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Image-Guided Hypofractionated Proton Therapy in Early-Stage Non–Small Cell Lung Cancer: A Phase 2 Study

Shivam M. Kharod, MD[1]; R. Charles Nichols, MD[1]; Randal H. Henderson, MD, MBA[1]; Christopher G. Morris, MS[1*]; Dat C. Pham, MD[2]; Vandana K. Seeram, MBBS[3]; Lisa M. Jones, MD[3]; Maria Antonio-Miranda MD[4]; Daniel A. Siragusa, MD[5]; Zuofeng Li, DSc[1]; Stella Flampouri, PhD, MSc[6]; Bradford S. Hoppe, MD, MPH[7]

[1]Department of Radiation Oncology, University of Florida, College of Medicine, Jacksonville, FL, USA
[2]Department of Medicine, Division of Hematology and Medical Oncology, University of Florida, College of Medicine, Jacksonville, FL, USA
[3]Department of Medicine, Division of Pulmonary, Critical Care and Sleep Medicine, University of Florida, College of Medicine, Jacksonville, FL, USA
[4]Orange Park Medical Center, Orange Park, FL, USA
[5]Department of Radiology, Division of Vascular and Interventional Radiology, University of Florida, College of Medicine, Jacksonville, FL, USA
[6]Department of Radiation Oncology, Emory Proton Therapy Center, Atlanta, GA, USA
[7]Department of Radiation Oncology, Mayo Clinic, Jacksonville, FL, USA

Abstract

Purpose: Due to the excellent outcomes with image-guided stereotactic body radiotherapy for patients with early-stage non–small cell lung cancer (NSCLC) and the low treatment-related toxicities using proton therapy (PT), we investigated treatment outcomes and toxicities when delivering hypofractionated PT.

Materials and Methods: Between 2009 and 2018, 22 patients with T1 to T2 N0M0 NSCLC (45% T1, 55% T2) received image-guided hypofractionated PT. The median age at diagnosis was 72 years (range, 58-90). Patients underwent 4-dimensional computed tomography simulation following fiducial marker placement, and daily image guidance was performed. Nine patients (41%) were treated with 48 GyRBE in 4 fractions for peripheral lesions, and 13 patients (59%) were treated with 60 GyRBE in 10 fractions for central lesions. Patients were assessed for CTCAEv4 toxicities with computed tomography imaging for tumor assessment. The primary endpoint was grade 3 to 5 toxicity at 1 year.

Results: The median follow-up for all patients was 3.5 years (range, 0.2-8.8 years). The overall survival rates at 3 and 5 years were 81% and 49%, respectively. Cause-specific survival rates at 3 and 5 years were 100% and 75%, respectively. The 3-year local, regional, and distant control rates were 86%, 85%, and 95%, respectively. Four patients experienced in-field recurrences between 18 and 45 months after treatment. One patient (5%) developed a late grade 3 bronchial stricture requiring hospitalization and stent.

Conclusion: Image-guided hypofractionated PT for early-stage NSCLC provides promising local control and long-term survival with a low likelihood of toxicity. Regional nodal and distant relapses remain a problem.

Keywords: radiation therapy; outcomes; toxicity; hypofractionated radiotherapy; adverse events

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Corresponding Author:
Bradford S. Hoppe
Mayo Clinic Radiation Oncology
4500 San Pablo Rd S
Jacksonville, FL 32224, USA
Phone: +904)-953-2000
Email: hoppe.bradford@mayo.edu

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Introduction

Stereotactic body radiation therapy (SBRT) has dramatically improved outcomes for patients with inoperable early-stage non–small cell lung cancer (NSCLC) [1], offering comparable rates of tumor control to surgical lobectomy [2]. Yet this treatment can sometimes result in a relatively high risk of serious adverse events, most commonly in patients with central tumors [3], tumors close to the brachial plexus [4], and large tumors [5].

In the treatment of early-stage NSCLC, particle therapy, particularly proton therapy, has generated interest in recent years due to the finite range of the proton beam as it penetrates tissue. More specifically, hypofractionated proton therapy has been shown to reduce radiation doses to critical normal structures, including the contralateral lung and heart [6–8]. In 2 phase II studies, these dosimetric benefits resulted in low toxicity rates and avoided grade 3 pulmonary toxicity [9, 10].

Due to the excellent outcomes of SBRT, and the low rate of treatment-related toxicities with proton therapy, we designed a phase II clinical trial to confirm the safety and efficacy of using hypofractionated image-guided proton therapy to treat early-stage NSCLC with a particular focus on centrally located tumors.

