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ORIGINAL ARTICLE

Acute hospitalizations after proton therapy versus intensity-modulated radiotherapy for locally advanced non–small cell lung cancer in the durvalumab era

Michelle Iocolano MD[1] | Nikhil Yegya-Raman MD[1] | Cole Friedes MD[1] | Xingmei Wang MS[2] | Timothy Kegelman MD, PhD[3] | Sang Ho Lee PhD[4] | Lian Duan MS[4,5] | Bolin Li BS[4] | William P. Levin MD[1] | Keith A. Cengel MD PhD[1] | Andre Konski MD[1,6] | Corey J. Langer MD[7] | Roger B. Cohen MD[7] | Lova Sun MD[7] | Charu Aggarwal MD[7] | Abigail Doucette MPH[8] | Ying Xiao PhD[4] | Boon-Keng Kevin Teo PhD[4] | Shannon O'Reilly PhD[4] | Wei Zou PhD[4] | Jeffrey D. Bradley MD[1] | Charles B. Simone II MD[9] | Steven J. Feigenberg MD[1]

[1]Department of Radiation Oncology, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania, USA

[2]Department of Biostatistics and Epidemiology, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania, USA

[3]Department of Radiation Oncology, Delaware Radiation Oncology Associates, Christiana Care Health Systems, Newark, Delaware, USA

[4]Department of Radiation Oncology, Division of Physics, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania, USA

[5]Department of Radiation Physics, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

[6]Leonard Davis Institute of Health Economics, University of Pennsylvania, Philadelphia, Pennsylvania, USA

[7]Division of Hematology/Oncology University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania, USA

[8]Abramson Cancer Center, University of Pennsylvania, Philadelphia, Pennsylvania, USA

[9]New York Proton Center, New York, New York, USA

Correspondence
Michelle Iocolano, Department of Radiation Oncology, Perelman Center for Advanced Medicine, 2-West 3400 Civic Center Boulevard, Philadelphia, PA 19104, USA.
Email: Michelle.Iocolano@pennmedicine.upenn.edu

Abstract

Introduction: It was hypothesized that use of proton beam therapy (PBT) in patients with locally advanced non–small cell lung cancer treated with concurrent chemoradiation and consolidative immune checkpoint inhibition is associated with fewer unplanned hospitalizations compared with intensity-modulated radiotherapy (IMRT).

Methods: Patients with locally advanced non–small cell lung cancer treated between October 2017 and December 2021 with concurrent chemoradiation with either IMRT or PBT ± consolidative immune checkpoint inhibition were retrospectively identified. Logistic regression was used to assess the association of radiation therapy technique with 90-day hospitalization and grade 3 (G3+) lymphopenia. Competing risk regression was used to compare G3+ pneumonitis, G3+ esophagitis, and G3+ cardiac events. Kaplan–Meier method was used for progression-free survival and overall survival. Inverse probability treatment weighting was applied to adjust for differences in PBT and IMRT groups.

Results: Of 316 patients, 117 (37%) received PBT and 199 (63%) received IMRT. The PBT group was older ($p < .001$) and had higher Charlson Comorbidity Index scores ($p = .02$). The PBT group received a lower mean heart dose ($p < .0001$), left anterior descending artery V15 Gy ($p = .001$), mean lung dose ($p = .008$), and effective dose to immune circulating cells ($p < .001$). On inverse probability treatment weighting analysis, PBT was associated with fewer unplanned hospitalizations (adjusted odds ratio, 0.55; 95% CI, 0.38–0.81; $p = .002$) and less G3+ lymphopenia (adjusted odds ratio, 0.55; 95% CI, 0.37–0.81; $p = .003$). There was no difference in other G3+ toxicities, progression-free survival, or overall survival.

Conclusions: PBT is associated with fewer unplanned hospitalizations, lower effective dose to immune circulating cells and less G3+ lymphopenia compared with

IMRT. Minimizing dose to lymphocytes may be warranted, but prospective data are needed.

KEYWORDS
carcinoma, hospitalization, intensity-modulated, lung neoplasms, lymphopenia, non-small cell lung, proton therapy, radiotherapy

INTRODUCTION

The addition of consolidative immune checkpoint inhibition (ICI) to concurrent chemoradiation (cCRT) for unresectable locally advanced non–small cell lung cancer (LA-NSCLC) in the PACIFIC trial demonstrated a significant improvement in both progression-free and overall survival (OS).[1] Treatment-related toxicities, however, remain a concern because patients may be precluded from receipt of ICI consolidation and, as a result, experience poorer cancer outcomes. Intensity-modulated radiation therapy (IMRT) was previously shown to decrease heart dose and rates of radiation pneumonitis compared with three-dimensional conformal radiotherapy, but the ability to deliver high-dose radiotherapy (RT) to the tumor is often limited by the tolerances of surrounding organs at risk.[2]

Proton beam therapy (PBT) has the potential to improve the therapeutic ratio and minimize toxicity given its ability to limit RT dose beyond the target. Early, randomized data comparing first-generation proton therapy PBT to IMRT in LA-NSCLC did not show a difference in toxicity or cancer outcomes, but only grade 3 (G3+) pneumonitis and local failure were evaluated as primary end points.[3] Studies using more conformal proton techniques, such as pencil beam scanning, suggest modern PBT may reduce toxicity with comparable tumor control and survival outcomes.[4–6] Moreover, treatment-related toxicity may manifest in other ways. For instance, our institution previously reported lower 90-day unplanned hospitalizations in patients treated with PBT compared with IMRT with concurrent chemotherapy across several solid tumor types.[7]

Thus, we performed a retrospective analysis to determine the association of PBT with unplanned hospitalizations in a modern cohort of patients with LA-NSCLC who received cCRT in the era of ICI consolidation. We hypothesized that PBT would reduce unplanned treatment-related hospitalizations compared with IMRT. Secondary objectives evaluated the association of PBT with G3+ pneumonitis, G3+ esophagitis, G3+ cardiac events, G3+ lymphopenia, progression-free survival (PFS), and OS.

