

Scientific Article

Scanning Beam Proton Therapy versus Photon IMRT for Stage III Lung Cancer: Comparison of Dosimetry, Toxicity, and Outcomes



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Abstract

Purpose: There are limited clinical data on scanning-beam proton therapy (SPT) in treating locally advanced lung cancer, as most published studies have used passive-scatter technology. There is increasing interest in whether the dosimetric advantages of SPT compared with photon therapy can translate into superior clinical outcomes. We present our experience of SPT and photon intensity modulated radiation therapy (IMRT) with clinical dosimetry and outcomes in patients with stage III lung cancer.

Methods and Materials: Patients with stage III lung cancer treated at our center between 2013 and May 2018 were identified in compliance with our institutional review board (64 patients = 34 SPT + 30 IMRT). Most proton patients were treated with pencil beam scanning (28 of 34), and 6 of 34 were treated with uniform scanning. Fisher exact test, χ^2 test, and Mann-Whitney test were used to compare groups. All tests were 2-sided.

Results: Patient characteristics were similar between the IMRT and SPT patients, except for worse lung function in the IMRT group. Mean dose to lung, heart, and esophagus was lower in the SPT group, with most benefit in the low-dose region (lungs, 9.7 Gy vs 15.7 Gy for SPT vs IMRT, respectively [$P = .004$]; heart, 7 Gy vs 14 Gy [$P = .001$]; esophagus, 28.2 Gy vs 30.9 Gy [$P = .023$]). Esophagitis and dermatitis grades were not different between the 2 groups. Grade 2+ pneumonitis was 21% in the SPT group and 40% in the IMRT group ($P = .107$). Changes in blood counts were not different between the 2 groups. Overall survival and progression-free survival were not different between SPT and IMRT (median overall survival, 41.6 vs 30.7 months, respectively [$P = .52$]; median progression-free survival, 19.5 vs 14.6 months [$P = .50$]).

Conclusions: We report our experience with SPT and IMRT in stage III lung cancer. Our cohort of patients treated with SPT had lower doses to normal organs (lungs, heart, esophagus) than our IMRT cohort. There was no statistically significant difference in toxicity rates or survival, although there may have been a trend toward lower rates of pneumonitis.

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Introduction

Lung cancer remains the leading cause of cancer death in the United States, and survival for locally advanced nonsmall cell lung cancer (NSCLC) remains limited at around 30% at 5 years.^{1,2} Efforts to improve outcomes by intensifying radiation treatment for unresectable NSCLC have encountered challenges, as Radiation Therapy Oncology Group 0617 showed that dose escalation to 74 Gy was inferior to 60 Gy.³ Radiation dose to normal organs remains a predictor of morbidity and mortality, with heart dose and esophagitis grade shown to be associated with survival, and lung dose associated with radiation pneumonitis.^{3,4} Although photon intensity modulated radiation therapy (IMRT) has dosimetric advantages over conformal photon radiation, dose to normal tissues continues to cause significant treatment toxicity.^{5,6} Proton beam therapy has been increasing in prevalence in the United States, and possesses different physical characteristics from photon radiation owing to the Bragg peak.⁷ Dosimetry studies have shown that proton beam therapy can improve dose to normal tissues while maintaining tumor dose coverage.^{8,9}

Multiple single-arm studies have been published, with promising results, using proton beam therapy and chemotherapy in locally advanced NSCLC.^{10,11} A National Cancer Database analysis of proton versus photon radiation therapy for NSCLC saw better survival with proton therapy in a retrospective analysis, although survival was not significantly different between proton and IMRT, which comprised 9% of the photon cohort.¹² The enthusiasm for proton therapy led to the conduct of a phase II randomized trial comparing photon IMRT versus conformal passive scattering proton therapy for unresectable NSCLC.¹³ The trial found that for patients who had IMRT and proton plans that could meet prespecified dosimetric constraints, passive scatter proton therapy did not improve mean radiation dose to the lungs and esophagus, and in fact increased lung volume, receiving at least 20 Gy to 80 Gy (V20-80 Gy), while reducing V5-10 Gy. There was also no improvement in the rate of pneumonitis with proton therapy, which may not be unexpected given the mean lung dose was similar between the 2 groups. However, the trial did note the rate of pneumonitis for the proton group declined over time in the trial, and authors theorize that this may be due to a learning curve in proton planning, as replans of earlier patients led to improved dosimetry. Compared with passive scattering proton therapy, newer proton centers typically have scanning beams, and intensity modulated proton therapy with scanning beam technology has dosimetric advantages over passive scattering proton therapy.^{9,14} The rate of pneumonitis in definitive chemoradiation for

lung cancer is especially important in the era of immunotherapy, as adjuvant durvalumab is now standard of care, and immune-mediated pneumonitis is also a treatment-limiting toxicity for patients.¹⁵ Beyond pneumonitis, there has also been clinical data that proton therapy can decrease heart dose compared with IMRT, and decrease lymphopenia, both of which may be associated with improved outcomes.^{13,16}

To address some of these open questions, we present here our institutional experience in patients with locally advanced lung cancer being treated with curative intent radiation therapy. We present real-life dosimetry and clinical outcomes with the newer generation scanning beam proton therapy and photon IMRT/volumetric modulated arc therapy (VMAT). In addition to real-life dosimetric comparisons between scanning-beam proton therapy (SPT) and IMRT, we also assess potential toxicity differences between the 2 patient groups.

