Original Article

Early Findings on Toxicity of Proton Beam Therapy With Concurrent Chemotherapy for Nonsmall Cell Lung Cancer

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BACKGROUND: Concurrent chemoradiation therapy, the standard of care for locally advanced nonsmall cell lung cancer (NSCLC), can cause life-threatening pneumonitis and esophagitis. X-ray (photon)-based radiation therapy (RT) often cannot be given at tumoricidal doses without toxicity to proximal normal tissues. We hypothesized that proton beam therapy for most patients with NSCLC could permit higher tumor doses with less normal-tissue toxicity than photon RT delivered as 3-dimensional conformal RT (3D-CRT) or intensity-modulated RT (IMRT). **METHODS:** We compared the toxicity of proton therapy+concurrent chemotherapy in 62 patients with NSCLC (treatment period 2006-2008) with toxicity for patients with similar disease given 3D-CRT+chemotherapy (n = 74; treatment period 2001-2003) or IMRT+chemotherapy (n = 66; treatment period 2003-2005). Proton therapy to the gross tumor volume was given with weekly intravenous paclitaxel (50 mg/m^2) and carboplatin (area under the curve 2 mg/mL/min). The primary endpoint was toxicity (Common Terminology Criteria for Adverse Events version 3.0). **RESULTS:** Median follow-up times were 15.2 months (proton), 17.9 months (3D-CRT), and 17.4 months (IMRT). Median total radiation dose was 74 Gy(RBE) for the proton group versus 63 Gy for the other groups. Rates of severe (grade $\geq$3) pneumonitis and esophagitis in the proton group (2% and 5%) were lower despite the higher radiation dose (3D-CRT, 30% and 18%; IMRT, 9% and 44%; $P<.001$ for all). **CONCLUSIONS:** We found that higher doses of proton radiation could be delivered to lung tumors with a lower risk of esophagitis and pneumonitis. A randomized comparison of IMRT versus proton therapy is underway. ***Cancer* 2011;000:000–000.** © *2011 American Cancer Society.*

KEYWORDS: lung cancer, toxicity, protein therapy, esophagitis, pneumonitis.

Lung cancer is the most common cause of death from cancer in the United States and in most urbanized countries. More than three-quarters of patients have the nonsmall cell lung cancer (NSCLC) histotype. Surgical resection is the preferred treatment for localized NSCLC, but more than one-third of patients present with locally advanced, unresectable tumors. Concurrent radiation therapy and chemotherapy is believed to offer these patients the highest potential for prolonged disease-free and overall survival.[1]

The main problems associated with concurrent chemoradiation therapy for lung cancer are acute and subacute toxicity, primarily esophageal reactions with odynophagia and treatment-related pneumonitis that can be life-threatening or lethal. These toxic effects adversely affect quality of life for the patients and limit the dose of radiation that can be administered. Advances in radiation techniques such as highly conformal intensity-modulated radiation therapy (IMRT) or proton therapy may reduce the risk of pneumonitis.[2]

Proton beam therapy differs from traditional x-ray (photon) therapy in that the maximum dose is concentrated in the tumor and the dose beyond the tumor is negligible. Treatment planning studies suggest that higher tumor doses can be achieved with proton therapy than with advanced x-ray techniques for locally advanced NSCLC, with a lower risk of common side effects.[3]

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Proton therapy was initiated at The University of Texas MD Anderson Cancer Center in May 2006 with a specific program in combined-modality treatment for NSCLC. We report here our early experience with acute and subacute toxicity from proton therapy and concurrent chemotherapy for locally advanced NSCLC.

MATERIALS AND METHODS

Patients

Between May 2006 and June 2008, 62 consecutive patients with locally advanced, unresectable NSCLC were enrolled in 1 of 2 phase 2 clinical trials that had been approved by the MD Anderson Cancer Center institutional review board. All participants provided written informed consent. The first protocol (NCT00495170) enrolled patients with previously untreated stage 3 NSCLC (according to the 2002 staging system of the American Joint Committee on Cancer[4]). The other protocol (NCT00991094) had more permissive inclusion criteria, allowing enrollment of patients with NSCLC at any stage, prior malignant tumors, and postoperative recurrences. Patients in the second protocol were typically selected for proton therapy because of comorbid conditions, especially limited pulmonary function. This early report of acute toxicity includes patients from both trials.

