5.0 toxicities (e.g., pneumonitis, esophagitis, bronchopulmonary hemorrhage, cardiac events, brachial plexopathy, and airway injury), and disease control (e.g., local control, regional control, distant control, and overall survival).

Follow-up Evaluation

Patients were most typically followed post-treatment with an FDG PET/CT scan 3 months following SBPT completion, CT chest scans every 3 months thereafter for 2 years, and then CT chest scans every 4-6 months. Treatment responses were quantified using RECIST 1.1 criteria.[29] Given that radiation-associated inflammatory changes can sometimes induce radiographic changes consistent with pseudoprogression, we assessed for and defined tumor control and progression rates using the consensus SWOG-NRG Oncology S1914 definition of disease progression.[30] Per S1914, one or more of the following must occur for the documentation of disease progression: (i) 20% increase in the longest diameter of the primary lung tumor over the smallest measurement observed using the same techniques as baseline *and* an absolute increase of at least 0.5 cm *and* accompanied by confirmatory study (unequivocal PET findings or biopsy); (ii) death due to disease without prior documentation of progression; (iii) unequivocal PET findings and/or biopsy confirming malignancy in the absence of growth is also sufficient to confirm progression.

Local failure was defined as progression, per S1914 criteria, in the region of the irradiated tumor or the involved lobe. The time to local failure was measured from the day of SBPT initiation to local progression. Regional failure was defined as progression in the mediastinal, hilar, supraclavicular, or scalene lymph nodes. The time to regional failure was defined as the time SBPT initiation to evidence of regional disease progression. Distant failure was non-locoregional disease progression, including progression of existing or development of new lesions for patients with preexisting distant metastatic disease, and including new lung metastases. The time to distant failure was defined as the time from initiation of SBPT to demonstrating distant disease progression. Patients who did not have documented evidence of a local, regional, or distant failure event were censored at the date of their last follow-up imaging. Overall survival was defined as the time from initiation of SBPT to death. Patients who were alive at their most recent post-treatment follow-up visit were censored at that time point.

Statistical analysis

Descriptive statistics are presented as frequencies for categorical variables and the mean ± standard deviation (SD) and median and interquartile range (IQR) for continuous variables.

For univariate comparisons, χ^2 analysis or Fisher's exact tests were used to evaluate categorical variables. Alternatively, comparisons of continuous variables between two groups were analyzed using the Student's t-test or Wilcoxon rank-sum test for normally and non-normally distributed data, respectively. Analysis of variance or Kruskal–Wallis tests were used for comparisons of three or more groups. Univariate estimates of local control, regional control, distant control, and overall survival were derived using the Kaplan-Meier method, and comparisons between groups were performed using the log-rank test. P values <0.05 were considered statistically significant. All tests were two-sided. Statistical analyses were performed using SPSS, version 27.0 (IBM Corp, Armonk, NY) software.

RESULTS

Patient Characteristics

Between December 2019 and November 2022, 27 patients with 29 lung tumors were treated with SBPT and met criteria for this analysis. Three subgroups of patients received SBPT: early-stage NSCLC (N=13, 48.1%), locally recurrent NSCLC (N=3, 11.1%), and metastatic tumors (N=11, 40.7%) **(Table 1)**. Among patients with metastatic disease, 6 (54.5%) had oligometastastic/oligoprogressive NSCLC, 4 (36.4%) had oligometastatic/oligoprogressive non-lung cancer

