Published in final edited form as:

Int J Radiat Oncol Biol Phys. 2011 August 1; 80(5): 1350–1357. doi:10.1016/j.ijrobp.2010.04.049.

Toxicity and Patterns of Failure of Adaptive/Ablative Proton Therapy for Early-Stage, Medically Inoperable Non-Small Cell Lung Cancer

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Abstract

Purpose—To analyze the toxicity and patterns of failure of proton therapy given in ablative doses for medically inoperable early-stage non-small cell lung cancer (NSCLC).

Methods and Materials—Eighteen patients with medically inoperable T1N0M0 (central location) or T2-3N0M0 (any location) NSCLC were treated with proton therapy at 87.5 Gy (relative biological effectiveness, RBE) at 2.5 Gy/fraction in this phase I/II study. All patients underwent treatment simulation with 4-dimensional (4D) computed tomography (CT); internal gross tumor volumes (iGTVs) were delineated on maximal intensity projection (MIP) images and modified by visual verification of the target volume in 10 breathing phases. The iGTV with MIP density was used to design compensators and apertures to account for tumor motion. Therapy consisted of passively scattered protons. All patients underwent repeat 4D CT simulations during treatment to assess the need for adaptive replanning.

Results—At a median follow-up time of 16.3 months (range, 4.8–36.3 months), no patient had experienced grade 4 or 5 toxicity. The most common adverse effect was dermatitis (grade 2, 67%; grade 3, 17%), followed by grade 2 fatigue (44%), grade 2 pneumonitis (11%), grade 2 esophagitis (6%), and grade 2 chest wall pain (6%). Rates of local control were 88.9%, regional lymph node failure 11.1%, and distant metastasis 27.8%. Twelve patients (67%) were still alive at the last follow-up; five had died of metastatic disease and one of preexisting cardiac disease.

Conclusions—Proton therapy to ablative doses is well tolerated and produces promising local control rates for medically inoperable early-stage NSCLC.

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Conflict of Interest Notification: Actual or potential conflicts of interest do not exist.

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Keywords

Proton therapy; non-small cell lung cancer; toxicity; patterns of failure

INTRODUCTION

Lung cancer remains the number one cause of death from cancer in the United States, with more than 161,000 deaths each year [1]. Roughly 16% of patients present with localized disease, for whom surgery has been the standard treatment. However, some patients with early-stage disease are not good candidates for surgery because of coexisting medical conditions such as cardiac disease and poor lung function, and these patients need an alternative treatment approach. One such approach, conventional photon radiotherapy (RT), produces 2-year progression-free survival rates of only 30%–50% when given in typical doses of 60 to 66 Gy for stage I non-small cell lung cancer (NSCLC) [2]. These rates are considerably lower than those achieved after surgical resection (70%–80%). Eradication of the local-regional tumor is an essential step for cure. Although radiation dose-response relationships have been noted for both local tumor control and survival in stage I NSCLC [3], toxicity related to the high dose of photon treatments limits the potential for dose escalation. Stereotactic body RT may be an effective alternative to surgery; reported local control rates typically exceed 90% when biologically effective doses (BEDs) in excess of 100 Gy are delivered to the tumor [4–10]. However, particular challenges are posed by tumors larger than 3 cm or those located centrally or superiorly in the thorax, near critical structures like the major vessels, spinal cord, esophagus, brachial plexus, and bronchial tree, because of potentially severe radiation-induced complications [9,10,7].

For a given level of normal tissue toxicity, the maximum tolerated dose of proton RT is likely higher than that of conventional photon RT because of the physical characteristics of the protons (e.g., the Bragg peak, finite range, and lower entrance dose). Therefore, proton RT may have an advantage over conventional photon RT in achieving local tumor control and improving survival with lower toxicity. A virtual clinical trial conducted at M. D. Anderson Cancer Center showed that escalation of proton doses to as high as 87.5 Gy (RBE) for stage I lung cancer were associated with considerably lower doses to normal tissue compared with photon RT at the standard dose of 66 Gy [11].

