

Scientific Article

High-Risk Non-Small Cell Lung Cancer Treated With Active Scanning Proton Beam Radiation Therapy and Immunotherapy



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Abstract

Purpose: Non-small cell lung cancer (NSCLC) is a deadly malignancy that is frequently diagnosed in patients with significant medical comorbidities. When delivering local and regional therapy, an exceedingly narrow therapeutic window is encountered, which often precludes patients from receiving aggressive curative therapy. Radiation therapy advances including particle therapy have been employed in an effort to expand this therapeutic window. Here we report outcomes with the use of proton therapy with curative intent and immunotherapy to treat patients diagnosed with high-risk NSCLC.

Methods and Materials: Patients were determined to be high risk if they had severe underlying cardiopulmonary dysfunction, history of prior thoracic radiation therapy, and/or large volume or unfavorable location of disease (eg, bilateral hilar involvement, supraclavicular involvement). As such, patients were determined to be ineligible for conventional x-ray–based radiation therapy and were treated with pencil beam scanning proton beam therapy (PBS-PBT). Patients who demonstrated excess respiratory motion (ie, greater than 1 cm in any dimension noted on the 4-dimensional computed tomography simulation scan) were deemed to be ineligible for PBT. Toxicity was reported using the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. Overall survival and progression-free survival were calculated using the Kaplan-Meier method.

Results: A total of 29 patients with high-risk NSCLC diagnoses were treated with PBS-PBT. The majority (55%) of patients were defined as high risk due to severe cardiopulmonary dysfunction. Most commonly, patients were treated definitively to a total dose of 6000 cGy (relative biological effectiveness) in 30 fractions with concurrent chemotherapy. Overall, there were a total of 6 acute grade 3 toxicities observed in our cohort. Acute high-grade toxicities included esophagitis (n = 4, 14%), dyspnea (n = 1, 3.5%), and cough

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Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

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($n = 1, 3.5\%$). No patients developed grade 4 or higher toxicity. The majority of patients went on to receive immunotherapy, and high-grade pneumonitis was rare. Two-year progression-free and overall survival was estimated to be 51% and 67%, respectively. COVID-19 was confirmed or suspected to be responsible for 2 patient deaths during the follow-up period.

Conclusions: Radical PBS-PBT treatment delivered in a cohort of patients with high-risk lung cancer with immunotherapy is feasible with careful multidisciplinary evaluation and rigorous follow-up.

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Introduction

The lung cancer mortality rate has declined substantially in recent years owing in large part to improved treatment options.¹ Despite these advances, lung cancer continues to be the leading cause of cancer-related death in the United States, making up approximately 25% of all cancer fatalities.² A unique challenge in the treatment of non-small cell lung cancer (NSCLC) is the narrow therapeutic window in high-risk patients. Delivering aggressive concurrent chemoradiation therapy in patients who on average are quite elderly and have significant cardiopulmonary dysfunction is challenging.^{3,4} The fragility of such patients is most notably manifested by the survival detriment observed with dose escalation in Radiation Therapy Oncology Group (RTOG) trial 0617, which serves as a cautionary tale.⁵ Nevertheless, RTOG 0617 demonstrated several critical factors implicit in modern radiation therapy management of NSCLC. First, lung dose, specifically V20 Gy, is significantly associated with severe pulmonary toxicity.⁶ Second, heart dose is correlated with overall survival (OS).⁶ Third, intensity modulated radiation therapy (IMRT) can improve upon the aforementioned dose-volume histogram parameters and optimize clinical outcomes.⁶ Hence, it is postulated that advanced proton therapy techniques may translate to further clinical improvements.

Proton beam therapy (PBT) has shown the ability to reduce cardiopulmonary radiation exposure compared with IMRT in numerous dosimetric studies.⁷⁻¹² Clinical results have been reported by multiple institutional series and have explored oncologic and toxicity outcomes of concurrent PBT chemoradiation for locally advanced NSCLC.¹³⁻¹⁷ However, the majority of publications to date have used passive scatter PBT as opposed to pencil beam scanning (PBS) systems, and to our knowledge none have reported treatment planning using Monte Carlo algorithms exclusively. Moreover, with improvements in systemic therapy, particularly immunotherapy, in the localized and metastatic setting, the therapeutic landscape of NSCLC has dramatically changed.¹⁸⁻²⁰ The majority of patients with NSCLC receiving chemoradiation will now go on to receive immunotherapy, either as consolidation or upon disease progression. With the addition of immunotherapy, there are concerns regarding an increased risk of overlapping side effects, particularly

pneumonitis, in this patient population. However, little data exists in this space for those receiving PBT.²¹

Despite the significant aforementioned advances in the management of NSCLC in the modern era, these improvements can be reduced by the effects of a pandemic. The cardiopulmonary frailty of patients with high-risk NSCLC, especially while undergoing immunosuppressive or immunostimulatory therapy, places them in arguably the highest-risk COVID-19 category, which has been demonstrated in a recent meta-analysis.²² In this article, we review the outcomes of patients with diagnoses of high-risk NSCLC treated with PBS-PBT followed by immunotherapy during the COVID-19 pandemic.