Materials and Methods

Under institutional review board approval, we developed and opened a phase II clinical trial (UFPTI 0901–LU03; NCT00875901) at the University of Florida for adults with medically inoperable pathologically confirmed (by biopsy or cytology) T1–T2N0M0 NSCLC (including bronchial alveolar carcinoma) diagnosed within 3 months prior to study enrollment. Required workup included a computed tomography (CT) scan of the chest and upper abdomen, or a positron emission tomography scan, pulmonary function testing, complete blood count with differential, and comprehensive metabolic panel. Mediastinal lymph node sampling was allowed but not required. Patients were required to have an absolute neutrophil count $>$1,800 cells/mm^3, platelet count $>$100,000 cells/mm^3, and hemoglobin level $>$8 g/dL. No concomitant local, regional, or systemic therapy was permitted during radiation therapy.

Fiducial marker placement prior to CT simulation was highly recommended but not required. Fourteen patients had markers placed using endobronchial ultrasound guidance, 4 using CT guidance, and 1 had markers placed during biopsy. For treatment planning, patients were immobilized in the supine position on a wing board with post hand grips. A small Vac-Lok (CIVCO, Kalona, Iowa) cushion was used on the wing board to stabilize the arms and the head. The pelvis and legs were stabilized with a larger vacuum bag. Patients lay on the table with a gap between the head and pelvic vacuum bags to minimize material in the beam path. They underwent 4-dimensional CT simulation scan with spacing $\leq$ 3 mm between slices. The target lesion was outlined and designated as the gross tumor volume in all 10 phases of the 4- dimensional (4D) CT using the lung window, although soft-tissue windows were used to help discern adjacent anatomy. The gross tumor volume was expanded to cover the entire space occupied by the tumor in the 4-dimensional CT scan, and labeled as the internal gross tumor volume (iGTV). Initially, a 6-mm uniform margin was used for expansion of the iGTV to an internal target volume (ITV) per our department's photon-based SBRT treatment guidelines at the time; however, the protocol was modified for a 0-mm expansion for the ITV to reflect departmental changes in target volumes for SBRT. The ITV was then expanded 5 mm uniformly to generate the planning target volume (PTV) to account for set-up errors and residual motion effects. A critical step in the treatment planning process involved overriding the iGTV with a Hounsefield unit of 50 (for muscle and solid tissue), for range modulation calculations and compensator design, to ensure an adequate beam range regardless of tumor position within the iGTV. This step was necessary because the Hounsfield values for pixels in the iGTV represented an average of Hounsfield units for lung tissue and tumor [11]. The ITV was used to calculate the proximal and distal margins of the treatment fields to account for range uncertainty. The distal margin comprised 2 components: a CT Hounsfield unit-to-proton stopping power conversion table uncertainty and a component that accounted for other range uncertainties, including equipment delivery variations [12]. The estimated range uncertainty was calculated to be 2.5% of the maximum of the CT volume-water-equivalent depth and was based on the accuracy of the CT numbers to proton-stopping-power conversion. A standard factor of 0.15 cm included equipment delivery variations based on in-house quality-assurance procedures that measured average and maximum (0.02 cm and 0.15 cm, respectively) deviations from the prescribed range in water phantoms. The proximal margins were the same as the distal margins or larger if the depth of the target increased with organ motion. To account for penumbra effects, the block aperture margins were expanded from the PTV and ranged from 0.7 cm to 1.2 cm based on the depth of the tumor.

Patients received either 4 fractions of proton therapy with 12 GyRBE per fraction for peripheral lesions or 10 fractions of proton therapy with 6 GyRBE per fraction for centrally located lesions (within 2 cm of the proximal bronchial tree). The dose

distribution was normalized so that 99% of the ITV was covered by the prescription isodose surface, and the ITV received a minimum of 95% of the prescription dose. Additionally, at least 85% of the PTV was conformally covered by the prescription isodose surface. Hot spots of up to 140% of the prescribed dose were permitted within the PTV. Dose-volume histograms were generated for all target volumes and normal-tissue regions for analysis.