MATERIALS AND METHODS

Patient population and treatment

We performed a retrospective review of consecutive patients with unresectable, LA-NSCLC treated with definitive cCRT from October 2017 (the start of the consolidation ICI era) to December 2021 in the University of Pennsylvania Health System, including six network sites. Patients were divided into a PBT cohort and IMRT cohort based on RT modality received. Mixed modality radiation plans were included in the PBT cohort if at least 50% of the plan included protons. Proton plans that used both double scattering and pencil beam scanning techniques were included. Patients who received less than 60 Gy, neoadjuvant/adjuvant RT without concurrent chemotherapy or thoracic reirradiation were excluded from the analysis.

Patients were treated per standardized institutional protocol using the same treatment planning system. Radiation to 60 to 70 Gy was delivered in 1.8- to 2.0-Gy fractions concurrently with platinum-based chemotherapy per physician preference. Patients underwent four-dimensional computed tomography simulation, and a pretreatment positron emission tomography and computed tomography scan was fused. The primary tumor and involved lymph node stations were included in the gross tumor volume (GTV). The GTV was expanded to an internal GTV to account for respiratory motion. The internal GTV was expanded (5–8 mm) to an internal target volume to account for microscopic disease. A planning target volume (PTV) was created based on a 5-mm isotropic expansion of the internal target volume. For proton therapy planning, proximal and distal margins (3.5% of the water-equivalent path) were added in addition to lateral margins to account for range uncertainties along the beam direction. Single field optimization planning was used. All proton doses included a generic factor for a mean relative biological effectiveness of 1.1. Adaptive replanning was not standard for either photon or proton therapy.

Dose constraints included mean lung dose (MLD) < 20 Gy, lung V20 Gy < 35%, lung V5 Gy < 75%, mean heart dose (MHD) < 20 Gy, heart V50 < 25%, mean esophagus dose <34 Gy, and esophagus V60 Gy < 17%. Radiation plans underwent peer review weekly at the main clinical site. Candidacy for consolidative ICI was determined per physician preference starting 4 to 6 weeks after completion of cCRT. Institutional review board approval was obtained before patient medical record review and data extraction.

Variables and end points

Demographic, clinical, treatment, and dosimetric variables were extracted from the electronic medical record, ARIA radiation oncology information and treatment planning systems (Varian Medical Systems, Palo Alto, CA). The University of Pennsylvania's oncology research and quality improvement datamart was used to automatically extract variables. The effective radiation dose to

immune cells (EDIC), a model of the incidental radiation dose to the immune system as a function of the MHD, MLD, integral total dose volume, and number of treatment fractions, was calculated.[8] All variables underwent physician review and were corrected as needed. Medical charts were manually reviewed by two physicians independently to determine if an unplanned inpatient hospital admission occurred within 90 days from the date of the first RT fraction. The frequency of hospitalizations within 90 days of treatment based on radiation modality for solid tumors was previously described.[7]

Reasons for inpatient admission were documented and grouped into the following categories based on physician review: (1) disease progression (as determined by documentation from the treating physician, radiographic findings, and/or pathologic confirmation), (2) toxicity definitely or probably related to chemoradiation (clinical sequelae including pneumonitis, esophagitis, neutropenia, nausea, vomiting, dehydration, failure to thrive, or new cardiac complication), (3) toxicity possibly related to chemoradiation (including infection in the absence of neutropenia, chronic obstructive pulmonary disease [COPD] exacerbation, or interstitial lung disease flare), or (4) comorbidities unrelated or unlikely related to cCRT. If there were multiple reasons for inpatient admission or if there were multiple admissions within 90 days of first RT fraction, episodes definitely, probably, or possibly related to cCRT were prioritized.

Baseline absolute lymphocyte count (ALC) was measured as the average of all available ALC data from 30 days before the start of RT to 1 week after RT start. The ALC nadir was chosen as the lowest recorded value from RT start to 1 month after the last RT fraction. Pneumonitis, cardiac events, esophagitis, and lymphopenia were graded using the Common Terminology Criteria for Adverse Events v5.0.[9]

Statistical analysis

Baseline characteristics between the PBT and IMRT groups were compared using the Chi-square test and two-sample *t* test. Logistic regression was used to assess associations with unplanned 90-day hospitalization and G3+ lymphopenia. The following variables were included in the analysis: age, sex, Eastern Cooperative Oncology Group performance status, Charlson Comorbidity Index (CCI), coronary artery disease, congestive heart failure, peripheral vascular disease, cerebrovascular accident, coronary heart disease (a Boolean of coronary artery disease, congestive heart failure, peripheral vascular disease, and cerebrovascular accident), atrial fibrillation/flutter, COPD, diabetes, hypertension, hyperlipidemia, smoking pack-years, T stage, N stage, clinical stage, tumor histology, tumor location, concurrent chemotherapy agent received, RT modality, GTV, and PTV. CCI excluded LA-NSCLC diagnosis. Factors significantly associated with hospitalization or G3+ lymphopenia ($p < .05$) on univariable analysis or those felt to be clinically relevant were included on multivariable analysis.