Methods and Materials

Patient eligibility

This single institutional review of consecutive patients treated with NSCLC was approved by the local institutional review board (2017-0695). All patients were evaluated by a multidisciplinary thoracic oncology team which included radiation oncology, interventional pulmonology, medical oncology, and thoracic surgery. All patients underwent diagnostic tests including computed tomography (CT) scan, positron emission tomography (PET)/CT scan, magnetic resonance imaging or CT scan of the brain, and pulmonary function tests. All patients underwent bronchoscopy and endobronchial ultrasound for biopsy of the primary mass and lymph node sampling. Patients were staged using the American Joint Committee on Cancer eighth edition staging system. Patients with implanted cardiac devices were not PBT candidates based on institutional practice. Patients were determined to be high risk if they had severe underlying cardiopulmonary dysfunction, history of prior thoracic radiation therapy, and/or large volume or unfavorable location of disease (eg, bilateral hilar involvement, supraclavicular involvement).

Simulation and contouring

All patients underwent CT-based radiation treatment planning simulation with accompanied 4-dimensional

computed tomography (4D-CT) for assessment of respiratory motion (GE LightSpeed RT16). Respiratory motion management in the form of abdominal compression was used in cases of excess motion, which was assessed at the time of simulation. A contrast CT scan was also obtained at the time of simulation and fused with the primary simulation CT scan. Diagnostic imaging including CT or PET/CT was fused with the simulation CT scan to assist in target volume delineation. Patients who demonstrated excess respiratory motion (ie, greater than 1 cm in any dimension noted on the 4D-CT simulation scan) were deemed to be ineligible for PBT. Target volume contours were generated using previously defined definitions from the RTOG 1308 protocol.²³ Elective nodal radiation was not incorporated for any definitive treatment. Organs at risk (OARs) were contoured and included lungs, heart, esophagus, spinal cord, brachial plexus, proximal bronchial tree, and skin (3 mm).

Treatment planning and delivery

Dose calculations and planning optimization were performed on the average phase of the simulation 4D-CT. Proton plans were generated using RayStation version 8A (RaySearch Laboratories, Stockholm, Sweden). Beam angles were created to optimize target volume coverage, mitigate dose degradation due to motion or geometric changes, and minimize exposure of normal structures (Fig. 1). Single-field optimization was used for all PBT plans. All plans were optimized using a Monte Carlo dose calculation algorithm, which is very rarely used in prior publications for lung cancer PBT treatment. Apertures were created using the Adaptive Aperture multileaf collimator system (Mevion Medical Systems, Littleton, MA).

Planning overrides were used for artifact created by fiducial markers, if present. Quality assurance 4D-CT scans were obtained at regular intervals, typically every 1 to 2 weeks during treatment (Supplementary Figure E1). PBT replans were performed on the 4D-CT scan average phase to ensure intrinsic anatomic changes during treatment did not significantly alter target coverage or OAR dose constraints. Replans were performed if target coverage or doses to OARs deviated from institutional standards. All patients were treated with standard fractionation. Patients were set up using orthogonal kV imaging with gross set up to bony anatomy and subsequent final adjustment based on the bronchopulmonary tree with or without fiducial marker adjustment.

Follow-up

Patients were seen for weekly on treatment visits and acute toxicity was defined as that occurring within 90 days of treatment completion. Late toxicity was defined as that occurring greater than 90 days after radiation therapy completion. Toxicity was reported using the Common Terminology Criteria for Adverse Events, version 5.0. All toxicities were graded by the attending radiation oncologist. Patients were typically followed using serial CT scans and multidisciplinary clinical examination at 3-month intervals for the first 2 years and every 6 to 12 months thereafter.

Statistical analysis

The Kaplan-Meier method was used to calculate OS and progression-free survival (PFS). All patients were