The Radiation Therapy Oncology Group (RTOG) 9311 trial [12], a phase I photon dose-escalation study, showed that acute toxicity rates were acceptably low for doses of up to 90.3 Gy (i.e., < 15% grade ≥ 3 pneumonitis). However, late toxicity was more pronounced, with grade ≥ 3 radiation pneumonitis occurring in 16% of patients with a $V_{20} < 25\%$ (typical for a small lung lesion) treated to 77.4 Gy in 2.15-Gy fractions and grade ≥ 3 esophagitis in 8% of patients treated to 70.9 Gy. The highest dose tested in the RTOG 9311 dose-escalation study was 90.3 Gy, given in 2.15-Gy fractions [12]. However, this dose regimen was considered to be too toxic because of high rates of grade 3 toxicity and two fatal complications (one pneumonitis and another esophagitis), and local control was still not optimal at only 75%. In RTOG 9311, 83.8 Gy was considered to be the highest tolerable dose of photons, but the local control rate among patients given that dose was only 55%.

On the basis of these findings, we conducted a phase I/II prospective study of proton RT for inoperable centrally or superiorly located stage IA (T1N0M0) NSCLC, any stage IB (T2N0M0) NSCLC, and selected stage II (T3N0M0) NSCLC, to a RBE-equivalent total dose of 87.5 Gy (RBE) (previously used unit: cobalt Gray equivalent, CGE, assumed RBE of 1.1) at 2.5 Gy (RBE)/fraction, which is equivalent to the highest-dose regimen tested in RTOG 9311 using 90.3 Gy photon dose given in 42 fractions of 2.15 Gy each (assuming a

tumor alpha/beta ratio of 10 Gy, this regimen corresponds to a BED₁₀ of 109.4 Gy). In this first report from this study, we focus on toxicity and patterns of failure among patients given the 87.5 Gy total dose. An objective of this study is to evaluate whether protons therapy could reduce the toxicity compared with photons therapy and allow us to treat difficult tumors with ablative doses.

METHODS AND MATERIALS

Patients, treatment, and study design

Eighteen patients with medically inoperable histologically or cytologically documented NSCLC, centrally and/or superiorly located T1N0M0 (stage IA) disease, T2N0M0 disease in any location (stage IB, tumor size > 3 cm with no upper size limit), or selected (chest wall, mediastinal pleura, parietal pericardium involvement) T3N0M0 (stage II) disease in any location, were enrolled in this phase I/II study approved by the institutional review board of The University of Texas M. D. Anderson Cancer Center. All patients provided written informed consent to participate. Medically inoperability was determined by a multidisciplinary thoracic team, including a thoracic surgeon, based on the one of the following criteria: severe cardiac disease, severe diabetes, or poor lung function, i.e., forced expiratory volume in 1 second (FEV1) and carbon monoxide lung diffusion capacity (DLCO) < 45% of predicted values. Disease in all cases was staged with magnetic resonance imaging (MRI) or computed tomography (CT) of the brain, CT of the chest, and positron emission tomography (PET) within 3 months prior to the beginning the RT. Medianoscopy or endobronchial ultrasound-guided biopsy was used to examine mediastinal or hilar lymph nodes suspected of harboring disease. Lesions were considered to be centrally or superiorly located if any tumor edge measured within 30 days prior to the beginning the RT by CT (either simulation CT or PET/CT on the lung window setting) was located within 2 cm of the bronchial tree (carina, right and left main bronchi, right and left upper lobe bronchi, bronchus intermedius, right middle lobe bronchus, lingular bronchus, right and left lower lobe bronchi, RTOG SBRT protocol definition of central lesion as described in reference 10), major vessels (aorta, pulmonary artery trunk, left/right pulmonary artery/vein main branches, superior/inferior vena cava, brachiocephalic artery trunk or left/right brachiocephalic vein, left/right subclavian artery/vein), esophagus, heart, tracheal, pericardium, mediastinal pleural and brachial plexus, or vertebral body, but showed no direct invasion.