Table 1. Demographics of patients treated with thoracic proton SBRT

N (%) or mean (SD) or median (IQR)	Overall (N=27)	Early-Stage NSCLC (N=13)	Locally Recurrent NSCLC (N=3)	Metastatic Disease (N=11)
Patient Characteristics				
Age, years				
Mean (SD)	69.2 (14.5)	73.2 (11.3)	69.0 (17.0)	64.5 (17.1)
Median (IQR)	69 (64-79)	75 (64.5-82.5)	69 (52-N/A)	68 (60-75)
Sex (female)	17 (63.0%)	7 (53.8%)	3 (100%)	7 (63.6%)
Race				
White	24 (88.9%)	11 (84.6%)	3 (100%)	10 (90.9%)
Black	1 (3.7%)	0 (0%)	0 (0%)	1 (9.1%)
Asian	2 (7.4%)	2 (15.4%)	0 (0%)	0 (0%)
Smoking history				
Former	17 (63.0%)	8 (61.5%)	3 (100%)	6 (54.5%)
Current	5 (18.5%)	4 (30.8%)	0 (0%)	1 (9.1%)
Never	5 (18.5%)	1 (7.7%)	0 (0%)	4 (36.4%)
Pack years				
Mean (SD)	34.8 (28.7)	48.1 (27.2)	54.7 (13.6)	13.6 (19.4)
Median (IQR)	40 (4-50)	45 (29.5-70.5)	50 (44.0-N/A)	4 (0-22)
COPD	13 (48.1%)	8 (61.5%)	2 (66.7%)	4 (36.4%)
Cardiovascular comorbidities				
N (%)	18 (66.7%)	9 (69.2%)	2 (66.7%)	7 (63.6%)
Mean (SD)	1.6 (1.6)	2.1 (1.9)	1.7 (1.5)	1.0 (1.2)
Median (IQR)	1 (0-3)	2 (0-3.5)	2 (0-N/A)	1 (0-1)
Active autoimmune disease with pulmonary manifestations	6 (22.2%)	5 (38.5%)	0 (0%)	1 (9.1%)
Interstitial lung disease	6 (22.2%)	6 (46.2%)	0 (0%)	0 (0%)
Baseline symptoms				
Cough	16 (59.3%)	8 (61.5%)	1 (33.3%)	7 (63.6%)
Dyspnea at rest				
No (without suppl oxygen)	18 (66.7%)	6 (46.2%)	2 (66.7%)	10 (90.9%)
No (if using suppl oxygen)	6 (22.2%)	5 (38.5%)	1 (33.3%)	0 (0%)
Yes (despite suppl oxygen)	3 (11.1%)	2 (15.4%)	0 (0%)	1 (9.1%)
Dyspnea on exertion				
No (without suppl oxygen)	8 (29.6)	3 (23.1)	1 (33.3)	4 (36.4)
Yes (without suppl oxygen)	10 (37.0)	3 (23.1)	1 (33.3)	6 (54.5)
Yes (despite suppl oxygen)	9 (33.3)	7 (53.8)	1 (33.3)	1 (9.1)
Chest wall pain	6 (22.2%)	0 (0%)	1 (33.3%)	5 (45.5%)
Supplemental oxygen requirement	8 (29.6%)	7 (53.8%)	0 (0%)	1 (9.1%)
Operable	2 (7.4%)	2 (15.4%)	0 (0%)	0 (0%)

histologies, and 1 (9.1%) had polymetastatic solitary fibrous tumors. The four oligometastatic/oligoprogressive non-lung cancer histologies were thymoma, solitary fibrous tumor, Ewing's sarcoma, and breast adenocarcinoma.

In the overall cohort, the median patient age was 69 (64-79) years old, and 17 (63.0%) of the 27 patients were female. The vast majority of patients were medically inoperable, whereas two (7.4%) patients were determined to be medically operable but decided to proceed with SBPT instead of surgery. The majority of patients in the overall cohort were former smokers (63.0%); however, patients with metastatic disease had less extensive smoking histories compared to patients with early-stage

NSCLC and locally recurrent NSCLC (≥20 pack years: 27.3% vs 84.6% vs 100%, respectively; p=0.006).

Patients with early-stage NSCLC who received SBPT were more likely to have significant interstitial lung disease (i.e., idiopathic pulmonary fibrosis, combined interstitial lung disease and emphysema, or active scleroderma with lung parenchymal manifestations) at baseline compared to patients with locally recurrent NSCLC or metastatic cancer (46.2% vs. 0% vs 0%, p=0.016). The poor baseline pulmonary function of the early-stage NSCLC patients was exemplified by their differential need for continuous supplemental oxygen compared to patients with locally recurrent NSCLC and metastatic cancers (53.8% vs. 0% vs. 9.1%, respectively; p=0.028)

Indications for SBPT and Tumor Features

The most common indications for SBPT were central (n=5) or ultra-central (n=20) tumor location (69.0%), severe COPD (48.1%), reirradiation (44.4%), interstitial lung disease (22.2%), and large tumor size >5 cm (18.5%) **(Table 2)**. Patients with metastatic tumors were more likely to have ultra-central tumors compared to those with locally recurrent NSCLC or early-stage NSCLC (p=0.035). As described earlier, interstitial lung disease was more commonly the rationale for treating early-stage NSCLC patients compared to locally recurrent NSCLC or metastatic patients. Early-stage NSCLC patients were less likely to undergo SBPT due to concern for reirradiation