A propensity score matched analysis was used in an effort to control for confounding and reduce bias. Propensity scores were computed using logistic regression to account for PBT and IMRT treatment selection. Baseline covariates used in this model included age, race, CCI, COPD, Eastern Cooperative Oncology Group performance status, smoking pack-years, T stage, N stage, GTV, concurrent chemotherapy agent, and tumor histology. Standard mean differences between the PBT and IMRT groups were evaluated to assess balance in covariates after propensity weighting (Figure S1). Stabilized weights were created using the inverse probability of treatment weighting (IPTW) method. The weights were then used in a multivariable regression as an estimation of the average treatment effect. This method is a doubly robust approach that requires the correct specification of either the propensity or outcome model, but not both.[10]

The cumulative incidence method was used to estimate G3+ pneumonitis, G3+ esophagitis, and G3+ cardiac events with death as a competing risk. Groups were compared using the Gray's test. The Kaplan–Meier method was used to estimate PFS and OS. Time to event data were calculated from the date of first RT fraction. The log-rank test was used to compare PFS and OS between groups. For all statistical tests, a two-sided $p < .05$ was considered significant. All analyses were conducted in SAS (SAS Institute, Cary, NC) and STATA (StataCorp, College Station, TX).

RESULTS

A total of 316 consecutive patients were included in the analysis (Figure S2): 117 (37%) received PBT and 199 (63%) received IMRT (Table 1). Patient selection for PBT was determined primarily by insurance status. Of the PBT group, 74 (63.2%) patients were treated with pencil beam scanning. The median age was 68.5 years (interquartile range, 62.8–74.3). The PBT group was older (median 71.1 vs 67.2 years, $p < .001$), had higher CCI (median 4 vs 3, $p = .02$), and were more likely to have a programmed death-ligand 1 tumor proportion score $\geq$1% (55.6 vs 43.2% patients, $p = .03$). Of the entire cohort, 67.7% of patients received ICI consolidation. There were no significant differences in other baseline, tumor characteristics, consolidative ICI receipt, or length of ICI receipt among patient cohorts.

The median RT dose delivered was 66.6 Gy (interquartile range, 65.9–70.0). The PBT group received a slightly higher total dose (median 66.7 vs 66.0 Gy, $p = .003$) but lower MHD (5.9 vs 10.8 Gy, $p < .0001$), mean dose to the left ventricle (0.3 vs 3.2 Gy, $p = .003$), left anterior descending artery V15 (0 vs 6.1% $p = .001$), MLD (14.7 vs 15.7 Gy, $p = .008$), lung V5 Gy (35.9 vs 57.9%, $p < .0001$), mean dose to ascending aorta (21.5 vs 34.0 Gy, $p < .0001$), mean dose to descending aorta (14.8 vs 19.0 Gy, $p = .043$) and EDIC (median 3.8 vs 5.0 Gy, $p < .0001$). The PBT group, however, had a higher esophagus V50 Gy (24.0% vs 15.4% $p = .002$) without a difference in mean esophagus dose (20.9 vs 20.5 Gy, $p = .93$).

In the entire cohort, 98 patients (31%) had an unplanned hospitalization within 90 days of RT start, of which 29 (29.6%) were in the PBT group and 69 (70.4%) in the IMRT group. The unplanned hospitalization rate was higher in the IMRT cohort: 69/199 (34.7%)

TABLE 1 Baseline characteristics.

Characteristic	All patients (n = 316) No. (%)	PBT (n = 117) No. (%)	IMRT (n = 199) No. (%)	p
Age, years (median, IQR)	68.5 (62.8–74.3)	71.1 (65.9–75.0)	67.2 (61.0–73.1)	<.001
Sex				.30
Male	147 (46.5)	50 (42.7)	97 (48.7)	
Female	169 (53.5)	67 (57.3)	102 (51.3)	
Race				.32
Caucasian	236 (74.7)	93 (79.5)	143 (71.9)	
Black/African American	60 (19.0)	18 (15.4)	42 (21.1)	
Other/unknown	20 (6.3)	6 (5.1)	14 (7.0)	
CCI (median, IQR)	3.0 (2.0–5.0)	4.0 (3.0–5.0)	3.0 (2.0–5.0)	.02
BMI (median, IQR)	27.2 (24.0–31.0)	27.5 (24.4–31.3)	26.9 (23.8–30.9)	.48
HTN	205 (64.9)	77 (65.8)	128 (64.3)	.79
HLD	154 (48.7)	59 (50.4)	95 (47.7)	.64
Diabetes	65 (20.6)	28 (23.9)	37 (18.6)	.26
COPD	134 (42.4)	42 (35.9)	92 (46.2)	.07
CVA	30 (9.5)	12 (10.3)	18 (9.0)	.72
CAD	93 (29.4)	35 (29.9)	58 (29.1)	.88
Atrial fibrillation/flutter	49 (15.5)	19 (16.2)	30 (15.1)	.78
CHF	32 (10.1)	15 (12.8)	17 (8.5)	.22
CHD[a]	130 (41.1)	51 (43.6)	79 (39.7)	.50
PVD	67 (21.2)	29 (24.8)	38 (19.1)	.23
ECOG PS				.83
0	108 (34.2)	42 (35.9)	66 (33.2)	
1	175 (55.4)	64 (54.7)	111 (55.8)	
2	33 (10.4)	11 (9.4)	22 (11.1)	
Smoking status				.18
Former	239 (75.6)	92 (78.6)	147 (73.9)	
Current	47 (14.9)	12 (10.3)	35 (17.6)	
Never	30 (9.5)	13 (11.1)	17 (8.5)	
Smoking pack-years (median IQR)	37.3 (17.0–50.0)	30 (15.0–50.0)	40 (17.5–53.0)	.21
Histology				.13
Adenocarcinoma	161 (50.9)	60 (51.3)	101 (50.8)	
Squamous	129 (40.8)	52 (44.4)	77 (38.7)	
Other	26 (8.2)	5 (4.3)	21 (10.6)	
Primary site				.79
Upper lobe	195 (61.7)	68 (58.1)	127 (63.8)	
Middle lobe	18 (5.7)	7 (6.0)	11 (5.5)	
Lower lobe	89 (28.2)	36 (30.8)	53 (26.6)	
Mediastinum	14 (4.4)	6 (5.1)	8 (4.0)	
Left sided	109 (34.5)	41 (35.0)	68 (34.2)	.87