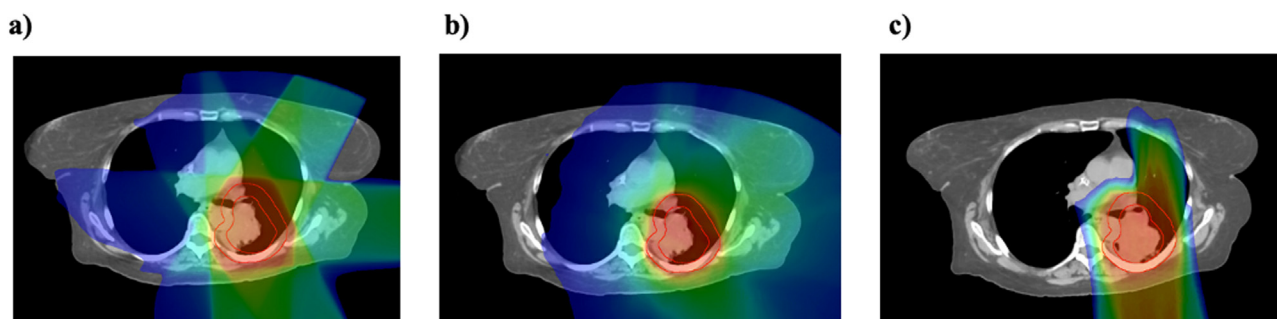


Figure 1 Seventy-two-year-old female patient with a diagnosis of non-small cell lung cancer of the left lower lobe, squamous cell carcinoma histology, clinical stage T3 N0 M0, stage IIB. She was deemed medically inoperable due to significant pulmonary dysfunction (FEV1 of 37% and diffusing capacity of the lungs for carbon monoxide 31%) and was treated with proton beam therapy to a total dose of 6000 cGy in 30 fractions with concurrent chemotherapy. Color-wash dose distribution is demonstrated for (a) 3-dimensional conformal radiation therapy comparative plan, (b) intensity modulated radiation therapy comparative plan, and (c) proton beam therapy plan using the Monte Carlo algorithm.

included for the acute toxicity analysis. Patients who did not progress during treatment and were not lost to follow-up were included in our OS and PFS analysis. OS was defined as the time from the end of treatment to death from any cause. PFS was defined as the time from the end of treatment to disease progression or death from any cause. Median follow-up was defined as time from the end of treatment to last clinical follow-up or death. Local control was defined as any new or progressing disease within the radiation treatment field per response evaluation criteria in solid tumors, version 1.1. Regional recurrence was defined as disease in the adjacent mediastinum or ipsilateral lobe(s) outside of the radiation field. Distant recurrence was defined as any recurrence not meeting the local or regional recurrence definition. All statistical analysis was performed using SPSS, version 24 (IBM, Armonk, NY).

COVID-19 analysis

We define the beginning of the COVID-19 pandemic as March 1, 2020. All patients included in the COVID-19 portion of the analysis of the present study were either treated during the pandemic or seen in follow-up thereafter. We reviewed the following COVID-19 data for this patient cohort: infection rate, severity of infection, and death rate (confirmed and suspected). We also reviewed the vaccination status of surviving patients.

Results

Patient and tumor characteristics

A total of 29 patients with high-risk NSCLC were consecutively treated from 2018 to 2020 with thoracic PBS-PBT. The median age of the cohort was 70 years (range, 49-86 years). A significant proportion of patients (24%) required supplemental oxygen before treatment due to severe baseline pulmonary disease. The most common diagnosed histology was adenocarcinoma (n = 14). Over half of the cohort had diagnoses of unresectable, locally advanced NSCLC stage IIIB-C. Most patients were considered high risk due to severe cardiopulmonary dysfunction (n = 16, 55%) or tumor location or size (n = 13, 45%). A notable proportion were considered high risk due to prior thoracic radiation therapy (n = 7, 24%), all for metachronous nonrelated malignancies. Of note, the median dose of the previous radiation therapy course was 6000 cGy (range, 3000-7380 cGy). The median volume of disease as measured by planning target volume was 471 cc (range, 45-1286 cc). Table 1 illustrates patient and tumor characteristics (dosimetric data can be found in Supplementary Table E1). Figure 1 illustrates comparative

Table 1 Patient and cancer characteristics

Characteristic	Number	Percentage
Age		
≤70 y	14	48%
>70 y	15	52%
Sex		
Female	17	59%
Male	12	41%
ECOG		
0	18	62%
1	10	34%
2	1	4%
Tobacco use (pack-years)		
≤10	4	14%
10-30	7	24%
≥30	18	62%
Oxygen dependent		
No	22	76%
Yes	7	24%
Stage (AJCC 8th edition)		
IA/B	2	7%
IIB	2	7%
IIIA	9	31%
IIIB	11	38%
IIIC	4	14%
IV	1	3%
Histology		
Adenocarcinoma	14	49%
Squamous cell carcinoma	10	34%
Undifferentiated	3	11%
Large cell carcinoma	1	3%
Spindle cell carcinoma	1	3%
<i>Abbreviations:</i> AJCC = American Joint Committee on Cancer; ECOG = Eastern Cooperative Oncology Group.		

radiation therapy plans for a patient treated in our cohort with underlying severe pulmonary disease.

