

Scientific Article

Clinical Outcomes After Proton Beam Therapy for Locally Advanced Non-Small Cell Lung Cancer: Analysis of a Multi-institutional Prospective Registry



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Received February 2, 2021; accepted July 16, 2021

Abstract

Purpose: For most disease sites, level 1 evidence is lacking for proton beam therapy (PBT). By identifying target populations that would benefit most from PBT, prospective registries could overcome many of the challenges in clinical trial enrollment. Herein, we report clinical outcomes of patients treated with PBT for locally advanced non-small cell lung cancer (LA-NSCLC).

Methods and Materials: Data were obtained from the multi-institutional prospective database of the Proton Collaborative Group (PCG). Inclusion criteria of our study were stage III de novo or recurrent LA-NSCLC, use of PBT, and availability of follow-up data. Overall survival (OS) time was calculated from the start of treatment until death or last follow-up. Kaplan-Meier curves were generated for groups of interest and compared with log-rank tests. Cox regression modeling was used to evaluate the multivariate association between selected covariates and OS.

Results: A total of 195 patients were included in the analysis. PBT was given with a median equivalent dose in 2 Gy fractions (EQD2) of 63.8 Gy (relative biological effectiveness). Pencil beam scanning was used in 20% of treatments. Treatment-related grade 3 adverse

Sources of support: The publication fee of the present article was paid by the Proton Collaborative Group.

Disclosures: R.R. reports personal fees (incidental expenses at meetings) from Ion Beam Applications (IBA) and is employed as medical director of the SCCA Proton Center outside the submitted work. L.R. reports honoraria and general stock ownership from IBA outside the submitted work. D.V.G. reports being on the advisory board and receiving honoraria from Sanofi, Accuray, Takeda, Merck-Pfizer, and Novartis outside the submitted work. A. J., F.C., K.B., J.C., W.H., G.L., P.M., L.M., M.R., H.T., and C.V. have nothing to disclose.

Research data are stored in an institutional repository and will be shared upon request to the Proton Collaborative Group.

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<https://doi.org/10.1016/j.adro.2021.100767>

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events were rare: 1 pneumonitis, 2 dermatitis, and 3 esophagitis. No grade 4 events were reported. Two cardiac-related grade 5 events occurred in patients with multiple risk factors. The median follow-up time for living patients was 37.1 months and the median OS was 19.0 months. On multivariate analysis, good performance status (hazard ratio, 0.27; [95% confidence interval, 0.15-0.46]; $P < .0001$), pencil beam scanning use (0.55; [0.31-0.97]; $P = .04$), and increased EQD2 (0.80; [0.71-0.90] - per 10 Gy increase; $P = .0002$) were associated with decreased mortality.

Conclusions: PBT appears to yield low rates of adverse events with an OS similar to other retrospective studies on PBT for LA-NSCLC. PBS use and increased EQD2 can potentially improve OS.

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Introduction

Lung cancer is the most common cause of cancer-related deaths worldwide.¹ Non-small cell lung cancer (NSCLC) is the most prevalent type of lung cancer, responsible for approximately 85% of cases.²

Radiation therapy (RT) is one of the cornerstones in the treatment of NSCLC.³ It is prescribed to approximately 60% of patients with locally advanced disease, often with concurrent platin-based chemotherapy.^{2,4} Most RT treatments are photon-based, but the use of newer techniques such as proton beam therapy (PBT) is increasing.

As PBT gains in accessibility for routine care, it is critical to assess its added value as a cancer treatment modality. Multiple studies have shown that the differences in physical properties of protons and photons result in an increased sparing of organs at risk (OARs).⁵⁻⁹

