Published in final edited form as:

Radiother Oncol. 2015 June ; 115(3): 367–372. doi:10.1016/j.radonc.2015.05.014.

Long-Term Outcomes after Proton Therapy, with Concurrent Chemotherapy, for Stage II-III Inoperable Non-Small Cell Lung Cancer

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Abstract

Purpose—We report long-term disease control, survival, and toxicity for patients with locally advanced non-small cell lung cancer prospectively treated with concurrent proton therapy and chemotherapy on a nonrandomized case-only observational study.

Methods—All patients received passive-scatter proton therapy, planned with 4D-CT-based simulation; all received proton therapy concurrent with weekly chemotherapy. Endpoints were local and distant control, disease-free survival (DFS), and overall survival (OS).

Results—The 134 patients (21 stage II, 113 stage III; median age 69 years) had a median gross tumor volume (GTV) of 70 cm³ (range, 5-753 cm³); 77 patients (57%) received 74 Gy(RBE), and 57 (42% received 60–72 Gy(RBE) (range, 60-74.1 Gy(RBE)). At a median follow-up time of 4.7 years, median OS times were 40.4 months (stage II) and 30.4 months (stage III). Five-year DFS rates were 17.3% (stage II) and 18.0% (stage III). OS, DFS, and local and distant control rates at 5 years did not differ by disease stage. Age and GTV were related to OS and DFS. Toxicity was tolerable, with 1 grade 4 esophagitis and 16 grade 3 events (2 pneumonitis, 6 esophagitis, 8 dermatitis).

Conclusion—This report of outcomes after proton therapy for 134 patients indicated that this regimen produced excellent OS with tolerable toxicity.

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Conflict of Interest statement: The authors declare no conflicts of interest.

Keywords

Proton beam therapy; passive scattering; survival; disease control; carboplatin; paclitaxel

INTRODUCTION

The standard of care for locally advanced inoperable non-small cell lung cancer (NSCLC) is concurrent chemotherapy and photon-based radiation therapy. However, disease recurrence, both local and distant, remains problematic and more effective treatments are actively being sought. One such treatment currently being investigated involves proton therapy, which has been shown in treatment-planning comparisons to deliver high-dose, highly conformal radiation to targets while minimizing damage to surrounding normal tissues. The potential for improving the therapeutic ratio by escalating the radiation dose to control the tumor while minimizing toxicity, even when concurrent chemotherapy is given, presumably would improve patient outcomes.

Although proton therapy has been used for decades, its early use in physics research facilities had numerous restrictions on field size, beam energy, and beam direction, which in turn limited the types of disease that could be treated at such facilities. However, as the numbers of proton facilities dedicated to clinical care increase across the world, proton beam therapy is increasingly being used to treat more diverse malignancies, including lung cancer. The experience with proton therapy for NSCLC to date has largely been confined to small (stage I) tumors treated with proton therapy alone; such therapy has resulted in high rates of local control even at long-term follow-up (1,2). Although several groups are testing proton therapy with concurrent chemotherapy for locally advanced (stages II and III) NSCLC (e.g., 3,4, and our own phase II study [5]), little is known of the long-term outcomes of such treatment.

Herein we report a series of patients enrolled in a prospective, nonrandomized case-only observational protocol to assess normal tissue toxicity arising from treatment with protons. Our intent is to report long-term outcomes, including disease control, survival, and toxicity, for patients with locally advanced lung cancer treated definitively with proton therapy to doses of up to 74 Gy(RBE), given with concurrent chemotherapy.

MATERIALS AND METHODS

Patient characteristics

In this prospective study, 134 patients diagnosed with stage II or III NSCLC received definitive chemotherapy and proton beam radiation therapy at a single institution from 2006 through 2010. All patients were enrolled on a protocol specifically designed to assess normal tissue effects (registered with the National Cancer Institute as NCT00991094). None had participated in the phase II trial reported by Chang et al. (5), and participation in a randomized trial was an exclusion criterion for this analysis.