Methods and Materials

Patients

Records from patients with stage III lung cancer treated in our department between 2013 and May 2018 were reviewed in an institutional review board–approved study. This period was chosen because our proton center opened in 2013, and therefore a contemporary group of proton and photon patients could be analyzed. Patients were excluded if they received <50 Gy or if they did not receive conventional fractionation (1.8-2.0 Gy fractions). A total of 64 patients were identified, 34 patients treated with SPT and 30 patients treated with IMRT. Of the 34 SPT patients, pencil beam scanning (PBS) was used in 28, and uniform scanning (US) was used in 6 patients. The decision to use protons versus IMRT was based on patient or physician choice and insurance coverage. All photon patients were treated with IMRT or VMAT. Clinical staging was based on the American Joint Committee on Cancer Staging, 8th edition. All patients underwent pretreatment workup including brain magnetic resonance imaging and positron emission tomography/computed tomography (CT).

Radiation treatment procedures

All patients were simulated supine with 4-dimensional CT at 2.5-mm thick slices. Gross target volume (GTV) was primary tumor and involved lymph nodes on CT, positron emission tomography/CT, or biopsy. Clinical target volume was the GTV plus a 0.5 to 1cm margin as appropriate to account for subclinical tumor extension. Internal target volume was generated

on 4-dimensional CT to account for motion, which was limited to <1 cm. Planned target volume (PTV) was a 5-mm expansion from clinical target volume in all directions. Beam-specific PTVs were used for proton plans. Our lung contours excluded the GTV.

Proton therapy was delivered using the Proteus Plus system (Ion Beam Applications, Louvain-la-Neuve, Belgium). Patients were treated with US from 2013 to March 2015 and PBS afterward because our center switched from US to PBS at that time. Treatment planning and delivery have been described previously.¹⁷ Briefly, in US beam delivery, patient-specific brass apertures were created, with wax range compensators for range uncertainty of 2.5% + 2 mm added to the distal and proximal ranges, as well as 1- to 2-cm smearing margins, designed using Xio treatment planning software (Impac Medical Systems, Maryland Heights, MO). For PBS delivery, treatment plans were created using RayStation (RaySearch Laboratories AB, Stockholm, Sweden). Single-field uniform dose optimization was used. Pretreatment quality assurance used ion chambers in water and the MatrixxPT ion chamber array device (IBA Dosimetry GmbH, Schwarzenbruck, Germany). Standard for verification was a gamma pass rate of >90% using acceptance criteria of 3% or 3 mm. To mitigate organ motion with PBS beam delivery (interplay effects), volumetric rescanning was used as needed.¹⁸ This approach has produced satisfactory results in phantom patients used for protocol credentialing at the center (Imaging and Radiation Oncology Core lung phantom). All patients underwent slow CT scans (GE Optima CT580; GE Hangwei Medical Systems, Beijing, China) at a slice thickness of 2.5 mm, revolution time 4 s/slice, 120 kV, for quality assurance and replanning at 15 Gy, 30 Gy, and 45 Gy to ensure target coverage and normal tissue dose were still within tolerance levels. A constant relative biological effectiveness factor of 1.1 was used to convert physical dose to relative biological effectiveness-adjusted dose.

Beginning in 2017, photon-based treatment planning was performed using the Pinnacle (Philips Medical Systems, Madison, WI) treatment planning system and Raystation. Both IMRT and VMAT were used. All plans were calculated on a 2-mm isotropic dose voxel grid, optimized for delivery by a clinically commissioned 6 MV Infinity LINAC with Agility collimator (Elekta, Stockholm, Sweden). VMAT dose was calculated by collapsed cone convolution.¹⁹

Endpoints and statistical analysis

Patients were followed at least every 3 months for the first 2 years and at least every 6 months thereafter. Adverse events were evaluated according to Common Toxicity Criteria (version 4.0). All new respiratory

symptoms posttreatment were classified as radiation pneumonitis, regardless of whether the source of the symptoms was felt to be related to radiation or immune mediated (for patients receiving immunotherapy) and whether fibrosis or effusions were possibly also contributing to the shortness of breath. There were no cases of respiratory symptoms posttreatment that were felt to be exclusively due to effusion or fibrosis without accompanying pneumonitis. Acute toxic effects were defined as occurring within 90 days after last treatment and late toxic effects thereafter. Statistical analysis was performed using Graphpad Prism software version 5.0 and Statistical Package for the Social Sciences 19.0 (SPSS Statistics for Windows; IBM Corp., Armonk, NY). Comparisons between groups were performed using Fisher's exact test, X^2 test, and Mann-Whitney test. Locoregional recurrence was defined as recurrence inside or adjacent to radiation fields at the site of first recurrence (which could present at the same time as distant recurrence). Survival times were calculated from the date of diagnosis and compared with Mantel-Cox. All tests were 2-sided and P values <.05 was considered to be statistically significant.