The vast majority of patients were treated with definitive intent (n = 26, 90%). Patients were treated to a median total dose of 6000 cGy (relative biological effectiveness) in 30 fractions (4500-6600 cGy relative biological effectiveness). The majority of patients (n = 25, 86%) received chemotherapy, with 84% receiving it concurrently. During treatment, 28% of patients (n = 8) had geometric target volume changes that significantly altered coverage and/or OAR dose constraints necessitating a PBT replan. Nearly all of these patients (n = 7) received

concurrent chemotherapy and were evenly distributed between adenocarcinoma (n = 3) and squamous cell carcinoma (n = 4) histology. Interestingly, none of the patients who required a replan went on to develop local or regional disease recurrence, perhaps reflective of the rapid treatment response identified during treatment. Table 2 lists specific treatment characteristics. Supplementary Figure E1 demonstrates radiation therapy changes seen during radiation treatment (ie, 3-week Quality Assurance-CT scan) as well as 2 years following treatment completion.

Acute PBT toxicity

Overall, there were a total of 6 acute grade 3 toxicities observed in our cohort. Acute high-grade toxicities included: esophagitis (n = 4, 14%), dyspnea (n = 1, 3.5%), and cough (n = 1, 3.5%). Notably, all patients who experienced grade 3 esophagitis received concurrent chemotherapy and had either bilateral mediastinal disease or disease directly invading the mediastinum. No patient experienced any grade 4 or higher acute toxicity. The most common low-grade toxicities (\leq grade 2) included fatigue

(n = 27, 15%), esophagitis (n = 22, 12%), and radiation dermatitis (n = 19, 10%). Detailed acute toxicity information is shown in Table 3.

Immunotherapy characteristics

The majority of eligible patients (20 of 21) went on to receive immunotherapy either for consolidation or upon disease progression. The most common immunotherapy used was durvalumab (n = 13). Ineligibility for immunotherapy was documented for the following reasons: (1) radiation delivered without radical intent (n = 3), (2) contraindications due to systemic autoimmune diseases (n = 2), (3) early-stage disease (n = 2), (4) targeted therapy used (n = 1), and (5) rapid disease progression (n = 1). Grade 2 or higher pneumonitis was identified in a total of 7 patients, 2 of whom were found to have grade 3 toxicity. Grade 2 or higher pneumonitis occurred at a median of 3.75 months following completion of radiation. Of these cases, 3 were attributed to radiation, 2 were attributed to immunotherapy, and 2 had an unclear etiology (ie, immunotherapy vs radiation). Of note, immunotherapy-related grade 3 thyroiditis and grade 3 colitis was identified in 2 additional patients.

Table 2 Treatment characteristics

Characteristic	Number	Percentage
Radiation approach		
Definitive	26	90%
Adjuvant	2	7%
Neoadjuvant	1	3%
Chemotherapy approach		
None	4	14%
Sequential	5	17%
Concurrent	20	69%
Reason for PBT*		
Comorbidities	16	55%
Reirradiation	7	24%
Adjacent OAR	13	45%
PBT replan required		
No	21	72%
Yes	8	28%
Immunotherapy regimen		
Durvalumab	13	65%
Pembrolizumab	4	20%
Nivolumab	2	10%
Ipilimumab/nivolumab	1	5%

Abbreviations: OAR = organs at risk; PBT = proton beam therapy.
* Multiple reasons for PBT per patient were possible.

Late PBT toxicity

A total of 7 high-grade (grade 3+) toxicities were observed in 5 patients. Nearly all of these toxicities were pulmonary and had the following distribution: pneumonitis (n = 2), pleural effusion (n = 2), lung infection (n = 1), dyspnea (n = 1), and esophageal stricture (n = 1). No grade 4 or higher late toxicities were observed. High-grade pneumonitis was attributed to immunotherapy in 1 case and had an unclear etiology (ie, immunotherapy vs radiation) in the other. The late grade 3 esophageal stenosis occurred in a patient who previously underwent a course of definitive thoracic irradiation, highlighting the risk of late normal tissue toxicity with reirradiation. The most commonly observed low-grade (\leq grade 2) late toxicities were cough (n = 9, 35%), fatigue (n = 9, 35%), and chest wall pain (n = 8, 30%). Low-grade acute toxicities demonstrated a clear improvement over time with fatigue, esophagitis, and radiation dermatitis dissipating with longer follow-up. Of note, 3 patients were lost to follow-up shortly after completion of radiation treatment and were excluded from late toxicity and survival analysis. Late toxicity information is illustrated in Table 4.