Disease was staged according to the 6th (2002) edition of the American Joint Commission on Cancer staging system. NSCLC was histopathologically confirmed in all cases. Patients

were evaluated with thoracic computed tomography (CT), positron emission tomography (PET)/CT, bronchoscopy with endobronchial ultrasonography or mediastinoscopy to stage mediastinal involvement. All patients were evaluated by a thoracic surgeon and were deemed to have either medical conditions that precluded surgery or unresectable disease. All patients received concurrent chemotherapy, most often with weekly carboplatin and paclitaxel as weekly intravenous infusions during proton therapy. The choice of chemotherapy, timing, and dose was at the discretion of the treating physician. In most cases, paclitaxel was administered at 50 mg/m² of body surface area, and carboplatin was given at an area under the curve level of 2 mg/nL/min; about 10% of patients received etoposide and paclitaxel because of renal insufficiency. Chemotherapy was withheld at the discretion of the treating physician in the event of abnormal laboratory values or toxicity. Treatment-related toxicity was assessed according to the Common Terminology Criteria for Adverse Effects version 3.0.

Proton beam treatment delivery

All patients were treated at the MD Anderson Proton Therapy Center-Houston by using a passive scattering method, the standard of care during the study period; a scanning beam system suitable for lung cancer did not become available until 2010. The passive scattering system uses a double-scattering range-modulating wheel to spread out the Bragg peak, a range shifter to determine the maximum depth of the proton beam, custom-made brass apertures to shape the field laterally, and customized compensators to conform the distal edge of the beam to the target volume. The treatment planning process for lung tumors involves the use of published formulas for calculating distal and proximal, range, and Hounsfield unit uncertainties (6). The compensators used for passive-scatter proton planning shape the dose distally to conform to the tumor boundaries; the compensators were designed with a drill bit with a 5-mm radius. Brass aperture blocking was used for the lateral margins, and a 1.3-cm uniform expansion from the clinical target volume (CTV) was used as a starting margin. The margins were adjusted slightly to increase or decrease coverage of the tumor. The proton beam energies available for the passive scattering system range from 100 MeV to 250 MeV.

Treatment plans were designed with Varian's Eclipse proton therapy system (Varian Medical Systems, Palo Alto, CA). All patients underwent 4D CT-based simulation to account for tumor motion. The internal gross tumor volume (IGTV) was defined as the envelope of motion of the GTV on a reconstructed maximum intensity projection image and verified across all phases of the 4-dimensional CT dataset (7). The internal clinical target volume (ICTV) was defined as the IGTV plus an 8-mm isotropic margin edited to cover possible tumor microextension. Nodes suspected of harboring disease on PET or mediastinoscopy were included in the high-dose region (70-Gy(RBE)) within the ICTV. Two or three treatment fields were delivered daily. All patients received 5 consecutive daily fractions per week at 2 Gy(RBE) per fraction. Prescription doses were determined by the treating physician, with an intended dose up to 74 Gy(RBE), based on our institutional upper limit for proton therapy for lung cancer. If dosimetric parameters could not be met, the dose was reduced to meet normal tissue constraints. Those dose constraints were as follows: spinal cord: D_{max} <45 Gy; lung: mean dose 20 Gy; V₂₀ (total lung volume minus GTV) 35%,

V₁₀ 45%, V₅ 65%; heart: V₃₀ 45%, mean dose <26 Gy; esophagus: D_{max} 80 Gy, V₇₀ <20%, V₅₀ <40%, mean dose <34 Gy; kidney: 20 Gy to <32% of bilateral kidney; liver: V₃₀ 40%, mean dose <30 Gy.

Treatment evaluations

Posttreatment evaluations took place every 3-6 months and consisted of interim history and physical examination, lab work, and CT or PET/CT scans. Toxicity was assessed at each follow-up visit and scored with the NCI's Common Terminology Criteria for Adverse Events, version 3.0.