Results

Patient characteristics

From 2013 through May 2018, 64 patients with stage III lung cancer were treated with definitive dose (>50 Gy) radiation at our institution. Patient characteristics are listed in Table 1. Most baseline characteristics were comparable between the proton and IMRT groups, except the IMRT group had worse forced expiratory volume in 1 second at baseline (only 42 patients had data), and there was a trend toward more photon patients being treated with concurrent chemotherapy. Chemotherapy regimens typically consisted of a platinum doublet, with carboplatin-paclitaxel and cisplatin/etoposide being the most common regimens.

Dosimetry comparison

Dosimetric comparisons between proton versus IMRT patients are summarized in Table 2. All treatment plans were approved for clinical treatment and delivered. Tumor volumes and prescription doses were similar between proton and IMRT patients. Mean lung dose was lower with proton therapy, with most of the advantage in the low-dose region (V5-20 Gy). For lung-PTV, mean dose was 9.70 Gy with proton therapy and 15.77 Gy with IMRT ($P < .001$), with V20 Gy at 18.81% for proton therapy and 27.98% for IMRT ($P < .001$). Esophageal mean dose was also lower with protons, with V5-30 Gy lower with proton therapy

Table 1 Patient characteristics

Characteristic	All, no. (%)	Proton no. (%)	IMRT no. (%)	P
No. of patients	64	34	30	
Sex				
Female	41 (64.1)	21 (61.8)	20 (66.7)	.796
Male	23 (35.9)	13 (38.2)	10 (33.3)	
Median age, years	67 (25-90)	67 (25-85)	66 (35-90)	.463
<65	28 (43.8)	16 (47.1)	12 (40.0)	.620
≥65	36 (56.3)	18 (52.9)	18 (60.0)	
Ethnicity				
White	53 (82.8)	28 (82.4)	25 (83.3)	.989
Black	4 (6.2)	2 (5.9)	2 (6.7)	
Asian	2 (3.1)	1 (2.9)	1 (3.3)	
Others	5 (7.8)	3 (8.8)	2 (6.7)	
ECOG				
0-1	61 (95.3)	32 (94.1)	29 (96.7)	1.000
2	3 (4.7)	2 (5.9)	1 (3.3)	
>2	0	0	0	
Smoking history				
Never	7 (10.9)	6 (17.6)	1 (3.3)	.109
Ever	57 (89.1)	28 (82.4)	29 (96.7)	
Median FEV ₁ , L (range)*	2.2 (0.83-4.2)	2.35 (0.83-4.2)	1.78 (0.96-3.38)	.080
Median FEV ₁ , % predicted (range)*	75.5 (39-149)	84 (44-149)	66 (39-113)	.020
Median DLCO, % predicted (range)†	63 (33-102)	65 (33-102)	62 (35-90)	.344
T stage				
T1	10 (15.6)	4 (11.8)	6 (20)	.913
T2	17 (26.6)	9 (26.5)	8 (26.7)	
T3	14 (21.9)	8 (23.5)	6 (20.0)	
T4	23 (35.9)	13 (38.2)	10 (33.3)	
N stage				
N0	5 (7.8)	3 (8.8)	2 (6.7)	.370
N1	2 (3.1)	0 (0.0)	2 (6.7)	
N2	42 (65.6)	24 (70.6)	18 (60.0)	
N3	15 (23.4)	7 (20.6)	8 (26.7)	
Stage				
IIIA	23 (35.9)	12 (35.3)	11 (36.7)	.824
IIIB	37 (57.8)	19 (55.9)	18 (60.0)	
IIIC	4 (6.3)	3 (8.8)	1 (3.3)	
Tumor histology				
Adenocarcinoma	36 (56.3)	19 (55.9)	17 (56.7)	.740
SCC	21 (32.8)	11 (32.4)	10 (33.3)	
NSCLC unspecified	1 (1.6)	0 (0.0)	1 (3.3)	
Small cell	6 (9.4)	4 (11.8)	2 (6.7)	
Induction chemotherapy				
Yes	15 (23.4)	9 (26.5)	6 (20.0)	.571
No	49 (76.6)	25 (73.5)	24 (80.0)	
Concurrent chemotherapy				
Yes	43 (67.2)	19 (55.9)	24 (80.0)	.061
No	21 (32.8)	15 (44.1)	6 (20.0)	
Adjuvant chemotherapy				
Yes	23 (35.9)	13 (38.2)	10 (33.3)	.796
No	41 (64.1)	21 (61.8)	20 (66.7)	
Any chemotherapy				
Yes	60 (93.8)	31 (91.2)	29 (96.7)	.820
No	4 (6.3)	3 (8.8)	1 (3.3)	
Receiving adjuvant radiation therapy (50-54 Gy)				
Yes	11 (17.2)	7 (20.6)	4 (13.3)	.443
No	53 (82.8)	27 (79.4)	26 (86.7)	