Oncologic outcomes

With a median follow-up of 17.36 months, median OS and PFS has not been reached. The 1- and 2-year

Table 3 Acute toxicity (Common Terminology Criteria for Adverse Events version 5.0)

Toxicity	Grade, n (%)			
	1	2	3	4
Dermatologic				
Radiation dermatitis	12 (41%)	7 (24%)	0	0
Skin hyperpigmentation	10 (34%)	2 (7%)	-	-
Pulmonary				
Cough	14 (48%)	4 (14%)	1 (3%)	-
Pleural effusion	3 (10%)	1 (3%)	0	0
Dyspnea	11 (38%)	5 (17%)	1 (3%)	0
Voice alteration	6 (21%)	7 (24%)	0	-
Atelectasis	4 (14%)	1 (3%)	0	0
Wheezing	4 (14%)	5 (17%)	0	0
Chest wall pain	5 (17%)	3 (10%)	0	-
Gastrointestinal				
Esophagitis	4 (14%)	18 (62%)	4 (14%)	0
Weight loss	8 (28%)	4 (14%)	0	-
Anorexia	11 (38%)	5 (17%)	0	0
Fatigue	16 (55%)	11 (38%)	0	-

estimated PFS was 60% and 51%, respectively (Fig. 2A). The 1- and 2-year estimated OS was 76% and 67%, respectively (Fig. 2B). Notably, progression of disease was typically observed within the first 6 months, and for those

patients who remained disease free, control appeared to be durable with extended follow-up. The predominant pattern of failure was distant progression with only 1 case of regional recurrence identified. A total of 10 patients

Table 4 Late toxicity (Common Terminology Criteria for Adverse Events version 5.0)

Toxicity	Grade, n (%)				
	1	2	3	4	5
Dermatologic					
Radiation dermatitis	1 (3%)	0	0	0	0
Superficial soft tissue fibrosis	1 (3%)	0	0	0	0
Pulmonary					
Cough	4 (14%)	5 (17%)	0	-	-
Pneumonitis	0	5 (17%)	2 (7%)	0	0
Pneumothorax	0	0	0	0	0
Lung infection	-	2 (7%)	1 (3%)	0	0
Pleural effusion	3 (10%)	0	2 (7%)	0	0
Dyspnea	3 (10%)	3 (10%)	1 (3%)	0	0
Atelectasis	3 (10%)	1 (3%)	0	0	0
Wheezing	1 (3%)	0	0	0	0
Chest wall pain	1 (3%)	7 (24%)	0	-	-
Gastrointestinal					
Esophageal stricture	0	0	1 (3%)	0	0
Anorexia	3 (10%)	0	0	0	0
Fatigue	9 (31%)	1 (3%)	0	-	-

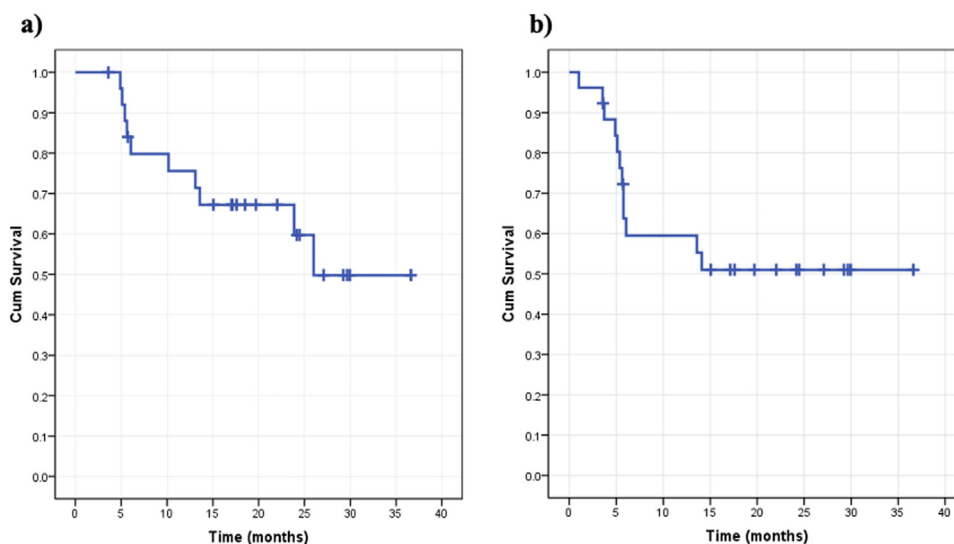


Figure 2 (a) Overall survival. (b) Progression-free survival.

died during the follow-up period. Cause of death distribution was as follows: cancer progression ($n = 4$), COVID-19 or suspected COVID-19 ($n = 2$), cardiac arrest due to substance abuse ($n = 1$), cerebral hemorrhage ($n = 1$), respiratory failure ($n = 1$), and unknown ($n = 1$).