TABLE 1 (Continued)

Characteristic	All patients (n = 316) No. (%)	PBT (n = 117) No. (%)	IMRT (n = 199) No. (%)	p
T stage				.31
T1	104 (32.9)	41 (35.0)	63 (31.7)	
T2	57 (18.0)	26 (22.2)	31 (15.6)	
T3	63 (19.9)	20 (17.1)	43 (21.6)	
T4	92 (29.1)	30 (25.6)	62 (31.2)	
N stage				.09
N1	54 (17.1)	15 (12.8)	39 (19.6)	
N2	189 (59.8)	79 (67.5)	110 (55.3)	
N3	73 (23.1)	23 (19.7)	50 (25.1)	
Clinical stage (AJCC 8th)				.29
II	18 (5.7)	5 (4.3)	13 (6.5)	
IIIA	145 (45.9)	59 (50.4)	86 (43.2)	
IIIB	121 (38.3)	44 (37.6)	77 (38.7)	
IIIC	32 (10.1)	9 (7.7)	23 (11.6)	
PDL1				.03
<1%	109 (34.5)	39 (33.3)	70 (35.2)	
≥1%	151 (47.8)	65 (55.6)	86 (43.2)	
Unknown	56 (17.7)	13 (11.1)	43 (21.6)	
Radiation dose, Gy (median, IQR)	66.6 (65.9–70.0)	66.7 (66.0–70.0)	66.0 (63.0–70.0)	.003
Concurrent chemotherapy				.06
Carboplatin/etoposide	3 (0.9)	1 (0.9)	2 (1.0)	
Carboplatin/paclitaxel	235 (74.4)	98 (83.8)	137 (68.8)	
Carboplatin/pemetrexed	25 (7.9)	8 (6.8)	17 (8.5)	
Cisplatin	2 (0.6)	0 (0.0)	2 (1.0)	
Cisplatin/etoposide	35 (11.1)	8 (6.8)	27 (13.6)	
Cisplatin/pemetrexed	16 (5.1)	2 (1.7)	14 (7.0)	
Consolidation ICI receipt	214 (67.7)	78 (66.7)	136 (68.3)	.76
Consolidation ICI, weeks (median, IQR)	35.0 (12.0–50.0)	32 (14.0–48.0)	38 (12.0–50.0)	.96
GTV, mL (median, IQR)	111 (52.2–218.2)	98.1 (49.4–219.7)	121.3 (55.5–210.2)	.51
Mean lung dose, Gy (median, IQR)	15.4 (12.3–17.9)	14.7 (12.1–17.0)	15.7 (12.5–18.1)	.008
Lung V5, % (median, IQR)	46.3 (36.0–60.9)	35.9 (28.3–40.8)	57.9 (46.3–66.9)	<.0001
Lung V20, % (median, IQR)	26.8 (21.4–31.4)	26.5 (20.4–30.9)	27.2 (21.6–31.8)	.23
Mean heart dose, Gy (median, IQR)	8.7 (4.8–14.1)	5.9 (3.4–9.5)	10.8 (6.1–17.0)	<.0001
LAD V15, % (median, IQR)	2.0 (0.0–22.1)	0.0 (0.0–13.1)	6.1 (0.0–27.4)	.001
Mean left ventricle dose, Gy (median, IQR)	2.3 (0.5–6.5)	0.3 (0.0–3.2)	3.2 (1.7–7.1)	.003
Mean ascending aorta dose, Gy (median, IQR)	30.8 (20.1–39.5)	21.5 (11.4–31.0)	34.0 (26.4–43.2)	<.0001
Mean descending aorta dose, Gy (median, IQR)	17.8 (8.6–28.0)	14.8 (4.6–27.9)	19.0 (10.2–28.8)	.043

(Continues)

TABLE 1 (Continued)

Characteristic	All patients (n = 316) No. (%)	PBT (n = 117) No. (%)	IMRT (n = 199) No. (%)	p
Mean esophagus dose, Gy (median, IQR)	20.6 (13.4–27.0)	20.9 (12.5–28.1)	20.5 (13.9–25.9)	.93
Esophagus V50, % (median, IQR)	17.2 (5.5–30.8)	24.0 (8.4–35.0)	15.4 (3.9–26.1)	.002
EDIC (median, IQR)	4.5 (3.5–5.6)	3.8 (3.0–4.5)	5.0 (4.0–6.1)	<.0001

Abbreviations: AJCC, American Joint Committee on Cancer; BMI, body mass index; CAD, coronary artery disease; CCI, Charlson Comorbidity Index; CHD, coronary heart disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; ECOG PS, Eastern Cooperative Group Performance Status; EDIC, effective dose to immune circulating cells; GTV, gross tumor volume; HLD, hyperlipidemia; HTN, hypertension; ICI, immune checkpoint inhibitor; IMRT, intensity-modulated radiotherapy; IQR, interquartile range; LAD, left anterior descending artery; PBT, proton beam therapy; PDL1, programmed death-ligand 1; PVD, peripheral vascular disease; Vx, volume of organ receiving > X Gy.