In 2006, a study comparing dose-volume histograms of passively scattered proton therapy (PSPT) with 3-dimensional conformal RT (3D-CRT) and photon-beam intensity modulated RT (IMRT) highlighted a reduction in the dose to the OARs when using PSPT relative to 3D-CRT and IMRT, even after dose escalation.¹⁰ Similar benefits were observed using intensity modulated proton therapy (IMPT), which has been replacing PSPT over the last years. A study comparing dosimetric data of IMPT with PSPT and IMRT reported a better sparing of OARs with IMPT compared with IMRT in the planning of 10 patients with stage IIIB NSCLC.¹¹ Furthermore, based on dosimetric analysis, IMPT seemed to allow safe dose escalation to a mean maximum tolerated dose of 74 Gy of relative biological effectiveness (RBE), compared with 63 Gy for IMRT, which could lead to an improvement in both local control and overall survival (OS).¹¹

Level 1 evidence in favor of PBT, however, is currently lacking for most cancers. NSCLC is no exception, as only 1 randomized controlled trial (RCT) comparing protons and photons has been performed. This study, published in 2018, compared PSPT with IMRT and showed no significant difference for the primary endpoints: rates of local failure were similar in both groups

(10.9% for IMRT, 10.5% for PSPT), and rates of grade 3 or higher pneumonitis were 6.5% for IMRT and 10.5% for PSPT.³ However, unlike in the IMRT arm, rates of pneumonitis and local failure significantly decreased during the trial in the PSPT arm, going from 31.0% in the first half to 13.1% in the second half of the trial,^{2,3} suggesting a learning curve in the proton treatment. Several criticisms have been made regarding this study and its design, including the PBT technique used (PSPT rather than IMPT) and the high number of randomized patients not receiving treatment (partly due to insurance refusal).^{2,12,13}

Prospective cohort studies recruiting patients treated with PBT could bring insight to guide the design of future randomized studies, helping to identify a subgroup that benefits more from PBT within the treated population. Using the Proton Collaborative Group (PCG) registry, a database gathering information from 16 centers across the United States, this study focused on patients with locally advanced NSCLC (de novo or recurrent stage III) treated with PBT and aimed to present the current clinical outcomes, such as adverse events (AEs) and OS.

Methods and Materials

Data collection

The data used for this research are part of a larger observational study titled “Evaluation Tracking Project: A Prospective Chart Review of Patients Treated With Radiation Therapy” (National Clinical Trial 01255748). The study, led by the PCG, initially included only patients treated solely with PBT in the participating centers, but has since been opened to patients treated with any other radiation modality. All participants provided informed consent. This study was approved after review by the board of directors of the sponsor.

The data set was extracted from the main electronic database on January 25, 2019, containing pseudonymized information on patients, their disease, prior and current treatments, and dosimetric and follow-up data collected until January 6, 2020. Only patients with NSCLC and treated with PBT were included, reaching a total of 444

patients. After exclusion of patients with conflicting diagnosis data ($n = 4$), lack of follow-up data ($n = 92$), and disease other than stage III at inclusion ($n = 153$), 195 patients remained in our study.

Staging was defined according to the American Joint Committee on Cancer tumor, nodes, metastases system. The 7th edition was used for cancers diagnosed until December 31, 2017 ($n = 190$), and was replaced by the 8th edition thereafter ($n = 5$).

Statistical methods

All analyses were performed using SAS Statistical Software (Version 9.4). P values under .05 were considered statistically significant, and all tests were two-sided. No adjustment was done for multiple testing.

Patient demographics and treatment characteristics were described using frequencies and percentages for categorical variables, while means, medians, ranges, and standard deviations (SD) were used for continuous variables.

Treatment doses delivered to target volumes were standardized to an equivalent dose in 2 Gy fractions (EQD2) assuming an α/β ratio of 10.

AEs were tabulated by grade according to the Common Terminology Criteria for Adverse Events v4.0 and entered during treatment and follow-up. Only the maximum grade reported was considered per patient and per event; baseline toxicities were not accounted for. AEs were classified as early (during treatment or <90 days posttreatment) or late (≥ 90 days posttreatment). Centers were contacted if additional information was needed regarding a severe AE.

OS was estimated using the Kaplan-Meier method. Survival time was calculated from the start of treatment until death, and patients last known to be alive were censored at their date of last follow-up. The log-rank test was used to compare Kaplan-Meier curves for groups of interest.