Simulation and target volume delineations

All patients underwent treatment simulation with 4-dimensional (4D) CT to account for tumor motion. The internal gross tumor volume (iGTV) was defined as the envelope of motion of the GTV on a reconstructed maximal intensity projection (MIP) image at the lung window level and verified across all phases of the 4D-CT dataset. An 8-mm isotropic expansion of the iGTV was added to encompass microextensions of the tumor, and the resulting volume was defined as the internal clinical target volume (iCTV=GTV+8 mm). This volume was edited by the attending radiation oncologist based on clinical experience of disease spread. For proton planning, conventional planning target volume (PTV) was not used. For each beam, the iCTV projection in the beam's eye view is expanded laterally by a margin that is the same as the one for photon planning (5 mm) to account for day-to-day set up uncertainties. In addition, beam-specific distal and proximal margins to the iCTV were assigned along the longitudinal axis of the beam to account for uncertainties in the range of protons. Two to three beams were used in each case. Proton plans were evaluated beam-by-beam to determine whether the iCTV plus the lateral, distal and proximal margins is adequately covered for each beam.

While conventional PTV is not used for proton planning, it is necessary for reporting dose distributions, computing dose-volume histograms and comparing proton plans among themselves and with photon plans. It is defined in the conventional way by expanding the iCTV isotropically by 5 mm.

Radiation doses

The total radiation dose for the tumor target was 87.5 Gy (RBE) at 2.5 Gy (RBE) per fraction, with fractions given once a day, 5 days per week. The goal was to cover 100% of the iCTV by the prescribed dose, and that was achieved by ensuring that each beam covered the iCTV plus the margins for not only the lateral uncertainties but also the range uncertainties. Treatment plans were normalized so that 95% of the iCTV + margins is covered with the prescribed dose. The minimum iCTV + margins dose was not allowed to fall below 95% of the prescribed dose. Treatment plans were designed in accordance with the dose-volume constraints listed in Table 1.

Passive scattering proton therapy planning and adaptive proton delivery

Treatment planning parameters, including distal and proximal margins, were calculated based on published formulae that were modified locally and adopted as the standard of practice at M. D. Anderson (11, 13–15). All treatment positions were verified with daily on-board kilovoltage radiographic imaging. In addition to the 4D CT simulation for treatment planning, 4D CT scans were obtained during week 3 or 4 of treatment or as clinically indicated as assessed by the treating physician. The original contours were transferred to the new 4D CT scans and reviewed by the attending physician, who determined whether new contours were necessary; if so, those contours were drawn and the new dose distribution calculated using the original beam configuration. If the changes derived from the new dose distribution could not meet the minimum target dose requirement of $\geq 95\%$ of the prescribed dose or exceeded normal tissue dose constraints, a new treatment plan was designed for the remainder of the treatments. Composites of the dose distribution received by each patient over the course of RT were computed.

Treatment evaluation and follow-up

Acute radiation reactions including esophagitis, pneumonitis, and other adverse events were evaluated weekly during the course of treatment. Adverse events were graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events, version 3.0. Laboratory studies included complete blood counts with differential and platelet counts every 3 weeks during the RT.

Patients were to be followed up at 6 weeks after completion of the RT, then every 3 months (± 1 month) for 2 years, then every 6 months (± 1 month) for 3 years, and then annually thereafter. A chest CT was to be obtained at the second follow-up visit, then every 3 months (± 1 month) for 2 years, then every 6 months (± 1 month) for 3 years, and then annually thereafter. PET scanning was required between 2–6 months after finishing RT.