Table 2. Tumor features and indications for SBPT

N (%) or mean (SD) or median (IQR)	Overall (N=27)	Early-Stage NSCLC (N=13)	Locally Recurrent NSCLC (N=3)	Metastatic Disease (N=11)
Tumor Features				
Histology				
Adenocarcinoma	11 (40.7%)	3 (23.1%)	3 (100%)	5 (45.5%)
Squamous cell carcinoma	7 (25.9%)	6 (46.2%)	0 (0%)	1 (9.1%)
Other	6 (22.2%)	1 (7.7%)	0 (0%)	5 (45.5%)
No biopsy	3 (11.1%)	3 (23.1%)	0 (0%)	0 (0%)
Tumor Size, cm				
Mean (SD)	3.1 (1.8)	2.6 (1.0)	4.8 (3.7)	3.3 (1.9)
Median (IQR)	2.8 (1.9-3.6)	2.4 (1.9-3.2)	3.4 (2.0-N/A)	3.0 (1.4-5.5)
Tumor SUV max (pre-SBPT)				
Mean (SD)	8.6 (5.4)	7.3 (3.7)	7.9 (3.0)	11.5 (8.0)
Median (IQR)	7.6 (5.6-10.8)	7.9 (3.4-9.1)	6.4 (6.0-N/A)	6.8 (5.4-21.5)
Tumor and Dosimetric Rationales for SBPT				
Tumor Location				
Peripheral	9 (31.0%)	6 (42.9%)	1 (33.3%)	2 (16.7%)
Central/Ultra-central	20 (69.0%)	8 (57.1%)	2 (66.7%)	10 (83.3%)
Central	5 (17.2%)	3 (21.4%)	1 (33.3%)	1 (8.3%)
Ultra-central	15 (51.7%)	5 (35.7%)	1 (33.3%)	9 (75.0%)
Proximal bronchial tree	6 (20.7%)	1 (7.1%)	1 (33.3%)	4 (33.3%)
Trachea	2 (6.9%)	1 (7.1%)	0 (0%)	1 (8.3%)
Esophagus	2 (6.9%)	1 (7.1%)	0 (0%)	1 (8.3%)
Pulmonary Artery	2 (6.9%)	0 (0%)	1 (33.3%)	1 (8.3%)
Ascending Aorta	1 (3.4%)	0 (0%)	0 (0%)	1 (8.3%)
Descending Aorta	2 (6.9%)	2 (14.3%)	0 (0%)	0 (0%)
Heart	7 (24.1%)	2 (14.3%)	0 (0%)	5 (41.7%)
Reirradiation	12 (44.4%)	3 (23.1%)	3 (100%)	6 (54.5%)
Tumor size >5cm	5 (18.5%)	1 (7.7%)	1 (33.3%)	3 (27.3%)

compared to locally recurrent NSCLC and metastatic patients (23.1% vs. 100% vs. 54.5%, respectively; p=0.013). Patients with locally recurrent NSCLC and metastatic cancers tended to have larger tumors than those with early-stage NSCLC.

Treatment Details

The most common SBPT regimen was 50 CGyE over 5 fractions, which was delivered to 17 (58.6%) of the 29 treated tumors in this study **(Table 3)**. All patients, with the exception of one patient (3.4% of tumors) who had a large (>5 cm) left-sided tumor abutting the diaphragm and had their target volume undercovered to protect the stomach, had at least 95% of their target volume covered by the prescription dose. Ablative doses (i.e., BED10 >100 CGyE) were administered to the tumors of all patients with early-stage NSCLC. Twenty-two (75.9%) tumors in the overall cohort received BED10 >100 CGyE. Most patients (58.6%) received daily SBPT; however, every other day SBPT regimens tended to be seen more frequently among patients with significant interstitial lung disease and/or active autoimmune disease with pulmonary manifestations (62.5% vs. 26.3%, p=0.075), tumors >5 cm (60.0% vs. 31.8%, p=0.24), and in patients with ultra-central tumors adjacent to the trachea or proximal bronchial tree (66.7% vs. 30.4%, p=0.10).