Cox regression modeling was used to measure the association between covariates of interest and overall mortality (failure for OS) using hazard ratios and 95% confidence intervals (CI). Univariate models applied for each variable of interest were used to identify relevant parameters for the multivariate model. A multivariate model was used using parameters that had $P < .1$ in their respective univariate model while also including patients' age at consent.

Results

Demographics

A total of 195 patients were included in the analyses (Table 1). The median age was 70 years (range, 48-93).

The majority of the tumors treated were located in the upper lobes (64%) and were right-sided (55%). The majority of patients had stage IIIA disease (51%), and 28% ($n = 55$) of the patients had recurrent stage III disease. Patients received concurrent chemotherapy in 64% of cases ($n = 125$).

Radiation treatment

Most patients were treated with PBT as the sole RT technique (93%) (Table 2). Reasons for using another treatment modality (most often IMRT) were, among others, PBT as a boost after IMRT or temporary substitution (eg, machine downtime). The median time from diagnosis to treatment was 1.8 months.

Uniform scanning was the most frequent proton modality, used in 80% of patients, whereas 20% of patients received pencil beam scanning (PBS). Sixty-six patients (34%) were treated with two or more treatment plans, often for a boost dose.

The mean proton dose, when it was the only treatment modality, was 61.2 Gy (RBE) (SD, 12.9), or an EQD2 of 61.8 Gy (RBE) (SD, 12.9). Fractions of 2 Gy were used for 71.8% of patients.

Adverse events

Table 3 summarizes the most typical AEs after PBT for LA-NSCLC (esophagitis, pneumonitis, and dermatitis), together with other severe AEs. Six grade 3, no grade 4, and two grade 5 AEs were reported.

Grade 2 or higher acute dermatitis occurred in 42 patients (21.5%), 2 of which (1.0%) were grade 3 events. Grade 2 or higher acute esophagitis affected 57 patients (29.2%), with 3 (1.5%) grade 3 events. Grade 2 late pneumonitis occurred in 4 patients (2.1%), with no grade 3 or higher events. There was also 1 case (0.5%) of grade 3 early pneumonitis.

Regarding the 2 patients (1%) with grade 5 toxicities, neither of them had received prior thoracic radiation. The first patient suffered from a cardiac arrest after 16 of 34 fractions (32 Gy). This patient's tumor invaded into the heart and great vessels. He had considerable cardiac history, including myocardial infarction, and had received concurrent chemotherapy (unknown drugs). The mean heart dose (MHD) was kept at 12.23 Gy (RBE) for the 34 planned fractions.

The second patient died of a myocardial infarction 10 months after the end of his treatment. He had been treated with concurrent cisplatin and etoposide and had multiple cardiovascular risk factors, including diabetes and a history of carotid stenosis. He had received a MHD of 9.31 Gy (RBE).

Table 1 Patient and disease characteristics (n = 195)

Characteristic	n	(%)	Characteristic	n	(%)
Age at consent (years)			Tumor location		
Median	70.0		Left lower lobe	16	(8.2)
Minimum	48.0		Left upper lobe	56	(28.7)
Maximum	93.0		Left lung, other	2	(1.0)
Sex			Main bronchus	10	(5.1)
Female	90	(46.2)	Right lower lobe	23	(11.8)
Male	104	(53.3)	Right middle lobe	7	(3.6)
Undifferentiated	1	(0.5)	Right upper lobe	68	(34.9)
Race			Right lung, other	9	(4.6)
Asian	3	(1.5)	Lung, NOS	4	(2.1)
Black	14	(7.2)	Histologic type		
White	165	(84.6)	Adenocarcinoma	82	(42.1)
Other	3	(1.5)	Squamous	78	(40.0)
Missing	10	(5.1)	NSCLC NOS	35	(18.0)
ECOG performance status			AJCC stage at original diagnosis		
0	82	(42.1)	IIIA	100	(51.3)
1	79	(40.5)	IIIB	39	(20.0)
2	22	(11.3)	IIIC	1	(0.5)
3	1	(0.5)	IIIA recurrent	35	(18.0)
Missing	11	(5.6)	IIIB recurrent	20	(10.3)
Smoking history			Clinical T-stage		
No	19	(9.7)	T0	2	(1.0)
Current smoker	26	(13.3)	T1	29	(14.9)
Past smoker	149	(76.4)	T2	56	(28.7)
Missing	1	(0.5)	T3	38	(19.5)
Concurrent chemotherapy			T4	48	(24.6)
No	70	(35.9)	TX	2	(1.0)
Yes	125	(64.1)	Missing	20	(10.3)
Prior thoracic radiation*			Clinical N-stage		
No	145	(74.4)	N0	17	(8.7)
Yes	50	(25.6)	N1	16	(8.2)
Prior surgery*			N2	105	(53.8)
No	159	(81.5)	N3	37	(18.9)
Yes	36	(18.5)	Missing	20	(10.3)
Prior chemotherapy*					
No	110	(56.4)			
Yes	85	(43.6)			