Statistical analyses

Outcomes in this study were local, marginal (regional), and distant control (measured from the completion of proton therapy) and disease-free and overall survival (measured from the beginning of proton therapy). Local recurrence was defined as radiographic or histologic evidence of disease progression within the high-dose [70-Gy(RBE)] region. Marginal (regional) recurrence was defined as radiographic evidence of recurrence within the 60- to 70-Gy(RBE) region adjacent to the high-dose region. Distant failure was failure at any other site. Disease-free survival was defined as survival without evidence of lung cancer at local, marginal, or distant sites. Overall survival was defined as the time to death from any cause; deaths from lung cancer were considered an event in this analysis, and patients who were alive or lost to follow-up were censored. . The Kaplan-Meier method was used for all time-to-event analyses, and log-rank tests were used to compare curves. All statistical analyses were done with Stata release 9 (StataCorp, College Station, TX). A Cox proportional hazards model was used for univariate and multivariate analysis of factors potentially associated with disease control or survival.

RESULTS

Patient, disease, and treatment characteristics are summarized in Table 1. Twenty-one patients (16%) had stage II disease and 113 (84%) had stage III disease. The median age at diagnosis was 69 years (range, 28-95 years), the median Karnofsky performance status (KPS) score was 80 (range, 60-100), the median radiation dose was 74.0 Gy(RBE) [range, 60-74.1 Gy(RBE)], and the median GTV was 70 cm³ (range, 5-753 cm³). The median follow-up time was 4.6 years (range 1.5-6.7 years).

The median overall survival times were 40.4 months for patients with stage II disease and 30.4 months for those with stage III disease. Neither overall nor disease-free survival rates differed by disease stage at 3 years or at 5 years (Table 2; Fig. 1A,B). Similarly, local and distant control did not differ by disease stage at 3 years or at 5 years (local+marginal [regional] failure-free survival rates for all patients were 55.8% at 3 years and 54.4% at 5 years [$P=0.762$], and distant metastasis-free rates were 50.3% at 3 years and 45.8% at 5 years [$P=0.861$]) (Table 2; Fig. 1C).

Variables evaluated for potential relationship with outcomes (local control, distant metastasis, disease-free survival, and overall survival) after proton-based chemoradiation were age, GTV, radiation dose, sex, tumor histology, KPS, and disease stage. Because

relatively few patients had stage II disease (n=21), we analyzed potential associations for the entire cohort (n=134) and for those with stage III disease (n=113) separately. On univariate analysis, GTV was related to both overall and disease-free survival, both for all patients and for the subset of patients with stage III disease. Age at diagnosis was related to overall survival both for all patients and for the subset of patients with stage III disease; however, age at diagnosis was associated with disease-free survival for only for the entire group (Table 3). Multivariate analysis with these variables produced findings similar to those of the univariate analysis (Table 3).

Toxicity was mild overall, with only 1 patient experiencing grade 4 toxicity (esophageal stricture) and 16 experiencing grade 3 toxicity (2 radiation pneumonitis, 6 esophagitis, and 8 dermatitis). Toxicity is summarized in Table 4.

DISCUSSION

To our knowledge, this study is the first report of long-term outcomes after proton-based chemoradiation therapy for a relatively large number of patients with locally advanced inoperable lung cancer. Our results indicated that this regimen was tolerable, with a grade 4 toxicity rate of 0.7% and grade 3 toxicity rate of 12%, and produced excellent median overall survival times (40.4 months for stage II and 30.4 months for stage III). Disease stage was not associated with 5-year rates of overall survival or local control, but not suprisingly, larger GTV and older age were associated with poorer prognosis.

Some evidence exists to support higher radiation doses being beneficial in terms of local disease control and survival, although this is still a topic of debate. An analysis of seven RTOG trials for locally advanced NSCLC showed that higher radiotherapy doses were associated with improved local-regional control and survival when radiation was given with chemotherapy (8). Several prospective trials ensued to evaluate the feasibility and benefit of delivering 74 Gy thoracic radiation therapy with concurrent chemotherapy for patients with inoperable stage I-III NSCLC (9,10)). Dose escalation up to 84 Gy seemed to indicate improved survival for patients receiving higher radiation doses if delivered safely to minimize toxicity (11). Phase I/II studies further demonstrated that higher radiation doses produced favorable outcomes, with improved median survival times (>20 months) and tolerable toxicity for patients with inoperable NSCLC (9-13).