[a]CHD is a Boolean of CAD, CHF, PVD, and CVA.

versus 29/117 (24.8%) in the PBT cohort. Reasons for hospitalization in the PBT and IMRT groups included disease progression (1.7% vs 1.5%), definitely or probably related to cCRT (12.0% vs 18.6%), toxicity possibly related to cCRT (7.7% vs 12.6%), or toxicity unrelated or likely unrelated to cCRT (3.4% vs 2.0%), respectively (Figure 1). IPTW-adjusted multivariable analysis showed proton therapy was associated with fewer 90-day unplanned hospitalizations compared with photon therapy (adjusted odds ratio [aOR], 0.55; 95% CI, 0.38–0.81; p = .002) (Table 2). Other variables associated with a higher likelihood of 90-day hospitalization included increased smoking rates in pack-years (aOR, 1.01; 95% CI, 1.00–1.02; p < .01), higher CCI (aOR, 1.29; 95% CI, 1.14–1.47; p < .0001) and larger GTV per 10 mL (aOR, 1.00; 95% CI, 1.00–1.01; p < .0001). Details regarding each hospitalization are shown in Table S1.

IPTW-adjusted multivariable analysis also showed that proton therapy (aOR, 0.55; 95% CI, 0.37–0.81; p = .003) was associated with less G3+ lymphopenia, whereas higher nodal stage (aOR, 2.43; 95% CI, 1.34–4.41; p = .004) and larger GTV per 10 mL (aOR, 1.00; 95% CI, 1.00–1.01; p = .0001) were associated with G3+ lymphopenia (Table 3). There was no difference between PBT or IMRT cohorts in the 1-year incidence of G3+ pneumonitis (1-year 6.0% vs 9.1%, p = .49), G3+ esophagitis (1-year 6.0% vs 6.5%, p = .71), G3+ cardiac events (1-year 15.4% vs 15.1%, p = .71), PFS (median 14.4 vs 15.1 months, p = .69), or OS (median 34.2 vs 29.4 months, p = .31) (Figures 2 and 3).

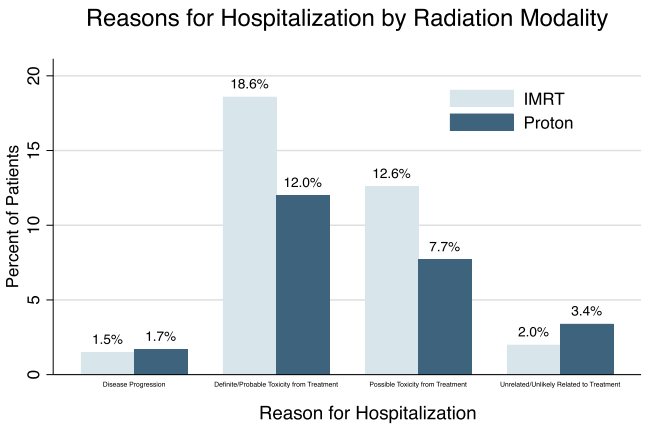

FIGURE 1 Bar chart representing the percentage of patients hospitalized in proton and IMRT cohorts based on hospitalization reason. Percentages were calculated based on the number of patients hospitalized for a given reason divided by the total number of patients in the specific RT modality cohort. IMRT indicates intensity-modulate radiation therapy; RT, radiotherapy.

DISCUSSION

Among a contemporary cohort of 316 patients with LA-NSCLC who received cCRT with or without consolidative ICI, we demonstrated that use of PBT was associated with fewer 90-day unplanned hospitalizations compared with IMRT. Additionally, treatment with PBT was associated with lower EDIC and less G3+ lymphopenia. There were no significant differences in G3+ pneumonitis, G3+ esophagitis, G3+ cardiac events, PFS, or OS. These findings are consistent with prior work from our group showing an association of PBT with lower EDIC and less G3+ lymphopenia, but not G3+ cardiac events, in a modern cohort of patients.[11,12]

Our main finding is consistent with previous institutional series that showed a reduction in unplanned hospitalizations among patients with solid tumors treated with PBT and concurrent chemotherapy. Similar to our study, 90-day hospitalizations were lower in the PBT cohort, despite this group having an older median age and higher CCI.[7] Our results demonstrated, however, that a higher percentage of PBT patients had an unplanned hospitalization compared with Baumann et al. (29.6% vs 11.5%, respectively), which may be indicative of greater treatment-induced morbidity in LA-NSCLC compared with other cancer types. To our knowledge, this study is the first to show PBT is associated with fewer unplanned treatment hospitalizations specifically among patients with LA-NSCLC treated with cCRT in the era of ICI consolidation.