Abbreviations: AJCC = American Joint Committee on Cancer; ECOG = Eastern Cooperative Oncology Group; NOS = not otherwise specified; NSCLC = non-small cell lung cancer.

* For this cancer

Survival

The median OS of all patients was 19.0 months (95% CI [14.2-22.5]; range, 0.69-71.8) (Fig 1). The median follow-up time of living patients was 37.1 months (range, 2.4-82.4). The 1, 3, and 5-year OS were 60%, 32%, and 20%, respectively.

There was no statistically significant difference in OS by clinical stage of the disease (log-rank $P = .46$): median OS was 18.1 months (95% CI [11.1-26.1]) for stage IIIA, 19.2 months ([9.4-36.9]) for stage IIIB/C, and 19.0 months ([12.0-29.6]) for patients treated for recurrent disease. Patients with a history of prior radiation had a median OS

of 16.0 months ([9.6-29.6]) compared with 19.6 months ([14.2-26.1]) for patients who did not ($P = .15$).

Patients who received concurrent chemotherapy had a significantly higher median OS (20.6 months [16.0-28.0]) than those who did not receive it (12.9 [7.2-19.8]; $P = .03$) (Fig 2). Patients with performance status (PS) in the categories 0 and 1 of the Eastern Cooperative Oncology Group (ECOG) classification had a longer OS (21.1 months; [16.3-30.0]) compared with patients in categories 2 or 3 (7.0 months; [3.9-11.3]) ($P < .0001$).

On univariate analysis, 6 parameters were significantly associated with better OS: female or undifferentiated gender, tumors located in the upper lobes, ECOG PS of 0/1,

Table 2 Radiation treatment characteristics (n = 195)

Characteristic	n	(%)	Characteristic	Gy (RBE)
Only protons			Cumulative dose*	
Yes	182	(93.3)	Mean	61.2
No	13	(6.7)	Median	61.0
Any PBS			Minimum	10.1
Yes	39	(20.0)	Maximum	80.1
No	156	(80.0)	Standard deviation	12.9
Start of RT (year)			Cumulative dose EQD2*	
2010	2	(1.0)	Mean	61.8
2011	4	(2.1)	Median	63.8
2012	22	(11.3)	Minimum	10.1
2013	42	(21.5)	Maximum	80.1
2014	36	(18.5)	Standard deviation	12.9
2015	30	(15.4)		
2016	20	(10.3)		
2017	30	(15.4)		
2018	9	(4.6)		
Number of treatment plans				
1	129	(66.2)		
2	52	(26.7)		
3	12	(6.2)		
4	2	(1.0)		

Abbreviations: EQD2 = equivalent dose in 2 Gy fractions; PBS = pencil beam scanning; RBE = relative biological effectiveness; RT = radiation therapy.