Treatments were delivered every other day for peripheral lesions and on consecutive days for central tumors; all treatments were completed within 1.3 to 2.3 weeks. Daily image guidance required fiducial markers and double exposure of orthogonal kilovoltage imaging at the peaks of inspiration and expiration. The fiducial marker volume, drawn at the time of simulation based on the maximum intensity projection image, was expanded 2 mm (fiducial + 2 mm) and superimposed on the kV imaging scans. Adjustments were made to ensure that the markers on inspiration and expiration fell within the fiducial + 2-mm volume. Patients also underwent verification CT scans on days 1, 2, 4, and 6 of treatment to confirm appropriate alignment. During the course of radiation therapy, patients were assessed by the treating physician weekly, and their toxicities were scored using the Common Terminology Criteria for Adverse Events, Version 4.0 [13]. After treatment completion, patients underwent follow-up at 1 month and then every 3 months for 1 year and every 6 months for 4 years. Posttreatment assessments included chest CT scan and positron emission tomography–CT if progressive disease was suspected on CT scan. A local recurrence was defined as a recurrence or persistence of disease at the edge of the radiation field or in the same lobe as the primary disease. A regional recurrence was defined as disease recurrence in the mediastinal or other at-risk lymphatic region.

The primary objective of this study was to confirm the safety of hypofractionated image-guided proton therapy in patients with early-stage NSCLC by assessing grade 3 through 5 toxicities 1 year after treatment. We estimated that 21 patients would be required for the analysis to achieve 80% power and 95% confidence that the 1-year rate of a radiation-induced serious adverse event is $<$20%. The secondary objective was to evaluate disease control, including local control, regional control, distant metastasis, and overall survival.

All statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, North Carolina). Overall survival was estimated with the Kaplan-Meier product limit method. To adjust for the competing risk of intercurrent death, estimates of local recurrence, regional recurrence, and distant recurrence were instead estimated with the cumulative incidence method using the CIF macro in SAS.

Results

Patient, Tumor, and Treatment Characteristics

In total, 22 patients enrolled on the study. Patient-, cancer-, and treatment-specific characteristics are summarized in **Table 1**, subdivided by peripheral and central tumors. Twenty-one patients (95%) had a smoking history, with a median pack-year history of 55 (range, 0-200). Overall, 9 patients (41%) were treated with 48 GyRBE in 4 fractions for peripheral lesions, and 13 patients (59%) were treated with 60 GyRBE in 10 fractions for central lesions. The median duration of radiation therapy was 7 days for patients receiving 48 GyRBE (range, 7-9) and 14 days for patients receiving 60 GyRBE (range, 11-14). No patients underwent elective regional nodal irradiation or treatment with systemic therapies as a part of their initial treatment course.

Toxicities

The 1-year rate of severe adverse events was 5%. One patient (5%) had a grade-3 acute toxicity. This patient experienced acute grade-3 hypoxia as a result of developing a pulmonary embolism following a 12-hour car ride, unrelated to radiation. No patients experienced grade-4 or grade-5 acute toxicities. Acute toxicity data are summarized in **Table 2**.

In total, 3 patients (14%) experienced grade-3 late toxicities. One patient (5%) who was treated with 60 GyRBE in 10 fractions for a central tumor experienced an adverse event in the form of a late grade-3 bronchial stricture, which required bronchoplasty, endobronchial stent placement, and several balloon dilations. This patient also had the largest PTV volume at 211 cm^3. Two patients (9%) had late grade-3 hypoxia requiring continuous oxygen, including the previously mentioned patient who developed a pulmonary embolism and a second patient who had respiratory decline secondary to congestive heart failure (mean heart dose $<$0.1 Gy) that worsened over time. No patients experienced late esophageal strictures, esophageal ulceration, hemorrhage, or radiation-induced malignancy. No patients experienced grade-4 or grade-5 toxicities from proton radiation treatment. Late toxicities are summarized in **Table 3**.

Table 1. Patient and tumor characteristics (N = 22 patients).