This evidence of a benefit from dose escalation makes the results of the recent Radiation Therapy Oncology Group (RTOG) protocol 0617 somewhat perplexing (14). The lack of an observed dose-response relationship for local control or survival was disappointing and was counter to findings of previous RTOG studies. More significantly, the poorer survival in the high-dose (74 Gy) group relative to in the lower-dose group (60 Gy) seems counterintuitive to basic radiobiology principles. Although further analysis of these findings is pending, one likely explanation for the lack of benefit in the higher dose arm is subclinical (in terms of adverse events reported) cardiopulmonary toxicity (15). Such toxicity has been hypothesized to reduce survival in other studies of outcomes after receipt of postoperative radiation, (16,17), particularly when that radiation is given with older, 2D techniques (18). Minimizing cardiopulmonary toxicity is particularly relevant to treating thoracic malignancies with

proton therapy. The near-absence of treatment-related pneumonitis and the low frequency of esophageal toxicity are reasonable surrogates for lower subclinical doses to lung and to the heart, which could translate to improvements in survival.

Thus we believe that proton therapy may be one way in which radiation dose can be safely escalated, as dose escalation with photons in RTOG 0617 led to compromised survival. However, other groups have raised the possibility that local control is a function of not only dose but also GTV and treatment time. Although the probability of local control by radiation is known to decrease as tumor volume increases, one group has posited that higher doses may effectively minimize the adverse outcomes associated with large GTVs in early-stage disease (19). Findings from the the CHARTWEL (ARO 97-1) trial showed that treatment intensification via highly accelerated radiation therapy led to improved local control relative to conventionally fractionated radiation, particularly for patients with advanced disease or those who received induction chemotherapy (20). A subgroup analysis of the CHARTWEL trial revealed that the negative effect of GTV on tumor control after radiotherapy was also influenced by treatment schedule; specifically, larger tumors were associated with greater risk of local failure after conventionally fractionated radiotherapy, but dose-intensification via highly accelerated radiotherapy could minimize that risk, particularly among patients with advanced disease or those who are not eligible for concurrent chemotherapy (21). Differences between the CHARTWEL study and that reported here include the design (randomized vs. nonrandomized data collection), the fractionation schedule (60 Gy was given in forty 1.5-Gy fractions three times a day over 2.5 weeks vs. 74 Gy(RBE) in thirty-seven 2-Gy(RBE) fractions, 5 days per week, over 7.5 weeks), the radiation type (3D-planned conformal X-ray therapy vs. proton therapy), the radiation dose (60 Gy vs. up to 74 Gy(RBE)), and the use of sequential vs. concurrent chemotherapy. Nevertheless, such a regimen may be effective for patients with advanced disease or those who cannot tolerate concurrent chemoradiation therapy.

Studies of proton therapy to date have been criticized for the relatively small numbers of patients with NSCLC treated in various series and the lack of sufficiently long follow-up to provide some measure of efficacy. Nakayama et al. reported that 35 patients with stage II-III NSCLC treated with a mean proton dose of 78 Gy(RBE) without chemotherapy had good local control, with 65.9% local progression-free survival at 2 years, and low toxicity (3). Investigators at the University of Florida treated 19 patients with locally advanced NSCLC with concurrent chemotherapy and proton therapy to a median dose of 74 Gy(RBE). At a median follow-up interval of 16 months, only 1 patient in that study had experienced local progression (4). One prospective randomized trial of proton therapy with concurrent chemotherapy vs. photon (X-ray) therapy and chemotherapy, combining the efforts of investigators from the Massachusetts General Hospital and The University of Texas MD Anderson Cancer Center, recently completed accrual. Another, the multi-institutional trial RTOG 1308, is randomly assigning patients with inoperable stage II or III NSCLC to 70 Gy of proton or photons; this trial is currently accruing patients. While we await the results of both of these trials, it is important to report our experience with patients who were not enrolled on those trials, either because they had been treated before the randomized trial was begun or because they had declined randomization in those trials owing to difficulties with

insurance coverage, unwillingness to participate in a randomized trial, or other patient or physician preferences.