* Cumulative proton dose when protons were used alone (n = 182)

Table 3 Early and late treatment toxicities (n = 195)

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	All grades
Early						
Cardiac events	-	-	-	-	1	1
Dermatitis	102	40	2	-	-	144
Esophagitis	43	54	3	-	-	100
Pneumonitis	-	2	1	-	-	3
Total early toxicities	145	96	6	-	1	248
Late						
Cardiac events	-	-	-	-	1	1
Dermatitis	1	-	-	-	-	1
Esophagitis	1	2	-	-	-	3
Pneumonitis	3	4	-	-	-	7
Total late toxicities	5	6	-	-	1	12

increased cumulative dose (EQD2), concurrent chemotherapy, and use of PBS.

On multivariate analysis, ECOG PS, cumulative dose (EQD2), and use of PBS remained statistically significant (Table 4).

In a subsequent stratified analysis by total EQD2, OS was higher in the group receiving ≥ 60 Gy versus < 60 Gy ($P = .03$). In a univariate analysis restricted to patients who received ≥ 60 Gy (n = 153), the association between EQD2 dose and survival was no longer statistically significant (hazard ratio, 0.83; [0.59–1.17]; $P = .29$).

Discussion

As the PCG registry enrolls patients without restrictive criteria, unlike interventional trials, the population studied in the present paper presented several differences in terms of demographics. The median age of 70 years (range, 48–93) seems higher than in the only RCT comparing photons to protons (66 years; range, 33–85)³ and in the Radiation Therapy Oncology Group (RTOG) 0617 trial, comparing standard (60 Gy) to high dose (74 Gy) radiochemotherapy (64 years; range, 38–83).¹⁴ An older population may be one of the factors associated with

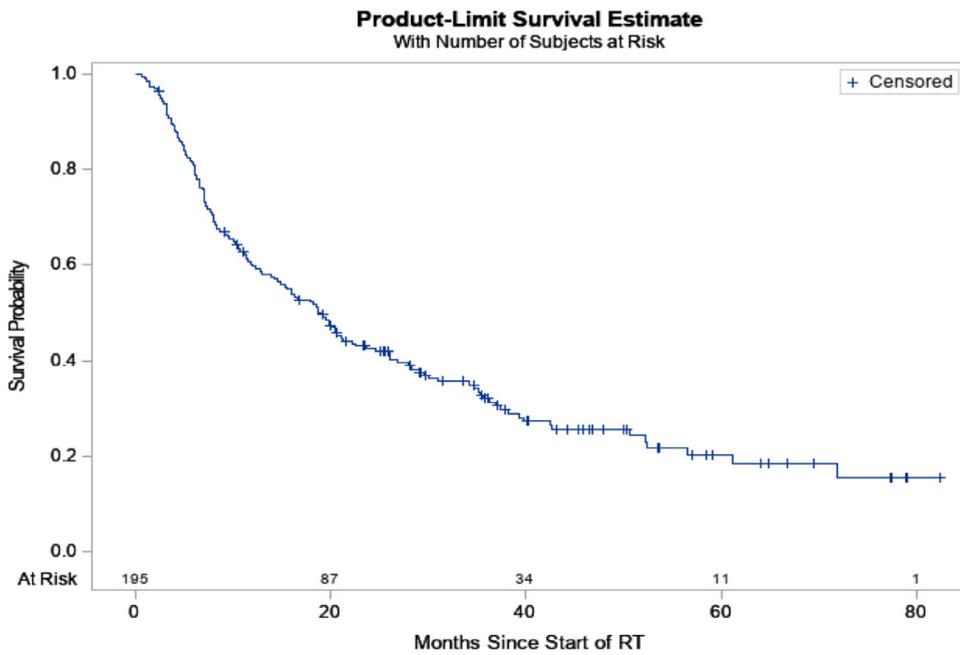


Figure 1 Survival probability for all patients.

poorer survival, a reason why these patients are often excluded from prospective studies. Yet, age was not found to be a significant parameter related to mortality in our analysis, possibly due to the limited sample size.

PBT has been shown to be safe and effective for previously irradiated patients with recurring NSCLC.¹⁵⁻¹⁷ In our cohort, a high percentage of patients (26%) had received thoracic radiation before this treatment. Care must be applied when interpreting these results as patients might have been selected for a new RT based on

PS. Although previous radiation data (site, fractionation, dose, and dates) were available for most reirradiated patients, cumulative dose to target volumes and OARs were not quantifiable as the degree of overlap between past and current treatment was unknown.