Characteristic	Peripheral tumors (n = 9), n (%)	Central tumors (n = 13), n (%)	All patients, n (%)
Age, median (range), y	73 (65–90)	71 (58–87)	72 (58–90)
Sex			
Male	6 (67)	7 (54)	13 (59)
Female	3 (33)	6 (46)	9 (41)
Race			
White	9 (100)	11 (84)	20 (91)
Black	0 (0)	2 (15)	2 (9)
Zubrod performance status			
0	7 (78)	5 (38)	12 (54)
1	1 (11)	6 (46)	7 (32)
2	1 (11)	1 (8)	2 (9)
3	0 (0)	1 (8)	1 (5)
Baseline oxygen use			
None	7 (78)	8 (62)	15 (68)
Nightly	1 (11)	4 (31)	5 (23)
Continuously	1 (11)	1 (8)	2 (9)
History of prior treated lung cancer			
No	8 (89)	13 (100)	21 (95)
Yes	1 (11)	0 (0)	1 (5)
History of prior lung surgery			
None	8 (89)	12 (92)	20 (91)
Wedge resection	0 (0)	1 (8)	1 (5)
Lobectomy	1 (11)	0 (0)	1 (5)
Tumor histology			
Squamous	5 (56)	7 (54)	12 (54)
Adenocarcinoma	3 (33)	5 (38)	8 (36)
Adenosquamous	1 (11)	0 (0)	1 (5)
Poorly differentiated	0 (0)	1 (8)	1 (5)
T stage			
T1a	2 (22)	0 (0)	2 (9)
T1b	3 (33)	0 (0)	3 (14)
T1c	2 (22)	3 (23)	5 (23)
T2a	2 (22)	9 (69)	11 (50)
T2b	0 (0)	1 (8)	1 (5)
Tumor location			
RLL	3 (33)	1 (8)	4 (18)
RML	1 (11)	0 (0)	1 (5)
RUL	3 (33)	7 (54)	10 (45)
LLL	2 (22)	2 (15)	4 (18)
LUL	0 (0)	3 (23)	3 (14)
Treatment dose			
48 GyRBE	9 (100)	0 (0)	9 (41)
60 GyRBE	0 (0)	13 (100)	13 (59)

Abbreviations: RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe; LLL, left lower lobe; LUL, left upper lobe.

Several other patients experienced adverse events during the follow-up period that were possibly related to radiation. One patient (5%) experienced a standing-height fall 1 year following completion of radiation, resulting in a rib fracture in a rib that was within the radiation field. Three patients (14%) were hospitalized for respiratory ailments, including dyspnea and pneumonia, 10, 17, and 37 months following treatment.

Table 2. Nonhematologic acute toxicities (n = 22).

Toxicity	Grade 1, n (%)	Grade 2, n (%)	Grade 3, n (%)	Grade 4 and 5, n (%)
Hypoxia	0 (0)	2 (9)	1 (5) [a]	0 (0)
Dyspnea	2 (9)	1 (5)	0 (0)	0 (0)
Cough	4 (18)	1 (5)	0 (0)	0 (0)
Esophagitis	4 (18)	0 (0)	0 (0)	0 (0)
Radiation Dermatitis	3 (14)	1 (5)	0 (0)	0 (0)
Chest wall pain	0 (0)	0 (0)	0 (0)	0 (0)
Fatigue	5 (23)	0 (0)	0 (0)	0 (0)
Weight loss	0 (0)	0 (0)	0 (0)	0 (0)

[a]Patient was not thought to have grade 3 hypoxia due to radiation. This patient developed chronic thromboembolic disease in the months after treatment completion.

Disease Control

The median follow-up was 3.5 years for all patients (range, 0.2-8.8 years) and 3.6 years for living patients (range, 0.7-8.8 years). No patients were lost to follow-up. Overall survival rates at 3 and 5 years were 81% and 49% (95% confidence interval [CI]: 27%, 76%), respectively (Figure A). Eight patients died due to intercurrent disease: 3 died of cardiac arrest, 2 of respiratory failure, 1 of an unrelated head and neck malignancy. One died of an unclear cause unrelated to lung cancer. Cause-specific survival rates at 3 and 5 years were 100% and 75% (95% CI: 48%, 95%), respectively (Figure B). The 3-year local, regional, and distant control rates were 86%, 85%, 95%, respectively (Figure C, D, and E).

In total, 7 patients (32%) experienced disease recurrences as of the last follow-up: 2 had a local recurrence only; 2 had a regional recurrence only; 1 had a local and distant recurrence; 1 had a local, regional, and distant recurrence; and 1 had a regional and distant recurrence. No patients had a distant recurrence as their first recurrence. Three of the 7 patients (43%) with recurrences were living as of their last follow-up. At 5 years, the rate of freedom from any lung cancer (primary, recurrent, or a new lung cancer) was 57% (95% CI: 34%, 81%) (Figure F).