COVID-19 effect

A total of 24 patients were included in our COVID-19 analysis. Of these, only 2 were found to have polymerase chain reaction–documented COVID-19 infections. For those who were found to have COVID-19 infections, 1 patient required hospitalization and subsequently died of their infection, and the other patient recovered quickly. In addition, due to difficulty with respect to follow-up and availability of polymerase chain reaction testing during the initial phase of the pandemic, 1 additional patient died at an outside hospital with a suspected COVID-19 infection but was never tested. Of the remaining 22 patients, 6 individuals died before the availability of the COVID-19 vaccine. A total of 16 patients were alive at the time of last follow-up with only 9 being vaccinated.

Discussion

The present article reports clinical outcomes for a cohort of patients with high-risk lung cancer at the intersection of novel advanced active scanning PBT in concert with immunotherapy delivered during the COVID-19 pandemic. The high-risk nature of our cohort reflects a more generalizable patient population that is often not reported upon in clinical trials. In the present study, over half of the cohort had diagnoses of unresectable stage

IIIB-C disease. Furthermore, 24% of the patients required supplemental oxygen at baseline, 24% had prior thoracic irradiation, and over half carried a diagnosis of severe cardiopulmonary dysfunction. Older patients with severe cardiopulmonary disease typically represent the rule rather than the exception in the average lung cancer clinical encounter. Moreover, prior publications not surprisingly demonstrate that the risk of radiation-related toxicity can escalate as age and medical comorbidities increase.^{24,25} As a consequence, these patients may be exquisitely sensitive to low doses of radiation to thoracic organs.²⁵ As such, many practitioners often recommend against aggressive definitive intent locoregional therapy in effort to avoid potential harm to the high-risk patient. Nevertheless, locoregional progression of lung cancer is strongly associated with morbidity and decreased quality of life and is a leading cause of lung cancer–related death.²⁶ Taken as a whole, it is critical to widen the therapeutic ratio in this patient population and a theoretical method of doing so is improved radiation technique such as the use of PBS-PBT.

Fundamentally, it is the physical dose superiority afforded by the Bragg peak that makes PBT an attractive radiation option particularly when minimization of integral radiation dose exposure is critical. The use of PBT in the treatment of locally advanced NSCLC has been well reported in the literature and has prompted the randomized control trial, RTOG 1308, comparing PBT with IMRT.¹⁵⁻¹⁷ The vast majority of PBT lung cancer literature uses older passive scatter technology, whereas we describe the clinical results of modern PBS delivery in concert with Monte Carlo-based planning, which will likely become standard for thoracic PBT in the near future.²⁷ Despite improvements in conformality with PBS-PBT, it is critical to monitor tumor response during treatment, particularly in heterogeneous

tissue such as the lung, to avoid target dose degradation and OAR overdosage. This is demonstrated by the fact that 28% of our cohort had geometric changes that required PBT replans during treatment. Ultimately, the comparative effectiveness of PBT versus x-ray–based therapy will be determined by randomized trials with particular attention placed on PBT toxicity mitigation, which is all the more important for a high-risk cohort such as that described in this article.

Without question the most meaningful therapeutic advance in lung cancer in the last several decades has been the development of immunotherapy. In cases of locally advanced NSCLC following curative treatment, the predominant pattern of failure has historically been distant, and the use of effective immunotherapy has yielded dramatic PFS and OS improvements. However, concerns regarding overlapping toxicities with radiation therapy, specifically pneumonitis, persist and appear to be higher than was initially reported in the PACIFIC trial.^{18,19,28} In the present study we identified limited severe radiation therapy– and immunotherapy-related pneumonitis ($n = 2$), with 5 additional patients with diagnoses of low-grade pneumonitis. Moreover, despite underlying comorbidities, the majority of patients who were eligible for immunotherapy went on to receive it after upfront radiation. It would appear with careful multidisciplinary evaluation and close follow-up, curative radical PBS-PBT in concert with immunotherapy in a high-risk cohort is feasible with manageable toxicity.

In 2020, patients with lung cancer simultaneously faced the deadliest cancer in America and the deadliest pandemic in modern history, often while immunosuppressed from antineoplastic treatment and handicapped by underlying medical comorbidities. As the COVID-19 pandemic initially flared, intense management decisions were made on the fly as our understanding of the virus evolved.^{29,30} With little effective treatment identified early in the pandemic, oncologists sometimes faced the decision of minimizing viral exposure or offering curative lung cancer treatment.³¹ As one of the first countries hit with COVID-19, Italy reported the consequences of the infection on radiation therapy with a 17% reduction in radiation treatments, but despite this drop, nearly half of patients who received a diagnosis of COVID-19 continued radiation therapy without interruption.³²

In contrast, data reported from the initial epicenter in the United States, New York City, the severity of COVID-19 infection in patients with lung cancer was more grim with a 62% hospitalization rate and a 25% mortality rate in consecutive patients treated from March 12, 2020, to May 6, 2020, at Memorial Sloan Kettering Cancer Center.³³ Although cancer-specific factors did not seem to affect the severity of infection, patient-specific factors such as smoking and pulmonary disease dramatically increased the risk of COVID-19 severity. Such comorbid factors placed the high-risk patient population of the present study at a profound risk during the pandemic

with 62% of patients having a greater than 30-pack-year smoking history and nearly 25% on pretreatment supplemental oxygen. In the present study, COVID-19 was responsible for 1 confirmed and 1 suspected death. Fortunately, the significant clinical impact seen at Memorial Sloan Kettering Cancer Center during the peak in New York City was not observed in the present cohort in Washington, DC.