(continued on next page)

Table 1 (continued)

Characteristic	All, no. (%)	Proton no. (%)	IMRT no. (%)	<i>P</i>
Surgery				
Yes	14 (21.9)	9 (26.5)	5 (16.7)	.381
No	50 (78.1)	25 (73.5)	25 (83.3)	
Immunotherapy				
Yes	23 (35.9)	15 (44.1)	8 (26.7)	.197
No	41 (64.1)	19 (55.9)	22 (73.3)	

Abbreviations: DLCO = diffusing capacity of the lung for carbon monoxide; ECOG = Eastern Cooperative Oncology Group; FEV₁ = forced expiratory volume in 1 second; IMRT = intensity modulated radiation therapy; NSCLC = nonsmall cell lung cancer; SCC = squamous cell carcinoma.

* Data available for 42 patients (20 SPT and 22 IMRT).

† Data available for 37 patients (17 SPT and 20 IMRT).

($P < .05$). There was a large reduction in heart dose with proton radiation, with a mean dose of 6.95 Gy with proton therapy and 14.04 Gy with IMRT ($P = .001$). Heart V5-35% were all significantly lower with proton therapy ($P < .05$).

Treatment toxicities

All patients completed the planned course of radiation therapy. Nonhematological toxicities are summarized in Table 3. No significant differences were seen in the rates of esophagitis, dermatitis, weight loss, or pneumonitis, except a trend toward lower pneumonitis with proton therapy (40.0% grade 2+ with IMRT vs 20.6% with protons, $P = .107$). Because adjuvant/postop patients received a lower dose of radiation than the definitive patients (50-54 Gy vs ≥ 60 Gy, respectively), we analyzed the grade 2+ pneumonitis rate in the definitive cohort and saw similar results (42.3% grade 2+ with IMRT vs 18.5% with protons, $P = .077$; Table E1, available online at <https://doi.org/10.1016/j.adro.2020.03.001>).

Changes in blood counts were tracked pre- and post-radiation. Median hemoglobin (Hb), white-blood-cell count (WBC), and neutrophil counts were all within normal limits at baseline pretreatment. Median Hb counts in SPT and IMRT groups were 12.0 and 12.45 g/L, respectively. Median WBC counts in SPT and IMRT groups were 6.97 and 7.63 $\times 10^3/\mu\text{L}$, respectively. Median neutrophil counts in SPT and IMRT groups were 4.62 and 5.61 $\times 10^3/\mu\text{L}$, respectively. Changes in weekly Hb, WBC, and neutrophil counts after starting radiation showed no statistically significant differences between the SPT versus IMRT groups (Fig 1, $P > .2$ for comparison of nadirs between SPT and IMRT).

Locoregional control and survival analysis

Median follow-up was 16.8 months (range, 3.1-63.8 months; 20.2 for IMRT group and 16.1 for

proton group). There was no statistically significant difference in overall survival (OS) and progression-free survival between proton and IMRT patients (Fig 2A,B; median OS, 41.6 months for protons and 30.7 months for IMRT, $P = .52$; median progression-free survival, 19.5 months for protons vs 14.6 months for IMRT, $P = .50$). Locoregional control was also not statistically significantly different between the 2 groups, with locoregional control of 59.7% for the proton group and 44.2% for the IMRT group ($P = .26$; Fig 2C).

Discussion

We present here our institution's experience in advanced SPT for locally advanced lung cancer, with real-life treated dosimetry (as opposed to dosimetric planning studies) and clinical outcomes. We also provide a retrospective comparison with our cohort of contemporary patients treated with photon IMRT/VMAT. For comparable tumor volumes in these 2 patient cohorts, patients treated with SPT had significantly lower mean dose to the heart and lungs, with most of the dosimetric advantage in the low-dose region. Esophageal mean dose was also lower with proton therapy but the magnitude of the difference was smaller than for heart and lungs. Toxicity rates seemed comparable between our proton therapy and IMRT cohorts, although there was a suggestion of lower pneumonitis with proton therapy. Survival and locoregional control were similar between the 2 patient groups.