The overall low rate of high-grade AEs, even in patients with prior radiation, is in favor of good tolerance of the PBT treatment, in line with previous reports.¹⁷ Previously irradiated patients and patients with recurrent disease had similar OS as other subgroups. These findings

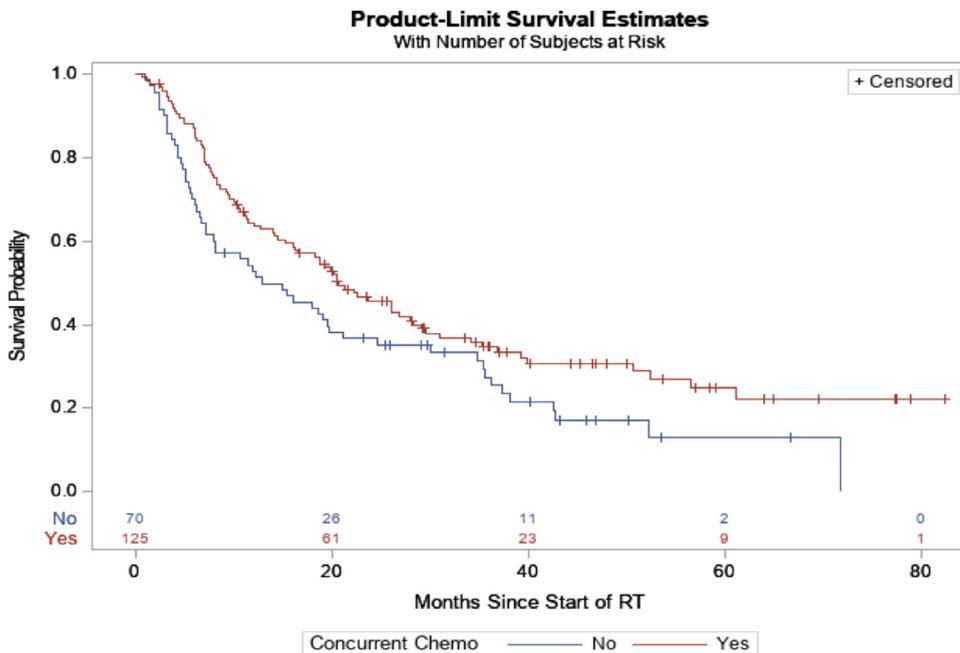


Figure 2 Survival probability by concurrent chemotherapy status.

Table 4 Multivariate Cox regression analysis for overall mortality

Variable	HR	95% CI	P value
Age at consent (years)			.52
Per 1 year increase	0.99	(0.97-1.01)	
Sex			.09
Female/undifferentiated	Reference		
Male	1.38	(0.95-2.00)	
Tumor location			.07
Other	Reference		
Upper lobes	0.71	(0.49-1.03)	
ECOG score			< .0001*
0	Reference		
1	1.33	(0.90-1.97)	
2/3	3.75	(2.17-6.48)	
Cumulative dose (EQD2)			.0002*
Per 10 Gy increase	0.80	(0.71-0.90)	
Any PBS use			.04*
No	Reference		
Yes	0.55	(0.31-0.97)	
Concurrent chemotherapy			.07
No	Reference		
Yes	0.70	(0.48-1.02)	

Abbreviations: CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; EQD2 = equivalent dose in 2 Gy fractions; HR = hazard ratio; PBS = pencil beam scanning.

* Statistical significance

could be due to the limited statistical power of small sample sizes. Another explanation could be that the selection process for reirradiating a patient with PBT might exclude patients who had early metastatic disease, therefore selecting more indolent tumors.