Disease Control

The initial post-SBPT imaging study almost always demonstrated a partial response (33.3%) or stable disease (63.0%) of the irradiated lesion using RECIST 1.1 criteria **(Table 4)**. In the overall cohort, only one irradiated tumor progressed per RECIST 1.1 criteria on initial imaging; however, this was likely radiographic pseudoprogression given that there have been no subsequent PET/CT or biopsy findings supportive of progression in this patient locally, regionally, or distantly with sustained follow-up. Using the S1914 definition for progression, none of the irradiated lesions progressed on their first imaging study. On first post-SBPT imaging, the irradiated lesion's long-axis diameter decreased by a mean of 23.3%. There were no statistically significant differences between the three cohorts, but patients with early-stage NSCLC, and especially those with squamous cell carcinoma histologies, tended to demonstrate a greater relative reduction in tumor long-axis diameter in response to SBPT compared to locally recurrent NSCLC and metastatic tumors. BED10 was significantly associated with local control (p=0.047).

At a median follow-up of 11.0 months, median overall survival was 14 (10-23) months for the overall cohort. There were no significant differences in overall survival between the three subgroups **(Table 4)**. SBPT was associated with excellent local control, with one-year

Table 3. Treatment characteristics

N (%) or mean (SD) or median (IQR)	Overall (N=27)	Early-Stage NSCLC (N=13)	Locally Recurrent NSCLC (N=3)	Metastatic Disease (N=11)
Proton SBRT Details				
Total dose, CGyE				
Mean (SD)	46.9 (10.7)	50.7 (2.7)	43.3 (11.5)	43.4 (14.8)
Median (IQR)	50 (45-50)	50 (50-50)	50 (30-N/A)	45 (27.8-60)
BED10, CGyE				
Mean (SD)	91.0 (24.8)	100.4 (1.3)	82.7 (30.0)	82.1 (34.3)
Median (IQR)	100 (86-100)	100 (100-100)	100 (48-N/A)	86 (48.8-105)
Number of fractions				
Median (IQR)	5 (5-5)	5 (5-5)	5 (5-N/A)	5 (5-5)
Mode	5	5	5	5
Treatment schedule				
Daily	17 (58.6%)	8 (57.1%)	2 (66.7%)	7 (58.3%)
Every other day	11 (37.9%)	5 (35.7%)	1 (33.3%)	5 (41.7%)
Other	1 (3.4%)	1 (7.1%)	0 (0%)	0 (0%)

Table 4. Disease control for patients who received thoracic proton SBRT

Outcome	Overall (N=27)	Early-Stage NSCLC (N=13)	Locally Recurrent NSCLC (N=3)	Metastatic Disease (N=11)
RECIST 1.1 response at first scan†				
Mean % change (SD)	−23.3 (22.1)	−28.0 (13.9)	−18.8 (14.6)	−19.0 (30.4)
Partial response	9 (33.3%)	5 (38.5%)	1 (33.3%)	3 (27.3%)
Stable disease	17 (63.0%)	8 (61.5%)	2 (66.7%)	7 (63.6%)
Progressive disease	1 (3.7%)	0 (0%)	0 (0%)	1 (9.1%)
Overall survival, months				
Median (IQR) months	14 (10−23)	15 (11−19)	29 (29−30)	11 (6−15)
3-year actuarial outcomes (%)				
Local control	77%	89%	100%	43%
Regional control	85%	89%	67%	86%
DMFS	52%	79%	100%	0%

†Irradiated tumor

Abbreviations: DMFS, distant metastasis-free survival; PFS, progression-free survival

actuarial rates of 89%, 100%, and 86% (per the S1914 definition) for early-stage NSCLC, locally recurrent NSCLC, and metastatic patients, respectively (p=0.10). This persisted for patients with early-stage and locally recurrent NSCLC, who exhibited 3-year actuarial local control rates of 89%, 100%, respectively. Among metastatic patients, however, those with oligometastatic/oligoprogressive NSCLC had a 3-year actuarial local control rate of 100%, whereas those with metastatic histologies other than NSCLC were treated with more palliative regimens with BED10 <100 Gy and all progressed locally within 2 years. Three-year actuarial rates of regional control for early-stage, locally recurrent, and oligometastatic/oligoprogressive NSCLC after SBPT were 89%, 67%, and 100% (p=0.60). In the early-stage and locally recurrent NSCLC cohorts, three-year actuarial rates of distant metastasis-free survival were 79% and 100%. All metastatic patients, however, experienced distant progression within two years (p=0.016).