Our results appear similar to other published proton patient series (see Table 4), such as 2 MD Anderson series with passive scattering proton therapy showing median OS of 26.5 to 30.4 months for patients with stage III NSCLC and another series with intensity modulated proton therapy showing median OS 33.9 months.^{10,20,21} Our grade 2+ pneumonitis rate of 20.6%

Table 2 Dosimetric comparison between SPT and IMRT

Characteristic	All	Proton	IMRT	P
Prescription dose (Gy/CGE)	61.2 (50.4-74.0)	61.2 (50.4-74.0)	61.5 (50.4-66.6)	.820
Median target volumes, cm ³ (range)				
PTV	599.1 (94.10-1639)	607.9 (94.10-1243)	587.6 (135.30-1639)	.845
GTV	156.1 (1.39-647.8)	173.5 (1.39-486.3)	131.5 (28.16-647.8)	.445
CTV	370 (37.49-1202)	382.5 (37.49-729.3)	334.2 (45.81-1202)	.755
Dosimetric comparison between proton and IMRT				
Lung				
Mean dose in Gy (CGE)	15.78 (1.4-24.35)	13.38 (5.11-24.35)	17.89 (1.40-22.69)	.004
V5 (%)	43 (5.21-73.83)	34.19 (18.90-73.83)	58.45 (5.21-72.42)	<.001
V10 (%)	37.28 (3.61-55.77)	29.26 (15.66-51.83)	44.44 (3.61-55.77)	<.001
V20 (%)	28.84 (1.86-42.27)	24.29 (9.99-41.1)	33.39 (1.86-42.27)	<.001
V30 (%)	21.74 (1.30-33.55)	19.99 (4.73-33.55)	24.21 (1.30-32.61)	.127
V40 (%)	17.27 (0-27.96)	17.05 (2.70-27.96)	18.88 (0.98-26.83)	.957
V50 (%)	12.05 (0-23.84)	12.99 (0.80-23.84)	11.43 (0.70-22.19)	.264
V60 (%)	5.84 (0-19.77)	7.30 (0-19.77)	4.52 (0-14.38)	.184
Lung-PTV				
Mean dose in Gy (CGE)	13.09 (1.28-19.77)	9.70 (4.87-17.53)	15.77 (1.28-19.77)	<.001
V5 (%)	39.14 (5.01-70.67)	29.02 (15.55-70.67)	57.53 (5.01-69.34)	<.001
V10 (%)	34.42 (3.41-55.19)	23.58 (13.86-47.19)	41.66 (3.41-55.19)	<.001
V20 (%)	24.69 (1.66-35.55)	18.81 (9.51-35.44)	27.98 (1.66-35.55)	<.001
V30 (%)	18.1 (1.10-27.17)	14.27 (4.22-27.17)	19.69 (1.10-26.82)	.015
V40 (%)	11.8 (0.78-21.72)	10.55 (2.18-21.72)	12.96 (0.78-21.06)	.341
V50 (%)	6.74 (0.09-17.25)	6.98 (0.29-17.25)	6.13 (0.09-13.71)	.400
V60 (%)	1.25 (0-12.48)	1.85 (0-12.48)	1.1 (0-5.96)	.245
Esophagus				
Mean dose in Gy (CGE)	29.76 (10.78-60.43)	28.19 (10.78-54.14)	30.91 (17.67-60.43)	.023
V10 (%)	58.28 (30.39-98.50)	56.1 (30.39-97.06)	64.53 (37.99-98.50)	.007
V20 (%)	52.76 (16.46-95.18)	51.5 (16.46-95.18)	59.54 (34.89-94.10)	.028
V30 (%)	48.80 (13.57-93.49)	45.5 (13.57-93.49)	53.1 (18.5-90.88)	.038
V40 (%)	42.8 (6.48-91.70)	41.92 (6.48-91.70)	45.67 (8.610-88.57)	.223
V50 (%)	34.19 (0-89.30)	32.35 (0-89.30)	36.63 (0.84-85.6)	.423
V55 (%)	27.17 (0-83.44)	26.36 (0-83.39)	30.56 (0-83.44)	.134
V60 (%)	15.26 (0-79.16)	16.52 (0-78.81)	14.6 (0-79.16)	.715
Heart				
Mean dose in Gy (CGE)	11.65 (0-39.51)	6.95 (0-39.51)	14.04 (0-35.43)	.001
V5 (%)	32.16 (0-100.0)	22.12 (0-100)	55.44 (0-98.39)	<.001
V10 (%)	28.32 (0-99.80)	18.87 (0-99.80)	41.9 (0-85.60)	<.001
V20 (%)	19.98 (0-94.63)	14.49 (0-94.63)	26.68 (0-71.33)	.006
V30 (%)	13.2 (0-83.45)	10.86 (0-83.45)	18.06 (0-58.18)	.020
V35 (%)	11.5 (0-71.30)	9.36 (0-71.30)	15.18 (0-51.27)	.043
V40 (%)	9.94 (0-44.89)	7.95 (0-44.89)	13.06 (0-43.39)	.079
V50 (%)	6 (0-36.57)	5.83 (0-26.09)	6.155 (0-36.57)	.312
V60 (%)	1.49 (0-20.91)	1.17 (0-20.36)	1.535 (0-20.91)	.838
Spinal cord				
D0.03cc Gy (CGE)	43.78 (0.63-53.35)	37.54 (0.63-49.96)	45.83 (31.4-53.35)	<.001