Pulmonary function and electrocardiographic activity were tested within 3 months before RT, during the first 3 to 6 months after completion of RT, and then annually for 2 years. If cardiac toxicity was a concern because of the treatment plan or abnormalities on electrocardiography, cardiac single photon emission CT scans were obtained as clinically indicated.

Local control at the primary tumor site was evaluated by serial thoracic CT scans with contrast. If lesions were suspected of harboring recurrent disease on CT scans, then PET or PET/CT was required and biopsy recommended to confirm recurrence. Unconfirmed

recurrent disease was to be followed up with CT or PET. The timing of the recurrence was scored as the time at which the first image (PET or CT) showed abnormalities. The presence of persistent or progressive disease on avid PET or biopsy was considered to indicate recurrence.

Statistics

We used two-tailed, paired-sample *t* tests for statistical analysis (SPSS software v.16.0, SPSS Inc., Chicago, IL). A *p* value of 0.05 was considered statistically significant.

RESULTS

Patient characteristics are listed in Table 2. The median age of the 18 patients was 73 years and the median Karnofsky performance status score was 70. Thirteen patients (73%) had T2 lesions, and 15 (83%) had central lesions (13 patients, 72%, met with definition of RTOG SBRT central lesion as described in reference 10). The median PTV was 236 cm³. Most patients had severe chronic obstructive pulmonary disease, with median pretreatment DLCO and FEV1 at 41% of predicted values. 6 patients (33%) underwent mediastinal lymph node biopsy for stage purpose. All patients completed the prescribed treatment. At a median follow-up time of 16.3 months (range, 4.8–36.3 months), no patient had experienced grade 4 or 5 toxicity. The most common adverse effect was dermatitis (grade 2, 12 patients [67%], grade 3, 3 patients [17%], see Figure 1), followed by grade 2 fatigue (8 patients [44%]), grade 2 pneumonitis (2 patients [11%]), grade 2 esophagitis (1 patient), and grade 2 chest wall pain (1 patient). A comparison of pulmonary function before and at 3–6 months after proton RT showed no differences in FEV1 or DLCO (*p* > 0.05). Some patients did show improvements in FEV1, which were thought to result from reductions in tumor-related airway obstruction. However, the patient number was low and follow up was too short to give a solid conclusion about lung function change after proton therapy in this group of patients. Median values and ranges of lung V₈₀ (i.e., the volume receiving ≥ 80 Gy (RBE)), to V₅ were shown in Table 3. Because of the unique physical characteristics of the proton beam, the median absolute increase of lung volume from V₅ to V₈₀ was only 2.4% for every 10-Gy increase. The median value for mean lung dose to the entire lung was 11.1 Gy (range, 29.7 to 16.5 Gy); the heart median V₄₀ was 1.5% (range, 0% to 29%); and the median esophagus V₆₀ was 0% (range, 0% to 24.7%). The median volume of bronchial tree receiving 80 Gy and above was 0 cm³ (range, 0 to 6.5 cm³).

To improve target coverage and spare critical structures, all patients had repeated 4-D CT simulations over the course of treatment (typically after three weeks of RT) and eight patients (45%) underwent adaptive replanning/therapy (typically started new adapted RT in the fourth week without treatment break).

Although the follow-up time to date renders data on disease control and survival somewhat preliminary, the rates of local control were 89% (16/18); regional lymph node failure, 11% (2/18); and distant metastasis, 28% (5/18). An example of local recurrence viewed on a PET/CT scan and confirmed by biopsy at 6 months after proton RT is illustrated in Figure 2. Disease-free survival and overall survival rates were 53.3% and 93.3% at 1 year and 45.5% and 54.5% at 2 years. At last follow-up, six patients had died, five (28%) of lung cancer and one of preexisting cardiac disease; hence 12 patients (67%) were alive.