Our study had some limitations, chief among them being its design. This was not, nor was it designed to be, a randomized study; rather, it was a nonrandomized, data collection/single-case observation study, and our methods of statistical analysis were applied accordingly. We specifically excluded patients who were enrolled in randomized trials in an attempt to minimize selection bias; we acknowledge that this may complicate interpretation of our findings. Other limitations are that only 77 patients (57%) received 74 Gy(RBE) (33 received 70-72 Gy(RBE) and 24 received 60-69.6 Gy(RBE)) and that this study included only patients treated at a single institution, with relatively strict normal-tissue constraints. Conversely, the strengths of this study also include its relatively large number of patients and long-term follow-up; exclusion of patients who were participating in randomized trials; and its conduct at a single 'high-throughput', high-volume center in which dose constraints were both strict and consistently adhered to. Indeed, every patient undergoing proton therapy at this institution is required to participate in a protocol, to gather sufficient data to document treatment-related toxicity and to generate realistic, reproducible normal-tissue dose constraints.

This series is the largest reported to date to include the standard treatment paradigm of concurrent chemotherapy and radiation with proton beam therapy. We found very good median survival times (40.4 months for patients with stage II disease and 30.4 months for those with stage III disease) and promising 5-year overall survival rates (25.3% for patients with stage IIIA disease and 31.8% for those with stage IIIB disease). This apparent difference in overall survival was not statistically significant, perhaps because fewer patients in this study had stage IIIB disease. Nevertheless, this improved survival relative to other reports of patients with stage III NSCLC could be explained by our ability to safely deliver a relatively high radiation dose of 74 Gy(RBE) with protons even to large bulky inoperable tumors. The potential advantage of proton beam therapy for lung cancer is the ability to safely deliver radiation to large tumors while minimizing cardiopulmonary toxicity, which could be contributing to mortality in patients with lung cancer. Findings from prospective studies, such as the Mass General–MD Anderson trial and RTOG 1308, will help to resolve open questions regarding these potential advantages.

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Figure 1.

(A) Overall survival, (B) local+marginal (regional) failure-free survival, and (C) distant metastasis-free survival by disease stage at diagnosis. No significant differences were found according to disease stage.

Table 1

Patient characteristics

Characteristic	Value or No. of Patients (%)
Sex	
Male	73
Female	61
Age, years	
<70	76
70	58
Performance status	
KPS <80	36
KPS 80	98
Disease stage	
IIA	6
IIB	15
IIIA	70
IIIB	43
Tumor histology	
Squamous	59
Nonsquamous	75
Gross tumor volume, cm ³	
Median (range)	70 (5-753)
Radiation dose	
60-69.6 Gy(RBE)	24 (18%)
70-72 Gy(RBE)	33 (25%)
74 Gy(RBE)	77 (57%)
Concurrent chemotherapy	134
Median follow-up time	4.7 yrs

Abbreviation: KPS, Karnofsky performance score

Table 2

Survival and Disease Control Outcomes by Disease Stage and Radiation Dose

Disease Stage	Overall		Survival Rates, %					
	3-y	5-y	Disease-Free		Local+Marginal Failure-Free		Distant Metastasis-Free	
	3-y	5-y	3-y	5-y	3-y	5-y	3-y	5-y
Disease Stage								
II	52.3	30.0	23.8	19.0	49.7	49.7	52.4	52.4
IIIA	41.0	25.3	24.3	17.4	58.7	55.7	50.0	43.3
IIIB	44.5	31.8	24.2	14.1	49.2	49.2	48.0	43.1
<i>P</i> Values	0.595		0.955		0.762		0.861	
Radiation Dose, Gy(RBE)								
60-72	45.1	32.7	22.8	12.2	49.5	46.4	49.1	39.2
74	42.9	23.8	25.3	17.8	58.6	58.6	50.7	50.7
<i>P</i> Values	0.804		0.687		0.227		0.429	