Local Recurrences

Four patients (18%) experienced a local recurrence as their first recurrence at 18, 18, 28, and 45 months, respectively, following treatment (median, 23 months [range, 18-45 months]). As part of this analysis, CT imaging taken at the time of local recurrence was fused with treatment planning imaging, and isodose lines were overlaid to confirm that the area of recurrence was within the prescription isodose volume. Of these 4 patients, 2 had an in-field recurrence only, and 2 had an in-field recurrence and developed satellite nodules. Of these 4 patients, 2 had fiducials placed for image guidance prior to treatment and 2 did not. Two of these patients had a 6-mm expansion from the iGTV to generate an ITV, while 2 did not as they were

Table 3. Nonhematologic late toxicities (n = 22).

Toxicity	Grade 1, n (%)	Grade 2, n (%)	Grade 3, n (%)	Grade 4 and 5, n (%)
Hypoxia	0 (0)	3 (14)	2 (9)[a]	0 (0)
Dyspnea	1 (5)	2 (9)	0 (0)	0 (0)
Bronchial stricture	0 (0)	1 (5)	1 (5)	0 (0)
Pneumonitis	3 (14)	0 (0)	0 (0)	0 (0)
Pulmonary fibrosis	12 (55)	0 (0)	0 (0)	0 (0)
Cough	5 (23)	0 (0)	0 (0)	0 (0)
Pleural effusions	1 (5)	2 (9)	0 (0)	0 (0)
Chest wall pain	7 (32)	0 (0)	0 (0)	0 (0)
Esophageal strictures	0 (0)	0 (0)	0 (0)	0 (0)
Esophageal Ulceration	0 (0)	0 (0)	0 (0)	0 (0)
Hemorrhage	0 (0)	0 (0)	0 (0)	0 (0)
Fatigue	8 (36)	0 (0)	0 (0)	0 (0)
Weight Loss	1 (5)	4 (18)	0 (0)	0 (0)

[a]Neither patient is thought to have grade 3 hypoxia toxicity due to radiation. One patient developed chronic thromboembolic disease in the months after treatment completion, and the second patient had respiratory decline secondary to congestive heart failure that worsened over time.