The current evidence supporting the use of PBT in LA-NSCLC remains inconclusive. A randomized phase 2 trial demonstrated lower heart dose, but no difference in G3+ radiation pneumonitis or local control between IMRT and PBT using a double scattering technique. The trial, however, randomized patients only if the IMRT and PBT plans met the same prespecified organ at risk constraints,

TABLE 2 Inverse probability of treatment weighting-adjusted logistic regression for 90-day unplanned hospitalizations.

	Univariable		Multivariable	
Variable	**aOR (95% CI)**	***p***	**aOR (95% CI)**	***p***
Protons	0.58 (0.41–0.83)	.003	0.55 (0.38–0.81)	.002
Age	1.04 (1.02–1.06)	<.001	1.01 (0.99–1.04)	.39
Male	1.25 (0.88–1.76)	.21		
CCI	1.30 (1.19–1.43)	<.0001	1.29 (1.14–1.47)	<.0001
BMI	0.99 (0.96–1.02)	.38		
HTN	1.08 (0.75–1.55)	.68		
HLD	1.23 (0.87–1.74)	.24		
Diabetes[a]	2.05 (1.36–3.08)	<.001		
COPD[a]	1.88 (1.33–2.67)	<.001		
CVA	1.02 (0.58–1.80)	.95		
CAD	1.36 (0.94–1.99)	.11		
Atrial fibrillation/flutter	1.36 (0.86–-2.17)	.19		
CHF	1.50 (0.90–2.50)	.12		
CHD[b]	1.25 (0.88–1.76)	.22		
PVD	1.47 (0.98–2.22)	.06		
ECOG PS (vs 0)				
1	1.63 (1.10–2.42)	.02	0.97 (0.62–1.52)	.90
2	1.90 (1.05–3.42)	.03	0.72 (0.34–1.52)	.39
Smoking pack-years	1.01 (1.01–1.02)	<.0001	1.01 (1.00–1.02)	<.01
Squamous histology	1.16 (0.81–1.67)	.41		
Left-sided tumor	1.11 (0.77–1.58)	.58		
T stage	1.25 (0.87–1.82)	.23	0.85 (0.54–1.35)	.49
N stage	0.94 (0.62–1.43)	.78		
Carboplatin/paclitaxel (vs other)	1.51 (0.99–2.30)	.05		
Clinical stage	1.11 (0.78–1.56)	.57		
GTV (per 10 mL)	1.00 (1.00)	<.0001	1.00 (1.00–1.01)	<.0001

Abbreviations: aOR, adjusted odds ratio; BMI, body mass index; CAD, coronary artery disease; CCI, Charlson Comorbidity Index; CHD, coronary heart disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; ECOG PS, Eastern Cooperative Group performance status; GTV, gross tumor volume; HLD, hyperlipidemia; HTN, hypertension; PVD, peripheral vascular disease.

[a]Diabetes and COPD were not included in the multivariable model because these variables are included in the CCI and are colinear.

[b]CHD is a Boolean of CAD, CHF, PVD, and CVA.

which may bias to the null.[3] Retrospective studies using modern techniques showed that PBT was associated with a reduction in both G3+ cardiopulmonary toxicity and severe lymphopenia, suggesting that mitigation of integral dose could still be of benefit in this patient population.[4,5,13] Although our study did not show a difference in G3+ cardiopulmonary toxicity or G3+ esophagitis between patient cohorts, PBT was significantly associated with a reduction in G3+ lymphopenia.

Previous research has shown that radiation-induced lymphopenia is associated with inferior cancer outcomes in both LA-NSCLC and other solid tumors.[14–19] In a secondary analysis of RTOG 0617, when the EDIC in circulating blood was modeled as a function of MHD, MLD, integral body dose, and number of fractions, it was found to be an independent risk factor for worse cancer outcomes.[8] These findings suggest that increasing RT dose may impair the antitumor activity of the immune system given the high radiosensitivity of circulating immune cells. Retrospective studies have since demonstrated that EDIC is associated with severe lymphopenia in other cancer types.[20–22] Our study demonstrates that proton therapy is associated with both lower EDIC and less G3+ lymphopenia compared with IMRT, thus providing a possible mechanism by which proton therapy reduces unplanned acute hospitalizations. This may

TABLE 3 Inverse probability of treatment weighting-adjusted logistic regression for grade 3 lymphopenia.

	Univariable		Multivariable	
Variable	**aOR (95% CI)**	***p***	**aOR (95% CI)**	***p***
Protons	0.53 (0.36–0.79)	<.002	0.55 (0.37–0.81)	.003
Age	1.01 (0.99–1.03)	.35		
Male	1.44 (0.98–2.13)	.06		
CCI	1.04 (0.95–1.15)	.40		
BMI	0.99 (0.97–1.02)	.73		
HTN	0.79 (0.53–1.18)	.25		
HLD	1.12 (0.76–1.63)	.57		
Diabetes	0.90 (0.56–1.43)	.65		
COPD	0.76 (0.52–1.12)	.16		
CVA	1.16 (0.61–2.22)	.65		
CAD	1.15 (0.74–1.76)	.54		
Atrial fibrillation/flutter	1.74 (0.94–3.23)	.08		
CHF	1.23 (0.66–2.28)	.51		
CHD[b]	1.31 (0.89–1.93)	.18		
PVD	1.20 (0.74–1.94)	.46		
ECOG PS (vs 0)				
1	0.76 (0.50–1.16)	.20	0.73 (0.47–1.13)	.16
2	1.54 (0.70–3.39)	.28	1.85 (0.80–4.28)	.15
Smoking pack-years	1.00 (0.99–1.01)	.89	1.00 (1.00–1.01)	.44
Squamous histology	1.33 (0.90–1.98)	.16		
Left-sided tumor	0.97 (0.65–1.44)	.88		
T stage	1.47 (0.94–2.27)	.09	1.13 (0.67–1.89)	.65
N stage	2.70 (1.52–4.76)	<.001	2.43 (1.34–4.41)	.004
Carboplatin/paclitaxel (vs other)	1.15 (0.75–1.77)	.51		
Clinical stage[a]	2.63 (1.72–3.85)	<.0001		
GTV (per 10 mL)	1.00 (1.00–1.01)	<.0001	1.00 (1.00–1.01)	.0001