AEs in the mediastinum were limited to 6 grade 3 events, but 2 grade 5 also occurred. The implication of PBT in the grade 5 cardiac events cannot be excluded. However, considering the substantial medical history of the patients, the chemotherapy received concurrently, and the relatively low mean dose of radiation reaching the heart, it is very difficult to isolate 1 factor as directly causal. Nevertheless, if PBT played a role in those events, it would probably also have been the case with conventional RT. Cardiac-related mortality after RT has been frequently studied in the past years. In 2013, Darby et al¹⁸ showed a linear correlation between the MHD and the risk of major coronary events in patients with breast cancer, starting soon after treatment completion and regardless of their cardiac history. In lung cancer, the possible effect on mortality of high heart doses gained attention after the results of the RTOG 0617 trial,¹⁴ where the high-dose arm showed a significantly lower OS than the standard-dose arm (20.3 vs 28.7 months); heart V5 and V30 were found to be predictive factors of shorter OS. Similar results were reported in a study using the contouring guidelines of RTOG 0617; heart V50 \geq 25% was associated with shorter OS and increased cardiac toxicity.¹⁹ In contrast, a European study (using data from the

Essen-Paris-Tübingen trial) was not able to confirm heart V5 as an independent predictor of OS.⁴ In comparison with photon-based RT, PBT reduces the mean dose to the heart and could therefore be used for dose-escalation while limiting cardiac-related mortality.^{3,11} Minimizing cardiac events seems even more important considering the improvements in OS of patients with LA-NSCLC treated with Durvalumab.²⁰ Further studies should explore the factors linked to a lower cardiac dose, as such patients could potentially benefit from dose-escalation.

Our analysis showed that with PBT, a higher cumulative EQD2 could lead to an increased OS. It is consistent with theoretical principles that PBT allows for dose-escalation while limiting the dose to OARs and hence improving OS.^{2,11,21} However, treatment doses were heterogeneous, and some patients received EQD2s inferior to the standard 60 Gy, used, for example, in the RTOG 0617 trial.¹⁴ This was due to either a low prescription dose or treatment interruption. When excluding patients who received <60 Gy from our analysis, the association was no longer significant. Studies with larger and more homogeneous cohorts are warranted to determine whether, unlike with photons, increased proton dose can improve OS.

IMPT, one of the optimization strategies for the delivery of PBS,²² improves the dose distribution compared with PSPT, similarly to the improvement of IMRT relative to 3D-CRT. This provides better tumor conformality and healthy tissue sparing, with consequent improved

local control and lower AE rates.^{7,22} However, PBS also has limitations: more sensitive to setup and range uncertainties, motion, and interplay effect than PSPT or IMRT, PBS makes treatment planning more difficult.^{22,23} Nonetheless, a study by Inoue et al²³ showed that robust optimization of IMPT plans limits the effect of the aforementioned factors. PBS is slowly becoming the modality of choice for PBT, but it has been implemented more recently than PSPT. This could potentially introduce a difference in our study groups (cohort effect).

PBS use was also correlated with improved survival in our study. Our novel finding is promising, as more PBT centers are adopting these delivery techniques despite their challenges. It should also encourage the conduction of clinical trials using the latest available technologies, such as PBS, as they could improve local control and survival. In their RCT, Liao et al³ did not evaluate PBS but reported no differences in local failure between PSPT and IMRT.

In 2017, Chang et al²⁴ evaluated the use of PBT in 64 patients with unresectable stage III NSCLC from a single-arm phase II study and reported 16% grade 2 and 12% grade 3 late pneumonitis. In the RTOG 0617 trial, Bradley et al¹⁴ reported AEs separately for 4 treatment groups (60 vs 74 Gy, with or without Cetuximab); grade 2 late pneumonitis rates ranged from 1% to 8%, whereas grade 3 ranged from 0% to 2%. The late pneumonitis rates in our study were low. Although these are similar to those reported by Bradley et al, an under-reporting of the late AEs such as pneumonitis cannot be ruled out as a factor influencing our findings. The nature of the PCG registry and of prospective registries as a whole could account for this limitation. As patients enter follow-up, centers sometimes fail to update the registry with follow-up information. This can lead to a bias in the number of late AEs. Regarding acute esophagitis, Chang et al also found 28% grade 2 and 8% grade 3, whereas Bradley et al reported rates of 24% to 30% for grade 2 and 6% to 19% for grade 3, similar to our results.