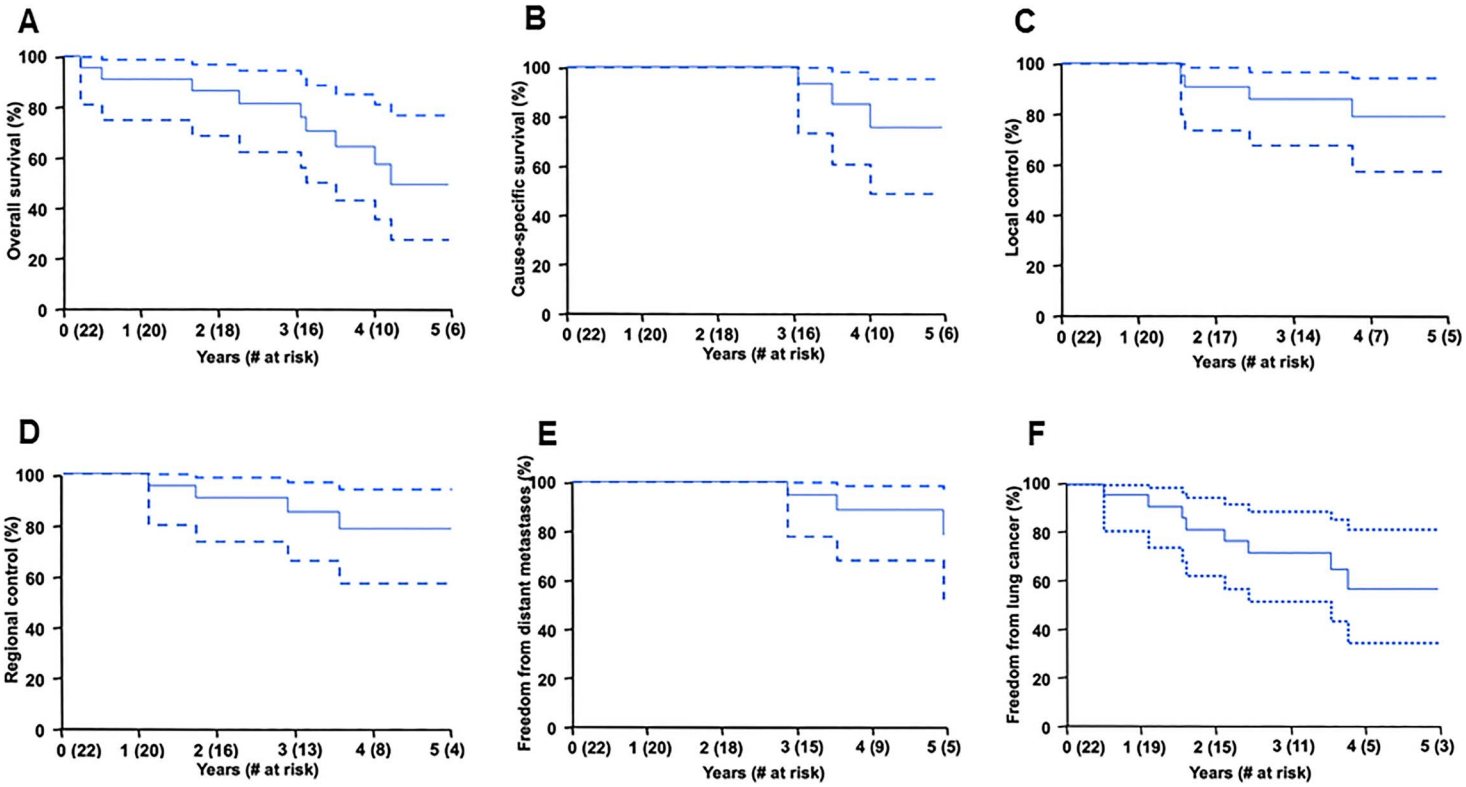

Figure. Cumulative incidence rates of (A) overall survival, (B) cause-specific survival, (C) local control, (D) regional control, (E) freedom from distant metastasis, and (F) freedom from lung cancer after adjusting for competing risk events.

treated after the protocol was modified to eliminate this expansion. The maximum tumor motion in the greatest dimension for each of 4 patients during their set-up and treatment was 0.4 cm, 0.6 cm, 1.4 cm, and 6 cm, respectively. Two of these patients underwent retreatment with SBRT using photons, and each lived 18 months after treatment completion, with 1 patient remaining alive. One patient received systemic therapy after a recurrence was detected and was alive 2 months after starting treatment. One patient underwent conventionally fractionated proton radiation to 60 GyRBE and lived 10 months before dying of an unrelated cardiac disease.

Regional Recurrences

Three patients (14%) developed a regional recurrence (mediastinal adenopathy) as their first recurrence. The median time to development of a regional recurrence from radiation treatment completion was 20 months (range, 12-42 months). One patient underwent treatment with systemic therapy, followed by conventionally fractionated photon radiation to the mediastinum, and died 10 months after completing salvage radiation. One patient received systemic therapy alone and died 5 months later. A third patient was treated with conventionally fractionated photon therapy and proton therapy to 60 Gy with concurrent chemotherapy and was alive with a performance status of 1, without evidence of disease, 6 years after recurrence.

New Primaries

In total, 4 patients developed new primaries during their follow-up period. All patients underwent treatment of these new lesions with SBRT. Two died 18 and 36 months after treatment while 2 were alive 7 and 38 months later.

Dosimetry

The median PTV size was 59.7 cm^3 (range, 31.5-211 cm^3). Dosimetric data for critical normal structures, which are summarized in Table 4, reveal limited exposure to the esophagus, heart, non-target lung, spinal cord, ipsilateral proximal bronchial tree, and chest wall.

Table 4. Dosimetric data for critical structures (n = 22).