DISCUSSION

Our current study showed that ablative dose of proton therapy can be safely delivered to target with large tumor size and/or challenging location with minimal toxicity using image-guided adaptive proton therapy in early stage NSCLC. Compared with RTOG 9311 data, it

appears that toxicity is improved and local control is promising. In RTOG 9311, in addition to high toxicity in >84 Gy cohorts, the local control remains sub-optimal (55% to 75%). It is possible that local control was compromised by prolonged treatment time in RTOG 9311 (42 treatments in 8.4 weeks), which may have resulted in cancer cell repopulation and repair. In the current study, in which 87.5 Gy (RBE) of protons was given in 2.5-Gy fractions for total of 35 treatment in 7 weeks, the BED₁₀ (109 Gy) was similar and the BED₃ for chronic toxicity was higher than that for the group in RTOG 9311 given 90.3 Gy of photons in 2.15-Gy fractions. Our findings, although preliminary, showed that our proton regimen improved local control rates (89% vs. 55%–75% in RTOG 9311) and resulted in considerably fewer incidents of $\geq$ grade 2 toxicity, especially pneumonitis (45% in RTOG 9311 to 11% in our study). Moreover, no patient in our study experienced any grade 4 or 5 toxic effects. The most common side effect and the only grade 3 toxic effect was dermatitis. These improvements may have been related to (1) a reduction in the impact of accelerated tumor cell repopulation owing to the reduced overall treatment time from 42 fractions to 35 fractions, and (2) a reduction in the dose to critical normal tissue structures due to the superior dose distribution of protons as compared with photons. As demonstrated by findings in table 3 and results, proton therapy achieved superior dose-volume distribution particularly for the low dose region in normal tissues. In addition to reduced high dose exposure to normal tissues, dramatic reduction of low dose exposure including decreased non-target integral dose (11) may have significant impact in the improvement of normal tissue tolerance, so called “bath and shower” effect. These factors may explain the minimal side effects experienced after aggressive, ablative doses of proton RT by these patients. Longer follow-up with additional patients will be needed to validate our contention that radiation doses given as proton therapy can be safely and effectively given at ablative doses for this challenging presentation.

The prevalence of dermatitis in the current study could be related to our using two or three proton beams, which reduced treatment time but led to relatively high skin doses. All three cases of grade 3 dermatitis happened in patients in whom two beams were used. It is also possible that the RBEs of protons for the skin may be higher than 1.1; biological research to investigate this possibility is ongoing.

All patients were followed up by clinical exam with PET/CT and serial CT images. Two local recurrences were confirmed by biopsy among the 18 patients. Local recurrence in these cases could have resulted from technical difficulties in defining the target volumes. In one case, the GTV contour was difficult to contour owing to the presence of a ground glass opacity lesion without clear margins; in another case, overriding the MIP density dose for a low-density lesion may have resulted in a “cold spot” near the low-density target. It is also possible that the margin may not have been adequate in these cases and/or the cancer cells were radiation resistant at the current dose. The rate of regional lymph node recurrence (11%) in all patients was not unexpected given the large size and location of the lesions in these patients. The dominant pattern of failure in all patients was distant metastasis (28%), indicating that effective chemotherapy is needed for patients with the types of tumors studied here. However, all patients did not receive chemotherapy because of poor performance status.

Several papers have been published supporting the efficacy and safety of proton therapy for early-stage lung cancer, although most studies used lower doses [16–19]. Shioyama and colleagues [14] reported the clinical outcome of 28 patients with stage I NSCLC treated with proton RT to median total dose of 76 Gy (RBE) (range, 49–93 Gy(RBE)) in median 3-Gy (RBE) fractions [range, 2–6 Gy (RBE)]. The 5-year overall survival rate was 70%, with a local control rate of 89% for patients with stage IA (< 3 cm) disease. However, the local control rate for those with larger tumors (stage IB) was considerably lower at 39%,