Toxicity

In the overall cohort, the incidence of any grade ≥2 treatment-related toxicity was 7.7% (n=2) **(Table 5)**. Grade ≥2 toxicity was independent of if patients did or did not receive prior in-field radiation therapy (1 of 12 vs. 1 of 15, respectively). Both grade ≥2 treatment toxicities were due to pulmonary events, and both events occurred in early-stage NSCLC patients with central tumors who received 50 CGyE in 5 fractions, whereas none of the 14 patients with locally recurrent NSCLC or metastatic disease experienced grade ≥2 pneumonitis. Notably, both patients who experienced grade ≥2 pneumonitis had significant baseline interstitial lung disease and also extensive cardiopulmonary comorbidities, and both also required continuous supplemental oxygen prior to SBPT. One of those two patients suffered from grade 5 pneumonitis 19 weeks following treatment that was considered probably related to SBPT. She was a 64-year-old woman with a 40-pack-year smoking history with recurrent locally advanced NSCLC, active scleroderma, severe COPD requiring standing daily prednisone, significant coronary artery disease status post myocardial infarction and stent placement, pulmonary hypertension, and hyperlipidemia. Less than two years prior to initiating SBPT, she received definitive chemoradiation for locally advanced NSCLC (T3N3cM0) in her contralateral lung, and that treatment course was complicated by high-grade radiation pneumonitis and carboplatin/paclitaxel-related colitis requiring early discontinuation of her chemotherapy. Her reirradiation SBPT V20, V5, and mean lung doses were 9.0%, 16.7%, and 4.7 Gy, respectively. The other patient developed radiation pneumonitis requiring an increase in their pre-SBPT continuous oxygen demand. There were no cases of grade ≥2 pneumonitis in early-stage NSCLC patients who did not have significant interstitial lung disease at baseline. There were no acute or late grade ≥2 toxicities related to esophagitis, cardiac injury, airway injury, bronchopulmonary hemorrhage, or brachial plexopathy.

Table 5. Toxicities for patients who received SBPT†

CTCAE 5.0 complications	Overall (N=27)	Early-Stage NSCLC (N=13)	Locally Recurrent NSCLC (N=3)	Metastatic Disease (N=11)
ECOG, median (IQR)				
Baseline	1 (0-2)	1 (0.5-2)	1 (0-N/A)	1 (0-1)
3 months	1 (1-2)	1 (0.5-2)	1 (0-N/A)	1 (1-1)
Pneumonitis				
Grade 2	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Grade 3	1 (3.7%)	1 (7.7%)	0 (0%)	0 (0%)
Grade 4	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Grade 5	1 (3.7%)	1 (7.7%)	0 (0%)	0 (0%)
Esophagitis				
Grade ≥2	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Bronchopulmonary Hemorrhage				
Grade ≥2	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Cardiac toxicities				
Grade ≥2	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Airway injury				
Grade ≥2	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Brachial plexopathy				
Grade ≥2	0 (0%)	0 (0%)	0 (0%)	0 (0%)

†Includes all acute and late events

DISCUSSION

This study demonstrates that intensity-modulated SBPT generally is a safe and effective treatment for many high-risk lung tumors. All patients treated with SBPT in this analysis had at least one high-risk factor for toxicity and/or poor local control if treated with photon SBRT, and the majority at two or more such high-risk features. These risk factors included central/ultra-central tumor location, prior in-field radiation, significant pulmonary fibrosis, active autoimmune disease, and large tumor size. Patients with prior in-field radiation, large tumors, and tumors immediately adjacent to critical OARs did exceptionally well, whereas those with active interstitial lung disease and an additional high-risk feature were more likely to develop toxicity from treatment.

The integration of photon SBRT as the preferred standard of care for inoperable peripheral early-stage NSCLC has improved survival in lung cancer.[31] The ability of SBRT to deliver ablative radiotherapy using higher doses per fraction improves local control and overall survival compared to conventionally fractionated radiotherapy.[5] Photon SBRT generates numerically superior local control compared to even moderately hypofractionated RT for peripheral and central NSCLC.[6] However, it is important to consider that not all photon SBRT is the same. Photon SBRT using a BED10 less than 100 Gy is associated with inferior local control and overall survival compared to treatment delivering a BED10 ≥100 Gy. This is a critical point since providers often initially deliver lower BED treatment courses or significantly undercover target volumes with photon SBRT when treating high-risk tumors in an attempt to reduce the risk of high-grade and potentially even fatal toxicities. Studies of nearly ablative ultra-hypofractionated photon RT (BED10 90-95.2Gy) for ultra-central lung tumors have reported notably higher grade ≥3 and grade 5 toxicity rates of 34-38% and 15-21%, respectively.[14,32] In contrast, none of the ultra-central patients in our study (n=15) experienced grade ≥2 toxicity despite nine of them receiving regimens with a BED10 ≥100 CGyE.