Limitations of the present study include its retrospective nature, limited patient numbers, and heterogeneous cohort. It is difficult to remark on the oncologic outcomes of the present study relative to previously published literature given the heterogeneity of our patient population and lack of similar publications for high-risk patients.³⁴ Certainly the high-risk nature of this group poses significant limitations on life expectancy. Nevertheless, we included a wide range of lung cancer stages some of which would be expected to achieve long-term disease control. Thus, direct comparison to previously published PBT literature¹³ or modern radiation therapy followed by consolidative immunotherapy¹⁸ is challenging.^{17,19} Moreover, the occurrence of the COVID-19 pandemic as a competing cause of mortality makes interpretation even more nebulous.

Conclusion

The present article reports a cohort of patients with high-risk lung cancer at the juncture of novel, advanced, active scanning PBT in concert with immunotherapy. Modern PBS-PBT with Monte Carlo-based planning was delivered for curative intent. Close monitoring of tumor changes was required as 28% of cases required a PBT replan during treatment. Despite their high-risk status, the vast majority of patients went on to receive immunotherapy and only 2 cases of severe pneumonitis were identified. A total of 6 acute grade 3 toxicities were observed, most commonly esophagitis. Seven severe late toxicities were identified, most commonly pulmonary in origin. Infection with COVID-19 was confirmed or suspected to be responsible for 2 patient deaths during the follow-up period. Two-year PFS and OS was estimated as 51% and 67%, respectively. Radical PBT treatment delivered in curative fashion in a cohort of patients with high-risk lung cancer appears to be feasible with careful multidisciplinary evaluation with rigorous follow-up.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at [doi:10.1016/j.adro.2022.101125](https://doi.org/10.1016/j.adro.2022.101125).