Abbreviations: CGE = cobalt Gy equivalent; CTV = clinical target volume; GTV = gross target volume; IMRT = intensity modulated radiation therapy; PTV = planned target volume; RBE = relative biologic effectiveness; SPT = scanning-beam proton therapy.

in our proton cohort appears similar to the rates of 14%, 23.5%, and 28% published in these 3 series. Our grade 3 esophagitis rate was 17.6% in our proton cohort, compared with 4%, 6%, and 12% in these 3 series. One reason for variable toxicity rates from different series may be related to intervention strategies,

as our institution intervenes with intravenous hydration and oral medications for early signs of esophagitis. A comparison of results from select published proton patient series is included in [Table 4](#).²²⁻²⁴

Heart dose has been found to be correlated with survival in some clinical series of locally advanced

Table 3 Nonhematological toxicities comparison between SPT and IMRT

	All	Proton	IMRT	P
Esophagitis				
Grade 0	7 (10.9)	4 (11.8)	3 (10.0)	.600
Grade 1	19 (29.7)	8 (23.5)	11 (36.7)	
Grade 2	29 (45.3)	16 (47.1)	13 (43.3)	
Grade 3	9 (14.1)	6 (17.6)	3 (10)	
Grade 4	0	0	0	
Grade 5	0	0	0	
Grade 0-1	26 (40.6)	12 (35.3)	14 (46.7)	.842
Grade ≥ 2	38 (59.4)	22 (64.7)	16 (53.3)	
Pneumonitis				
Grade 0	4 (6.3)	3 (8.8)	1 (3.3)	.198
Grade 1	41 (64.1)	24 (70.6)	17 (56.7)	
Grade 2	11 (17.2)	3 (8.8)	8 (26.7)	
Grade 3	4 (6.3)	2 (5.9)	2 (6.7)	
Grade 4	2 (3.1)	0/0	2 (6.7)	
Grade 5	2 (3.1)	2 (5.9)	0	
Grade 0-1	45 (70.3)	27 (79.4)	18 (60.0)	.107
Grade ≥ 2	19 (29.7)	7 (20.6)	12 (40.0)	
Acute dermatitis				
Grade 0	4 (6.3)	1 (2.9)	3 (10.0)	.379
Grade 1	38 (59.4)	19 (55.9)	19 (63.3)	
Grade 2	19 (29.7)	13 (38.2)	6 (20.0)	
Grade 3	3 (4.7)	1 (2.9)	2 (6.7)	
Grade 4	0	0	0	
Grade 5	0	0	0	
Grade 0-1	42 (65.6)	20 (58.8)	22 (73.3)	.294
Grade ≥ 2	22 (34.4)	14 (41.2)	8 (26.7)	
Acute weight loss (lbs)				
Grade 0	41 (64.1)	19 (55.9)	22 (73.3)	.139
Grade 1	17 (26.6)	11 (32.4)	6 (20.0)	
Grade 2	5 (7.8)	4 (11.8)	1 (3.3)	
Grade 3	1 (1.6)	0	1 (3.3)	
Grade 4	0	0	0	
Grade 5	0	0	0	
Grade 0-1	58 (90.6)	30 (88.2)	28 (93.3)	.345
Grade ≥ 2	6 (9.4)	4 (11.8)	2 (6.7)	

Abbreviations: IMRT = intensity modulated radiation therapy; SPT = scanning-beam proton therapy.

NSCLC, and more stringent dose constraints have been recommended for the heart in recent years.^{3,6} Our cohort of patients treated with proton therapy had significantly reduced mean heart dose compared with our cohort of patients treated with IMRT or VMAT. However, we did not see a significant difference in survival between proton therapy and IMRT in our patient groups, although the absolute numbers were better in the proton group. We are limited by our small sample size.