Structures or organs at risk	Peripheral (n = 9), median of parameter (range)	Central (n = 13), median of parameter (range)	All patients (n = 22), median of parameter (range)
Planning target volume, cm^3	49.9 (31.5–13.6)	70.9 (32.3–210.9)	59.7 (31.5–211)
Esophagus			
Absolute dose at 0.1 cm^3, GyRBE	0.00 (0.00–21.8)	20.4 (0.00–64.4)	1.85 (0.00–64.4)
Absolute dose at 5 cm^3, GyRBE	0.00 (0.00–12.4)	1.20 (0.00–37.3)	0.03 (0.00–37.3)
Mean dose, GyRBE	0.00 (0.00–4.74)	2.50 (0.00–7.91)	0.04 (0.00–7.91)
Heart			
Absolute dose at 0.1 cm^3, GyRBE	3.40 (0.00–29.2)	26.8 (0.00–63.3)	18.9 (0.00–63.3)
Absolute dose at 15 cm^3, GyRBE	0.00 (0.00–12.2)	2.80 (0.00–29.4)	1.75 (0.00–29.4)
V5, %	0.00 (0.00–3.50)	1.50 (0.00–5.64)	0.93 (0.00–5.64)
Mean dose, GyRBE	0.00 (0.00–10.8)	0.18 (0.00–1.54)	0.15 (0.00–10.8)
Lungs			
Absolute dose at 1500 cm^3, GyRBE	0.00	0.00 (0.00–0.40)	0.00 (0.00–0.40)
Absolute dose at 1000 cm^3, GyRBE	0.00	0.10 (0.00–2.00)	0.00 (0.00–2.00)
V20, %	5.30 (4.00–11.0)	8.90 (4.10–14.7)	7.00 (4.00–14.7)
V5, %	11.1 (6.21–18.5)	15.4 (7.90–21.2)	13.7 (6.21–21.2)
Mean dose, GyRBE	2.70 (1.80–4.91)	4.80 (2.30–7.80)	4.03 (1.80–7.80)
Ipsilateral lung			
Absolute dose at 1500 cm^3, GyRBE	0.00	0.00	0.00
Absolute dose at 1000 cm^3, GyRBE	0.00	0.00 (0.00–1.78)	0.00 (0.00–1.78)
V20, %	9.40 (7.13–19.6)	20.1 (6.90–27.3)	14.0 (6.90–27.3)
V5, %	20.2 (11.6–33.8)	31.3 (13.5–42.0)	26.2 (11.6–42.0)
Mean dose	4.90 (0.04–9.00)	10.6 (3.90–14.5)	7.44 (0.04–14.5)
Nontarget lung			
Absolute dose at 1500 cm^3, GyRBE	0.00	0.00 (0.00–0.40)	0.00 (0.00–0.40)
Absolute dose at 1000 cm^3, GyRBE	0.00	0.10 (0.00–2.00)	0.00 (0.00–2.00)
V20, %	4.90 (3.80–10.9)	8.70 (3.60–13.5)	6.70 (3.60–13.5)
V5, %	10.7 (5.91–16.9)	14.7 (7.50–21.1)	13.5 (5.91–21.1)
Mean dose, GyRBE	2.53 (1.74–4.10)	4.50 (2.00–6.61)	3.45 (1.74–6.61)
Spinal cord			
Absolute dose at 0.1 cm^3, GyRBE	5.20 (0.00–17.1)	15.8 (0.20–22.7)	13.6 (0.00–22.7)
Ipsilateral bronchus			
Absolute dose at 0.1 cm^3, GyRBE	5.40 (0.00–30.0)	62.8 (2.20–64.9)	42.3 (0.00–64.9)
Absolute dose at 4 cm^3, GyRBE	0.00 (0.00–4.30)	28.0 (0.00–61.1)	3.15 (0.00–61.1)
Chest wall			
Absolute dose at 4 cm^3, GyRBE	48.9 (0.00–49.6)	41.6 (26.8–61.9)	43.8 (0.00–61.9)
Absolute volume at 35 Gy, cm^3	30.5 (0.08–67.9)	15.2 (0.00–189)	24.4 (0.08–113)

Abbreviations: V5, percent of the total volume of the organ of interest that receives 5 Gy of radiation; V20, percent of the total volume of the organ of interest that receives 20 Gy of radiation.

Discussion

This study demonstrated that hypofractionated proton therapy for early-stage NSCLC was an effective treatment, with a 3-year overall survival rate of 81% and a 5-year overall survival rate of 49%. Proton treatment was also a safe treatment, with a 1-year rate of severe adverse events of 5%. Only 14% of patients developed a new grade-3 or higher late toxicity, only 1 of which we believe was related to radiation treatment. These results are noteworthy considering the various comorbidities typical to patients with inoperable lung cancer, and the fraction of patients with centrally located tumors. Despite excellent tumor control, regional nodal and distant relapses remained a problem. In total, 14% of patients developed regional nodal disease as their first recurrence in the absence of a local recurrence.

Outcomes after SBRT for inoperable early-stage NSCLC have been promising, with 5-year overall survival rates of 40% and 5-year local control rates of 80% [14]. Our 3- and 5-year rates of local control and overall survival in this study were in line with the long-term results of Radiation Therapy Oncology Group (RTOG) trial 0236 [14], NRG/RTOG trial 0813 [15], and previously

published proton SBRT studies [9, 16]. In our study, the cause-specific survival rates at 3 and 5 years were 100% and 75%, respectively, which is considerably higher than overall survival, underscoring the role of competing comorbidities in this medically frail population of patients.