Our study demonstrates that dose de-escalation and target undercoverage for high-risk lung tumors is gener-

ally unnecessary if using intensity-modulated SBPT for definitive indications in non-metastatic patients. This is consistent with a prior dosimetric comparative analysis of photon SBRT versus SBPT for centrally located early-stage NSCLC, which showed that twice as many patients were able to satisfy both >95% PTV coverage and maximum tolerated dose constraints with passive scatter SBPT compared to photon SBRT.[33] This is likely because proton SBRT can better allow for normal tissue sparing that enables more optimal irradiation doses to be delivered to the target volume.[34] All 13 early-stage NSCLC patients in our study received ablative SBRT (i.e., BED10 >100 CGyE) despite the majority having central or more commonly even ultra-central tumors, significant pre-SBPT pulmonary fibrosis and/or active autoimmune diseases, and/or requiring baseline supplemental oxygen, as well as nearly one-quarter being reirradiation cases.

Furthermore, in addition to demonstrating that patients with moderate-to-severe pulmonary comorbidities and high-risk tumors do not need to be dose de-escalated and rather can be safely treated with ablative SBPT, this study also demonstrates that patients who have high-risk tumors and no significant interstitial lung disease *can be dose-escalated*.[35–37] In this study, the two patients without comorbid interstitial lung disease who had large (>5cm) ultra-central tumors adjacent to the proximal bronchial tree received dose-escalated SBPT to 60 CGyE in 5 fractions. Both patients achieved marked early local responses and sustained local control with no grade ≥2 acute or late toxicities. These two tumors were in patients with metastatic cancers (one adenosquamous NSCLC, one breast cancer); however, this suggests that it is likely safe and effective to deliver dose-escalated SBPT to high-risk central/ultra-central early-stage NSCLC when patients do not have significant interstitial lung disease at baseline.

This study is not without limitations. First, given that NYPC treated its first patient in August 2019, many patients lack mature long-term follow-up, so future studies will need to determine if longer-term follow-up demonstrates additional late toxicities. Additionally, subsequent larger patient cohorts are needed to confirm the excellent local control rates demonstrated in our series, especially when BED10 ≥100 Gy were delivered. Finally, despite favorable toxicity data for the vast majority of patients, there were two patients who developed high-grade pneumonitis, including one grade 5 event. Clearly, the physical and dosimetric advantages of protons have limitations, and this case serves as a reminder that there are extreme outliers for who SBPT may do more harm than good. Patients with the combination of significant pulmonary fibrosis on baseline oxygen, active autoimmune disease requiring standing immunosuppression, and prior severe radiotherapy-associated pneumonitis should avoid high-dose per fraction lung radiotherapy – even with protons. It is possible that such patients may be more safely treated with more mild hypofractionation, although additional study is needed to assess the safest dose fractionation regimen in this patient population. Furthermore, while proton therapy can often be the safest and most optimal external beam radiotherapy modality for delivering reirradiation for thoracic malignancies,[38–40] significant caution should be heeded when delivering reirradiation in the setting of prior radiation-induced pneumonitis to avoid high grade and potentially fatal toxicities.[41]

Of course, the two patients who experienced grade ≥2 pneumonitis were outliers, and many patients in this study who had other similar substantial comorbidities and high-risk tumor features did not experience any grade ≥2 events. While Veterans Affairs Radiation Oncology Quality Surveillance Program and American Society for Radiation Oncology dose constraints for SBRT have recently been published,[42] future studies identifying safer dose constraints for patients with severe pulmonary comorbidities are warranted.

CONCLUSION

Patients with inoperable high-risk lung tumors should not need to make tradeoffs between higher toxicity risk or worse disease control. SBRT delivered with intensity-modulated proton therapy is a safe and effective alternative treatment option to photon SBRT, and most patients with contraindications to ablative photon SBRT can be safely treated with ablative SBPT without sacrificing target volume coverage. Furthermore, select patients with high-risk tumors (e.g., central/ultra-central, >5cm, etc.) can be safely dose-escalated with SBPT while meeting normal tissue dose constraints. Future larger studies and longer follow-up are warranted to assess the long-term tumor control and late toxicities of SBPT.

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