indicating that higher radiation doses were needed. Recurrence in 21% of cases was reported in the mediastinum, and the 5-year overall survival rate was 15%. Only one case of grade 3 acute toxicity and little late toxicity was observed. Because PET was not used for clinical staging in this study, it is possible that the stage IB cases had been understaged, particularly with regard to disease in the mediastinal lymph nodes. In another study of proton RT for stage I NSCLC, Bush and others [17] treated 68 such patients with proton therapy to a total dose of 60 to 70 Gy (RBE) in 10 fractions. This regimen resulted in a local control rate of 87% in T1 lesions and 49% in T2 lesions and the 3-year disease-free survival rate of 72%. No patients developed G2 and above pneumonitis or esophagitis. Hata and others [18] reported preliminary results of a study of hypofractionated proton therapy for 21 patients with stage I NSCLC (tumors < 4.2 cm); the dose was 50 to 60 Gy, given in 10 fractions. Local progression-free rate and disease-free rate were 95% and 79% at 2 years, with no grade 3 or higher toxicities. In a similar study, Nihei and colleagues [19] treated 36 patients with stage I NSCLC with proton RT to a total dose of 70–94 CGE delivered in 20 fractions and found similarly high rates of local control (92.6%) and overall survival (81%) at 2 years. No grade 2 or higher acute toxicity was observed, but late grade 3 toxicity was observed in three patients. Among the 19 patients with stage IB disease, two had local progression and eight developed regional lymph node or distant metastasis. Compared with most published study, our patients had larger sizes of tumors and/or more challenging location. We delivered ablative dose (BED>100 Gy) to the target which were higher than most of the published studies and achieved promising local control with minimal toxicity.

These findings and our own suggest that passively scattered proton therapy has the potential for delivering ablative radiation doses with little toxicity in early-stage lung cancer. Further improvements in conformality for cases involving complicated anatomy, such as tumors that curve around sensitive critical structures, can be achieved by intensity-modulated proton therapy (IMPT) [20,21]. IMPT, delivered with scanning beams rather than scattered beams, can simultaneously optimize the intensities and energies of all pencil beams by using an objective function that accounts for targets as well as normal tissue constraints. However, tumor and organ motion is the main concern for proton therapy with IMPT [14,15,21]. At M. D. Anderson, 4D CT simulation is required for the evaluation of organ and tumor motion in all patients who undergo proton therapy. We previously showed that in addition to breath-holding or gated treatment, using 4D iGTV, with override of the maximal density projection, with an averaged CT data set for compensator and aperture design provided better target coverage while sparing more of critical normal structures than did other approaches [15]. In addition to intrafraction tumor motion, interfraction motion and anatomic changes can drastically alter the radiation dose distribution [22,23]. In our series, eight patients (45%) did undergo adaptive replanning over the course of treatment to improve target coverage and spare critical structures.

In summary, we found that proton therapy led to substantial sparing of critical normal structures and allowed ablative doses of radiation to be delivered to the target in patients with large or centrally/superiorly located early-stage NSCLC. The toxicity was minimal and local control was excellent. Our findings from this phase-I study support the validity of conducting a phase II study using this approach; such a trial is currently being conducted at M. D. Anderson Cancer Center and Massachusetts General Hospital.

Acknowledgments

We thank the thoracic radiation oncology and Proton Therapy Center teams at M. D. Anderson Cancer Center for their help and support and Ms. Christine Wogan of the Division of Radiation Oncology at M. D. Anderson for editorial assistance.

This research was supported in part by National Cancer Institute grants R01 CA74043, P01 CA 021239, and a Developmental Project Award to Dr. Chang from P50 CA70907, a Specialized Program of Research Excellence (SPORE) in Lung Cancer. This work was presented in abstract form at the World Conference on Lung Cancer, July 31-August 4, 2009, San Francisco, CA.

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Figure 1.