Compared with 3-dimensional conformal radiotherapy and intensity-modulated radiotherapy, proton therapy has been shown to reduce the radiation exposure to normal tissue in various disease sites of the body [17–19]. In the context of early-stage NSCLC, the dosimetric data comparing photon-based SBRT to proton-based SBRT has not been as dramatic [6, 20, 21]; however, investigators have acknowledged that the differences may have been understated due to the location of the tumors and proton planning techniques used. In a dosimetric comparative study from our institution involving 8 patients with peripheral NSCLC, double-scatter proton therapy significantly reduced the dose to the bilateral lungs, ipsilateral lungs, heart, esophagus, trachea, ipsilateral bronchus, and spinal cord [8]. Uncertain of whether these statistically significant differences in dosimetry could lead to clinically significant differences in treatment toxicity, we opened this prospective phase II clinical trial to understand the clinical differences.

Overall, toxicities in our study were low. Three patients experienced a late grade-3 toxicity. The most serious toxicity occurred in a patient who experienced a late grade-3 bronchial stricture that required numerous surgical interventions. This patient's tumor was central and abutted the ipsilateral proximal bronchial tree. As a consequence, the patient's ipsilateral bronchial tree received a dose of 63.9 GyRBE at 0.1 cm^3 and 61.1 GyRBE at 4 cm^3. Our late toxicity data for proton therapy compare favorably to data from RTOG 0236, wherein 16% of patients experienced a grade 3 or higher pulmonary toxicity [22], and NRG/RTOG 0813, wherein 21% to 29% of patients experienced a grade 3 or higher toxicity in the high-dose arms of treatment [15]. We recognize, however, that the treatment planning techniques and treatment volume specifications varied between the 2 studies. Investigators from Loma Linda University and the National Cancer Center of Korea analyzing hypofractionated proton therapy for early-stage NSCLC have reported no grade 3 through 4 treatment toxicities [16], acute pneumonitis, or late esophageal and cardiac toxicities [9]. A meta-analysis that compared photon-based radiation to particle-based radiation for early-stage NSCLC also found lower rates of grade 3 through 4 pneumonitis and grade 3 through 4 irreversible dyspnea in patients who received proton therapy [23]. These findings suggest that the dosimetric advantages offered by proton therapy may be associated with fewer toxicities. Proton therapy might be particularly useful in the treatment of patients with central tumors, for whom results from RTOG 0813 reveal a 7% likelihood of a grade-5 adverse event. We have separately published the results of using image-guided hypofractionated double-scattering proton therapy for centrally located early-stage NSCLC, and reported that proton therapy may provide safer treatment than photon-based treatments due to its dosimetric advantages [24].

Limitations

Our study has several limitations. We enrolled a relatively small number of patients over the time period, and, thus, there were not enough events to accurately identify prognostic factors related to treatment outcomes. The poor accrual is in part due to implicit physician bias concerning patients with smaller, peripheral tumors who were typically not offered proton therapy since the dosimetric advantages did not appear to provide a clinically meaningful benefit [25]. These patients were treated with photon-based SBRT with cone-beam CT image guidance. Recently, a group from MD Anderson Cancer Center (Houston, Texas) described a similar phenomenon in their phase II trial comparing photon and proton SBRT, which closed early due to poor enrollment [26]. Finally, almost all patients were treated with orthogonal x-ray–based image guidance rather than cone-beam CT-based image guidance, which is the standard for SBRT at many institutions today.

Conclusions

Overall, our results encourage us to believe that hypofractionated proton therapy will play a larger role in the management of patients with medically inoperable early-stage NSCLC due to excellent tumor control rates, dosimetric advantages, and low rates of treatment toxicities compared with photon-based SBRT. As treatment planning technologies and dose calculation algorithms improve, and more proton centers open, we anticipate further utilization of hypofractionated proton therapy. These advantages may be even more useful for patients with central tumors, for whom treatment-related toxicities using photon radiation present a significant challenge [19], and patients with larger peripheral tumors. Meanwhile, we encourage centers with experience using hypofractionated protons for treatment of early-stage NSCLC to publish their results.

ADDITIONAL INFORMATION AND DECLARATIONS

Conflicts of Interest: Bradford S. Hoppe, MD, MPH, is an associate editor of the *International Journal of Particle Therapy* and a scientific consultant for Merck & Co., Inc., and Bristol-Myers Squibb.
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