Abbreviations: aOR, adjusted odds ratio; BMI, body mass index; CAD, coronary artery disease; CCI, Charlson Comorbidity Index; CHD, coronary heart disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; ECOG PS, Eastern Cooperative Group performance status; GTV, gross tumor volume; HLD, hyperlipidemia; HTN, hypertension; PVD, peripheral vascular disease.

[a]Clinical stage was not included in the multivariable model as this is likely colinear with T stage and N stage.

[b]CHD is a Boolean of CAD, CHF, PVD, and CVA.

be more clinically meaningful in ICI era; if protons can better spare the immune system before initiation of consolidation ICI, perhaps outcomes can be further improved by allowing for a better response to and/or synergy with ICI.

There is growing evidence that protons may be effective at reducing severe radiation-induced lymphopenia across a variety of cancers.[23–26] For instance, secondary analysis of a phase 2 randomized trial showed that proton therapy was associated with a reduction in grade 4 lymphopenia for patients with esophageal cancer undergoing cCRT.[27] In LA-NSCLC specifically, retrospective studies have shown that in addition to proton therapy, larger PTV, higher thoracic vertebral body V5 Gy, aorta V5 Gy, and lung V5 Gy were found to be important predictors of severe lymphopenia in those undergoing definitive treatment.[5,28] Our results also demonstrated that larger GTV and higher nodal stage were associated with G3 lymphopenia, suggesting that larger irradiated volumes could lead to a higher degree of lymphocyte depletion. In contrast to our results, other studies also found that severe radiation-induced lymphopenia was associated with inferior survival outcomes.[11] We eagerly await the results of RTOG 1308 (NCT01993810), a randomized phase 3 trial that recently completed enrollment and will provide prospective evidence comparing proton and photon therapy in patients with LA-NSCLC with regard to survival outcomes and lymphopenia.[29]

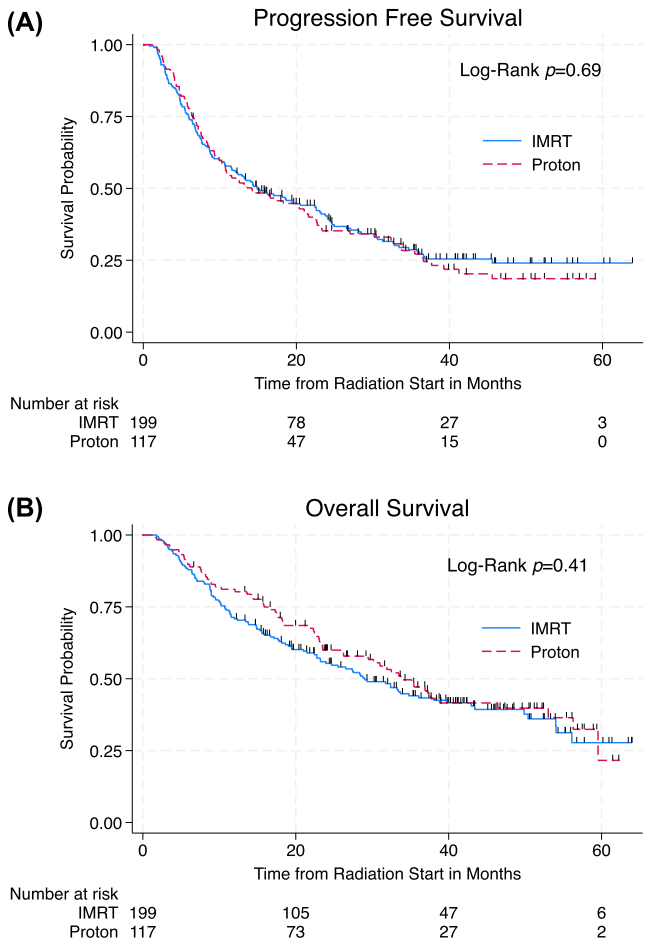

FIGURE 2 Disease outcomes for the entire cohort. (A) Progression-free survival (PFS). (B) Overall survival (OS). Tick marks represent censored events. The *p* value is calculated from the log-rank test for Kaplan–Meier curves.

Our study has several limitations. Confounding by indication remains a concern in this nonrandomized, retrospective comparative cohort study. In an attempt to minimize potential bias, consecutive patients were assessed, and IPTW was used to balance covariates between groups, but this statistical approach may not account for all unmeasured confounders. For example, lack of insurance approval may have precluded some patients from receiving proton therapy; this was not accounted for in our analysis. Additionally, the reasons for hospitalization were identified by nonblinded, manual chart review, which may be subject to observer bias. Nonetheless, our results are consistent with prior institutional work and are supported by a plausible biologic mechanism (i.e., lower EDIC and G3+ lymphopenia).