Complete clinical response with acute grade 3 dermatitis in a 71-year-old man with T2N0M0 non-small cell lung cancer. A. PET images obtained before and 3 months after proton therapy show complete disappearance of large, avid lesion in the right lung. B. Acute grade 3 skin reaction in the chest wall toward the end of proton therapy. C. Isodose distribution of proton therapy using a two-beam arrangement showed relative high dose in the affected chest wall.

Figure 2.

Local recurrence after 87.5 Gy of proton therapy for a low-density T2 lesion close to chest wall. A, CT image and treatment plan isodose distribution obtained before proton therapy. B, CT and PET/CT images obtained at the indicated times after treatment illustrate the presence of a local recurrence at 6 months (confirmed by biopsy) that was still evident as PET avidity 3 months later, after the patient had undergone chemotherapy.

Table 1

Dose volume constraints for critical structure (2.5 Gy/fraction)

Organs at Risk	Dose Limits	Description
Normal Lung	20 Gy (RBE) < 40% 10 Gy (RBE) < 50% 5 Gy (RBE) < 60% Mean lung dose < 20 Gy (RBE)	Normal lung, GTV contoured on mid-ventilation data set
Esophagus	60 Gy (RBE) < 50% 74 Gy (RBE) < 10 cm ³ Max dose < 80 Gy (RBE)	Esophagus contoured on any data set
Spinal Cord	Max dose < 45 Gy (RBE)	Spinal canal
Spinal Cord PRV	Max dose < 60 Gy (RBE)	Spinal canal + 5 mm radial expansion
Brachial Plexus	Max dose < 74 Gy (RBE) 70 CGE < 10 cm ³	
Liver	30 Gy (RBE) < 40%	
Kidney	20 Gy (RBE) < 50%	Both kidneys combined if both are functional
Functional kidney	20 Gy (RBE) < 25%	If only one kidney is functional, it should be contoured separately
Bronchial tree PRV	87.5 Gy (RBE) < 10 cm ³	Bronchial tree contoured down to the tertiary bronchi on a lung window/level scan
Major vessels PRV	87.5 Gy (RBE) < 10 cm ³	
Heart, Atria	70 Gy (RBE) < 10% 60 Gy (RBE) < 15% 50 Gy (RBE) < 20% 45 Gy (RBE) < 30% 40 Gy (RBE) < 40% 30 Gy (RBE) < 50%	
Heart, Ventricles	70 Gy (RBE) < 5% 60 Gy (RBE) < 10% 50 Gy (RBE) < 15% 45 Gy (RBE) < 20% 40 Gy (RBE) < 30% 30 Gy (RBE) < 40%	

PRV, planning organ at risk volume.

Table 2

Patient characteristic before proton therapy

Age (Years)	
Median	74
Range	61–83
> 70	12
< 70	6
Sex	
Male	7
Female	11
Karnofsky Performance Score	
Median	70
Range	60–90
Tumor histology	
Squamous cell carcinoma	8
Adenocarcinoma	5
Squamous + adenocarcinoma	1
Non-small cell	4
Tumor size	
≤ 3 cm	6
> 3 cm ≤ 5 cm	10
> 5 cm	2
T status	
T1	4
T2	13
T3	1
Planning Target Volume (cm ³)	
Median	236
Range	89–706
Pretreatment Pulmonary Function	
FEV1	
Median	41%
Range	23%–100%
DLCO	
Median	41%
Range	26%–98%

FEV1, forced expiratory volume in 1 second; DLCO, carbon monoxide lung diffusion capacity

Table 3

Lung volume (%) received dose ≥ 5 Gy to 80 Gy (V5 to V80) for all patients treated with proton to 87.5 Gy

	V5	V10	V20	V30	V40	V50	V60	V70	V80
Median	22.1	20.2	17.6	14.9	12.5	10.3	7.7	5.9	4.3
Maximal	38.8	35.3	26.2	21.1	19	17.6	16	14.1	11.2
Minimal	7.2	6	4.6	3.6	2.9	2.4	0	0	0