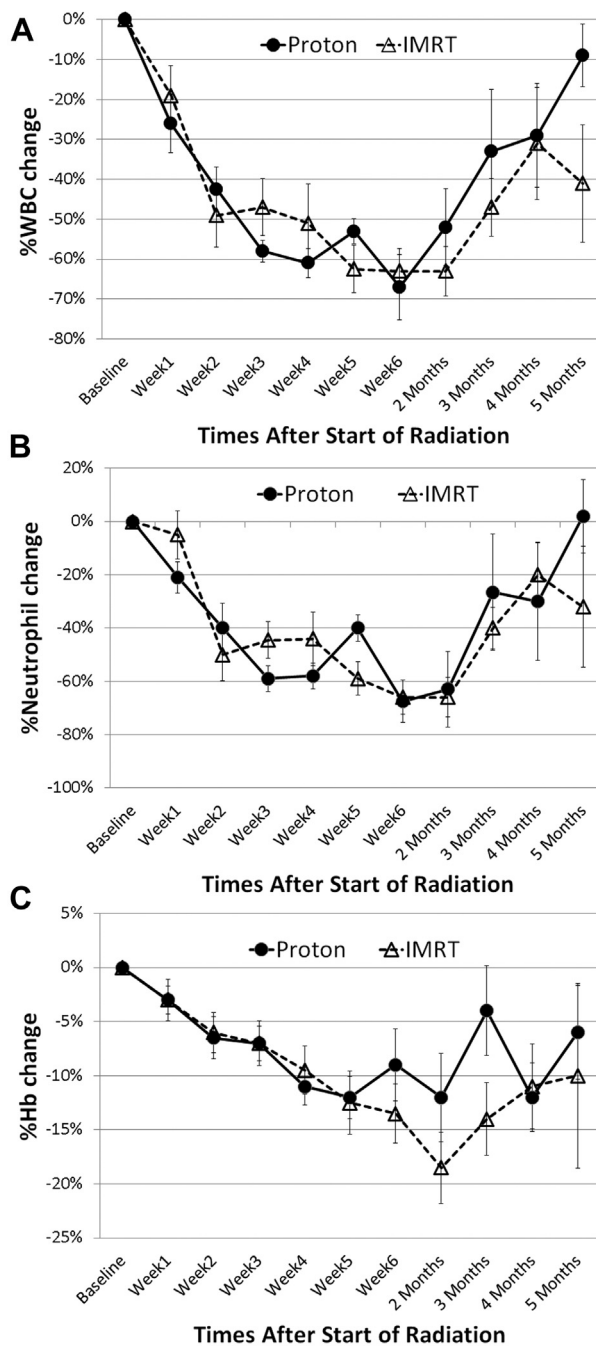


Figure 1 Hematological toxicity comparison of scanning-beam proton therapy (SPT) and intensity modulated radiation therapy (IMRT) treatment using percent changes in blood counts from baseline after the start of radiation therapy. (A) White blood cell count (WBC); (B) neutrophil; (C) hemoglobin. Error bars represent standard error of the mean.

Perhaps related to heart dose, there is also increasing clinical data on the negative effect of lymphopenia on survival, with the suggestion that

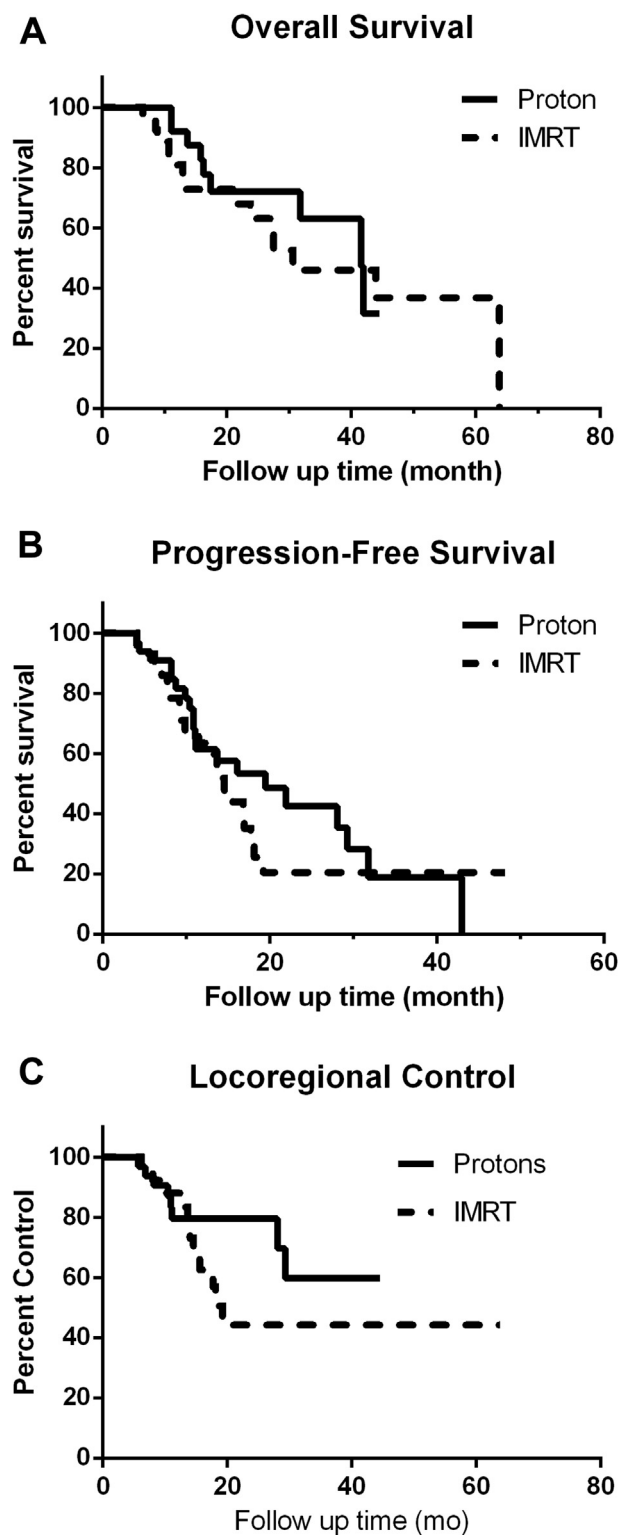


Figure 2 Overall survival (A), progression free survival (B), and locoregional control (C) comparison between scanning-beam proton therapy (SPT) and intensity modulated radiation therapy (IMRT) treatment.