In conclusion, our study suggests that PBT is associated with fewer unplanned hospitalizations, lower EDIC, and less G3+ lymphopenia. Radiation planning with attention to limiting dose to circulating lymphocytes may be warranted to improve cancer outcomes and decrease adverse events, but randomized data are needed.

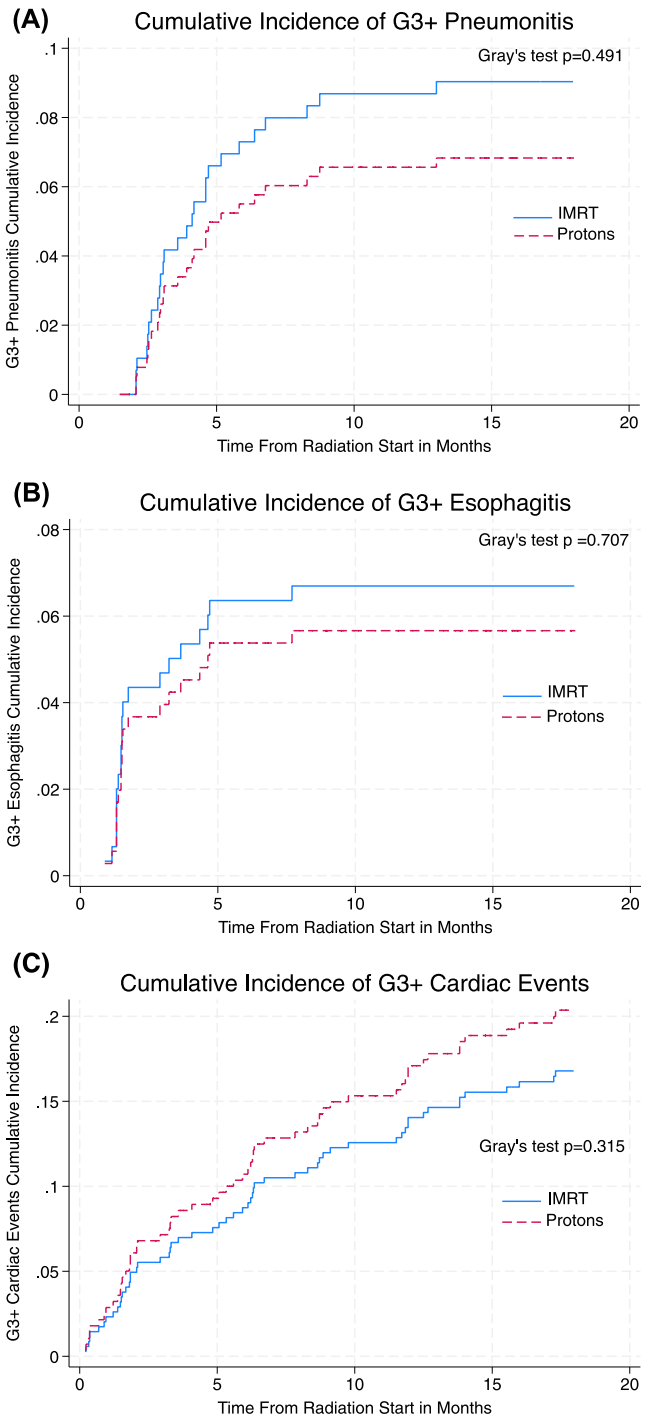

FIGURE 3 Cumulative incidence of select toxicities for the entire cohort. (A) G3+ pneumonitis. (B) G3+ esophagitis. (C) G3+ cardiac events. The *p* value is calculated from the Gray test for competing risk regression with death as a competing risk.

AUTHOR CONTRIBUTIONS

Michelle Iocolano: Conceptualization; data curation; investigation; methodology; project administration; responsible for overall content; validation; visualization; and writing-original draft. **Nikhil Yegya-Raman:** Conceptualization; data curation; investigation; methodology; supervision; visualization; and writing-reviewing & editing. **Cole**

Friedes: Data curation; investigation; methodology; and writing-reviewing & editing. **Xingmei Wang:** Methodology; formal analysis; software; and visualization. **Timothy Kegelman:** Writing-reviewing & editing. **Sang Ho Lee:** Writing-reviewing & editing. **Lian Duan:** Writing-reviewing & editing. **Bolin Li:** Writing-reviewing & editing. **William P. Levin:** Resources and writing-reviewing & editing. **Keith A. Cengel:** Resources and writing-reviewing & editing. **Andre Konski:** Resources and writing-reviewing & editing. **Corey J. Langer:** Resources and writing-reviewing & editing. **Roger B. Cohen:** Resources and writing-reviewing & editing. **Lova Sun:** Resources and writing-reviewing & editing. **Charu Aggarwal:** Resources and writing-reviewing & editing. **Abigail Doucette:** Methodology; software; resources; and writing-reviewing & editing. **Ying Xiao:** Resources and writing-reviewing & editing. **Boon-Keng Kevin Teo:** Resources and writing-reviewing & editing. **Shannon O'Reilly:** Resources and writing-reviewing & editing. **Wei Zou:** Resources and writing-reviewing & editing. **Jeffrey D. Bradley:** Resources and writing-reviewing & editing. **Charles B. Simone II:** Resources and writing-reviewing & editing. **Steven J. Feigenberg:** Conceptualization; funding acquisition; investigation; methodology; project administration; resources; supervision; and writing-reviewing & editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Michelle Iocolano https://orcid.org/0000-0002-6125-0754
Charles B. Simone II https://orcid.org/0000-0002-0867-3694

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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