In terms of survival, the median OS of 19 months is slightly superior to the OS described by Higgins et al²⁵ in their retrospective analysis, comparing protons with photons. In their subset of 193 patients with stage II/III NSCLC, the median OS (from start of radiation) was 17.4 months for PBT, not significantly different from IMRT and 3D-CRT (17.2 and 15.2 months, respectively). Analyses of prospective registries are often limited by a short follow-up of living patients (13.6 months in our initial analyses). After the aforementioned update, the median follow-up was increased to 37.1 months for living patients, giving more robustness to our results. Yet, compared with the largest prospective series studying PBT on stage III patients, our follow-up and OS are considerably inferior.²⁴ With a median follow-up of 79.6 months for living patients, Chang et al reported a median OS of 26.5 months for the 64 patients who received PBT at 74 Gy

(RBE) concurrently with chemotherapy. The OS in our study is also inferior to that reported for both groups by Bradley et al.¹⁴ This could be due to the difference in populations, as registries like the one from our study often recruit all patients without the strict exclusion criteria of RCT.

In the future, such cohort studies may become increasingly important, due to the difficulties of conducting RCTs. As an example, at least 2 phase II proton studies have been prematurely closed in recent years, partly due to poor accrual.^{26,27} Some authors have raised awareness about the problem of lack of clinical equipoise getting in the way of well-conducted RCTs.^{5,6,28} The fact that PBT reduces the dose to the normal tissues has been widely accepted for many years now.^{5,7,11,29} Knowing that no radiation dose is beneficial to healthy tissues,^{5,29} some clinicians find themselves in front of an ethical dilemma, refusing to randomize patients. Another factor limiting the recruitment of patients in RCTs comparing protons and photons is insurance denial, due to the higher cost of PBT.^{26,27} Nevertheless, some large RCTs are currently enrolling patients in the United States.⁷ Results from the RTOG 1308 trial, comparing proton to photon RT with concomitant platinum-based chemotherapy in patients with stage II to IIIB NSCLC, are expected in 2024, approximately ten years after its start.³⁰ With such a fast-changing technology, however, the RT techniques may be outdated by the time the results are published.^{6,8} This is well illustrated in this trial, where recruitment began with patients in the proton group being treated with PSPT, compared with IMRT in the photon group.^{12,30}

The Netherlands' model-based approach is one of the alternatives to RCTs.^{6,8} Another possibility (or rather supplement) would be the use of phase IV studies for RT, or radiovigilance, similar to what is done in pharmacovigilance, as mentioned by Bentzen²⁸: "The point here is that nonrandomized, or 'observational,' studies should be seen as a complement to, rather than a substitute for, randomized controlled trials of treatment outcome."

The limiting factor to the acceptance of PBT seems to be mainly financial; PBT is more expensive than even the most advanced forms of photon-based RT.^{5,29,31} A study published in 2018 estimated the cost of a 30-course PBT treatment with concurrent chemotherapy for stage III NSCLC to be 72% higher than IMRT.³¹ More than physicians, health technology assessment experts are the ones who need evidence to evaluate whether the clinical benefit brought by PBT is worth the financial surplus.^{5,28,29}

Finally, it is important to put these financial costs into perspective. The cost of RT is a small part of the global budget for cancer care.^{5,28} Although it is true that the wider use of PBT would increase its share in the total cost, it would still be minimal compared with some

modern drugs that can improve the OS by a few months in the palliative setting.^{5,13,28}

Conclusions

This study confirms the safe use of PBT with low rates of AEs and promising OS in spite of the unselected population. Besides, the use of PBS and increased treatment dose (EQD2) have shown to be associated with an increased OS.

With the difficulty to conduct RCTs and fast technological improvements, prospective registries such as the one created by the PCG will have great importance in the future. Nonetheless, it is essential that participating centers meticulously update follow-up information, without which survival and late AE reports will not reflect the clinical reality.

Acknowledgments

We would like to thank the PCG and its members for the access to the database as well as their support throughout the project.

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