References

- Howlader N, Forjaz G, Mooradian MJ, et al. The effect of advances in lung-cancer treatment on population mortality. *N Engl J Med*. 2020;383:640-649.
- Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. *CA Cancer J Clin*. 2022;72:7-33.
- Torre LA, Siegel RL, Jemal A. Lung cancer statistics. *Adv Exp Med Biol*. 2016;893:1-19.
- de Groot PM, Wu CC, Carter BW, Munden RF. The epidemiology of lung cancer. *Transl Lung Cancer Res*. 2018;7:220-233.
- Bradley JD, Paulus R, Komaki R, et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): A randomised, two-by-two factorial phase 3 study. *Lancet Oncol*. 2015;16:187-199.
- Chun SG, Hu C, Choy H, et al. Impact of intensity-modulated radiation therapy technique for locally advanced non-small-cell lung cancer: A secondary analysis of the NRG Oncology RTOG 0617 randomized clinical trial. *J Clin Oncol*. 2017;35:56-62.
- Chang JY, Li H, Zhu XR, et al. Clinical implementation of intensity modulated proton therapy for thoracic malignancies. *Int J Radiat Oncol Biol Phys*. 2014;90:809-818.
- Chang JY, Zhang X, Wang X, et al. Significant reduction of normal tissue dose by proton radiotherapy compared with three-dimensional conformal or intensity-modulated radiation therapy in stage I or stage III non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys*. 2006;65:1087-1096.
- Ohno T, Oshiro Y, Mizumoto M, et al. Comparison of dose-volume histograms between proton beam and X-ray conformal radiotherapy for locally advanced non-small-cell lung cancer. *J Radiat Res*. 2015;56:128-133.
- Stuschke M, Kaiser A, Pöttgen C, Lübcke W, Farr J. Potentials of robust intensity modulated scanning proton plans for locally advanced lung cancer in comparison to intensity modulated photon plans. *Radiother Oncol*. 2012;104:45-51.
- Wu CT, Motegi A, Motegi K, et al. Dosimetric comparison between proton beam therapy and photon radiation therapy for locally advanced non-small cell lung cancer. *Jpn J Clin Oncol*. 2016;46:1008-1014.
- Zhang X, Li Y, Pan X, et al. Intensity-modulated proton therapy reduces the dose to normal tissue compared with intensity-modulated radiation therapy or passive scattering proton therapy and enables individualized radical radiotherapy for extensive stage IIIB non-small-cell lung cancer: A virtual clinical study. *Int J Radiat Oncol Biol Phys*. 2010;77:357-366.
- Chang JY, Verma V, Li M, et al. Proton beam radiotherapy and concurrent chemotherapy for unresectable stage III non-small cell lung cancer: Final results of a phase 2 study. *JAMA Oncol*. 2017;3:e172032.
- Harada H, Murayama S. Proton beam therapy in non-small cell lung cancer: State of the art. *Lung Cancer (Auckl)*. 2017;8:141-145.
- Hoppe BS, Henderson R, Pham D, et al. A phase 2 trial of concurrent chemotherapy and proton therapy for stage III non-small cell lung cancer: Results and reflections following early closure of a single-institution study. *Int J Radiat Oncol Biol Phys*. 2016;95:517-522.
- Hoppe BS, Flampouri S, Henderson RH, et al. Proton therapy with concurrent chemotherapy for non-small-cell lung cancer: Technique and early results. *Clin Lung Cancer*. 2012;13:352-358.
- Nguyen QN, Ly NB, Komaki R, et al. Long-term outcomes after proton therapy, with concurrent chemotherapy, for stage II-III inoperable non-small cell lung cancer. *Radiother Oncol*. 2015;115:367-372.
- Antonia SJ, Villegas A, Daniel D, et al. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. *N Engl J Med*. 2017;377:1919-1929.
- Antonia SJ, Villegas A, Daniel D, et al. Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. *N Engl J Med*. 2018;379:2342-2350.
- Gandhi L, Rodriguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N Engl J Med*. 2018;378:2078-2092.
- Higgins KA, O'Connell K, Liu Y, et al. National cancer database analysis of proton versus photon radiation therapy in non-small cell lung cancer. *Int J Radiat Oncol Biol Phys*. 2017;97:128-137.
- Tagliamento M, Agostinetti E, Bruzzone M, et al. Mortality in adult patients with solid or hematological malignancies and SARS-CoV-2 infection with a specific focus on lung and breast cancers: A systematic review and meta-analysis. *Crit Rev Oncol Hematol*. 2021;163:103365.
- Giaddui T, Chen W, Yu J, et al. Establishing the feasibility of the dosimetric compliance criteria of RTOG 1308: Phase III randomized trial comparing overall survival after photon versus proton radiochemotherapy for inoperable stage II-IIIB NSCLC. *Radiat Oncol*. 2016;11:66.
- McFarlane MR, Hochstedler KA, Laucis AM, et al. Predictors of pneumonitis after conventionally fractionated radiotherapy for locally advanced lung cancer. *Int J Radiat Oncol Biol Phys*. 2021;111:1176-1185.
- Shepherd AF, Iocolano M, Leeman J, et al. Clinical and dosimetric predictors of radiation pneumonitis in patients with non-small cell lung cancer undergoing postoperative radiation therapy. *Pract Radiat Oncol*. 2021;11:e52-e62.
- Nichols L, Saunders R, Knollmann FD. Causes of death of patients with lung cancer. *Arch Pathol Lab Med*. 2012;136:1552-1557.
- Maes D, Saini J, Zeng J, Rengan R, Wong T, Bowen SR. Advanced proton beam dosimetry part II: Monte Carlo vs. pencil beam-based planning for lung cancer. *Transl Lung Cancer Res*. 2018;7:114-121.
- Saito G, Oya Y, Taniguchi Y, et al. Real-world survey of pneumonitis and its impact on durvalumab consolidation therapy in patients with non-small cell lung cancer who received chemoradiotherapy after durvalumab approval (HOPE-005/CRIMSON). *Lung Cancer*. 2021;161:86-93.
- Wang A, Chang SH, Kim EJ, et al. Dynamic management of lung cancer care during surging COVID-19. *Front Surg*. 2021;8: 663364.
- Shankar A, Saini D, Bhandari R, et al. Lung cancer management challenges amidst COVID-19 pandemic: Hope lives here. *Lung Cancer Manag*. 2020;9:3.
- Singh AP, Berman AT, Marmarelis ME, et al. Management of lung cancer during the COVID-19 pandemic. *J Oncol Pract*. 2020;16:579-586.
- Buglione M, Spiazzi L, Guerini AE, et al. Two months of radiation oncology in the heart of Italian "red zone" during COVID-19 pandemic: Paving a safe path over thin ice. *Radiat Oncol*. 2020;15:191.
- Luo J, Rizvi H, Preeshagul IR, et al. COVID-19 in patients with lung cancer. *Ann Oncol*. 2020;31:1386-1396.
- Gjysli O, Xu T, Elhammali A, et al. Toxicity and survival after intensity-modulated proton therapy versus passive scattering proton therapy for NSCLC. *J Thorac Oncol*. 2021;16:269-277.