Table 3

Univariate and multivariate analyses of factors affecting outcome

Variable	Overall Survival			Disease-Free Survival		
	All Patients (n=134)	Patients with Stage III Disease (n=113)	Patients with Stage III Disease (n=113)	All Patients (n=134)	Patients with Stage III Disease (n=113)	Patients with Stage III Disease (n=113)
	HR (95% CI)	P Value	HR (95% CI)	HR (95% CI)	P Value	P Value
Univariate						
100-cm ³ increase in GTV	1.433 (1.1641-1.7654)	0.00069	1.437 (1.1531-1.7918)	1.297 (1.0754-1.5631)	0.0065	1.277 (1.0506-1.5631)
Sex (male)	0.818 (0.542-1.233)	0.3366		0.637 (0.436-0.93)	0.0196	
Age (continuous)	1.032 (1.0092-1.0558)	0.0123		1.023 (1.0053-1.0472)	0.0135	
Age (70)	1.436 (0.953-2.165)	0.0837		1.351 (0.928-1.968)	0.1164	
KPS 80-100	1.027 (0.645-1.637)	0.9091		1.245 (0.81-1.914)	0.3172	
KPS 90-100	0.829 (0.509-1.35)	0.4513		0.723 (0.456-1.147)	0.1687	
Tumor histology (squamous)	1.385 (0.922-2.081)	0.1171		1.24 (0.853-1.801)	0.2598	
Dose (70-92 Gy(RBE))	1.183 (0.602-2.324)	0.6259		0.917 (0.516-1.629)	0.7676	
Dose (74 Gy(RBE))	1.172 (0.64-2.145)	0.6076		0.879 (0.531-1.456)	0.6013	
Multivariate						
Age (continuous)	1.032 (1.008-1.057)	0.0099	1.026 (1.001-1.052)	1.025 (1.003-1.048)	0.0284	—
100-cm ³ increase in GTV	1.485 (1.198-1.1.841)	0.0003	1.474 (1.177-1.845)	1.34 (1.104-1.628)	0.0031	1.277 (1.0506-1.5631)

Abbreviations: HR, hazard ratio; CI, confidence interval; GTV, gross tumor volume; KPS, Karnofsky performance status score

Table 4

Toxicity

Type of Toxicity	No. of Patients Experiencing Toxicity (%)					P Value*
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	
Dermatitis	74 (55)	33 (25)	19 (14)	8 (6)	0	0.5469
60-66 Gy(RBE)	14 (61)	5 (22)	2 (9)	2 (9)	0	
70-72 Gy(RBE)	19 (56)	9 (26)	4 (12)	2 (6)	0	
74 Gy(RBE)	41 (52)	19 (25)	13 (17)	4 (5)	0	
Esophagitis	69 (51)	25 (19)	33 (25)	6 (4)	1 (1) [†]	0.4162
60-66 Gy(RBE)	10 (43)	3 (13)	8 (35)	2 (9)	0	
70-72 Gy(RBE)	24 (71)	6 (18)	3 (9)	1 (3)	0	
74 Gy(RBE)	35 (45)	16 (21)	22 (29)	3 (4)	1 (1)	
Radiation pneumonitis	68 (51)	35 (26)	29 (22)	2 (1.5)	0	0.525
60-66 Gy(RBE)	14 (61)	5 (22)	4 (17)	0	0	
70-72 Gy(RBE)	20 (6)	9 (26)	5 (15)	0	0	
74 Gy(RBE)	34 (44)	21 (27)	20 (26)	2 (3)	0	

* Two-sided Fisher's exact test

[†] Esophageal stricture