proton therapy may be correlated to less severe lymphopenia compared with photon therapy.^{16,25,26} We do

not have lymphocyte data available for our patients, but changes in total WBC count, neutrophils, and hemoglobin were not different between proton therapy and IMRT in our series. Based on modeling series, even a low dose of radiation to a small portion of the circulation per fraction results in the entire circulation being radiated after 30 fractions.²⁷ Therefore, although proton therapy drastically reduces the heart dose, it may not have an effect on lymphopenia in conventionally fractionated radiation treatment.

Beyond retrospective comparisons such as our series presented here, there are ongoing efforts to generate prospective randomized evidence to evaluate the benefit of proton therapy, such as “Radiation Therapy Oncology Group 1308 (NCT01993810): Comparing Photon Therapy to Proton Therapy to Treat Patients With Lung Cancer.”²⁸ Given the heterogeneity of patients with locally advanced NSCLC, it is unclear whether testing across an unselected treatment population will ever prove the value of a new technology.⁷ Given the clear dosimetric advantage of proton therapy in some clinical scenarios, other methods have been proposed in value-based care, such as using normal tissue complication probability models (NTCP) to select patients most likely to benefit from proton therapy.^{29,30} Typically, a threshold is set for improvement in toxicity based on NTCP modeling, and if a proton treatment plan meets that threshold, patients are recommended to receive proton therapy instead of photon therapy. However, it is not clear which endpoint or combination of endpoints should be used in modeling, and to date, NTCP models are based on photon-treated patients, and it is not clear whether the models will be the same for proton patients.

Implementing any new technology comes with a learning curve, including proton therapy.¹³ There are guidelines for implementing PBS for thoracic tumors, which is an especially challenging region from the technical perspective owing to a mix of factors including motion (both tumor and normal tissues) and tissue heterogeneity.³¹ At our center, we follow the best practice recommendations and limit motion to <10 mm with compression or breath hold as needed.³¹

In conclusion, we showed that for 2 contemporary cohorts of patients with locally advanced lung cancer, the cohort treated with SPT had lower normal tissue doses compared with the IMRT cohort, with most of the dosimetric differences in the low-dose region. There was no statistically significant difference in toxicity rates or survival, although there may have been a trend toward lower rates of pneumonitis. Large patient numbers will be needed to demonstrate whether this dosimetric difference translates into better clinical outcomes.

Table 4 Outcomes comparison between select published proton series on locally advanced NSCLC

Patient no.	Proton technology	Overall survival	Locoregional control	Pneumonitis	Esophagitis
Present study 34	Scanning beam	Median, 41.6 mo	59.7%	Grade 2+, 20.6%; Grade 3+, 11.8%	Grade 2+, 64.7%; Grade 3+, 17.6%
Oshiro et al ²² 57	Passive scatter	Median, 21.3 mo	2-y, 64.1%	Acute grade 2+, 12.3%; Acute grade 3+, 5.3%	Grade 2+, 1.8%; Grade 3+, 0%
Hatayama et al ²³ 27	Passive scatter	2-y, 51.5%	1-y local control, 68.1%; 2-y local control, 36.4%	Grade 2+, 29.6%; Grade 3+, 7.4%	Grade 2+, 22.2%; Grade 3+, 3.7%
Chang et al ²⁰ 64	Passive scatter	Median, 26.5 mo	72%	Grade 2+, 28%; Grade 3+, 12%	Acute grade 2+, 36%; Acute grade 3+, 8%; Late grade 2+, 9%; Late grade 3+, 4%
Liao et al ¹³ 57	Passive scatter	Median, 26.1 mo	1-y local control, 89.5%; 5-y, ~65% (estimated from figure)	1-y grade 3+, 10.5%;	
Elhammali et al ²¹ 51	Intensity modulated proton therapy	Median, 33.9 mo	64.5%	Grade 2+, 15%; Grade 3+, 0%	Grade 2+, 49%; Grade 3+, 6%
Yu et al ²⁴ 33	Intensity modulated proton therapy	1-y, 68%	1-y, 86%	Grade 3, 6.1%	Grade 3, 6.1%

Abbreviation: NSCLC = nonsmall cell lung cancer.

Supplementary data

Supplementary material for this article can be found at <https://doi.org/10.1016/j.adro.2020.03.001>.

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