Pretreatment Evaluation and Exclusion Criteria

Findings from a complete history and physical examination, including performance status, weight loss, and concurrent nonmalignant disease, were recorded. Exclusion criteria were prior thoracic irradiation, malignant pleural effusion, Karnofsky performance status[5] score <60, and weight loss $>10\%$ during the 6 months before diagnosis. Laboratory studies included complete blood counts with differential and platelet count and measurement of serum creatinine, blood urea nitrogen, electrolytes, lactate dehydrogenase, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and total bilirubin levels. Plain chest films, computed tomography (CT) of the thorax and upper abdomen, and positron emission tomography (PET) were required. Mediastinal lymph nodes suspected of harboring disease but with negative PET findings were sampled via mediastinoscopy with biopsy or by bronchoscopy with endobronchial ultrasonography and fine needle aspiration. CT or magnetic resonance imaging scans of the brain were required before proton therapy; pulmonary function tests were recommended but not required. Disease was staged according to the 2002 criteria of the American Joint Committee on Cancer.[4]

Treatments

Radiation therapy

All patients in the proton group received concurrent proton therapy and chemotherapy; no patient in the proton group received x-ray (photon) irradiation as any component of treatment. Proton therapy was delivered using a variable energy synchrotron in doses expressed as Gy(RBE), where Gy is the absorbed dose and RBE (relative biological effectiveness) is the radiation weighting factor, which was 1.1. We used 3-dimensional (3D) conformal techniques to plan and deliver the proton therapy, with 2-4 fields used for each patient.[3] Treatment simulations took place while the patients lay supine, with arms extended over the head, in a custom-fitted vacuum cushion (Vac-Lok, CIVCO Medical Solutions, Kalona, Iowa) that also immobilized the lower extremities. Four-dimensional CT[6] was used to identify the path of the tumors throughout the respiratory cycle. Tumor delineation was aided by PET. Gross tumor volume (GTV) included all nodal disease documented via imaging (CT or PET) or tissue analysis (mediastinoscopy or bronchoscopy). Ipsilateral hilar lymph nodes were included in the GTV if mediastinal or subcarinal lymph nodes showed evidence of disease. Contralateral mediastinal, contralateral hilar, or supraclavicular lymph nodes were included in the GTV only when those nodes showed abnormalities on imaging or pathological analysis. For the 26 patients (42%) who received induction chemotherapy, the GTV consisted of gross disease measured after chemotherapy plus any lymph node stations considered abnormal before chemotherapy. An 8-mm margin was extended beyond the GTV for presumed microscopic tumor extension. Another 5-mm margin was added to account for range and set-up uncertainties.

Constraints on the radiation doses to specific organs were:

Spinal cord: 0% to receive $\geq$45 Gy(RBE);

Normal lung: $<35\%$ to receive 20 Gy(RBE); mean dose to entire lung: <20 Gy(RBE);

Heart: $<100\%$ to receive 40 Gy(RBE); $<50\%$ to receive 50 Gy(RBE);

Esophagus: $<50\%$ to receive 60 Gy(RBE).

Chemotherapy

All patients received concurrent carboplatin-and-paclitaxel chemotherapy as weekly intravenous infusions

during proton therapy. Paclitaxel was administered at 50 mg/m^2 of body surface area, and carboplatin was given at an area under the curve level of 2 mg/mL/min. Standard anti-emetics were allowed at the discretion of the medical oncologist. Concurrent chemotherapy could be withheld or the doses modified if toxicity was encountered as follows. If the absolute neutrophil count decreased to $<$1000/μL or the platelet count decreased to $<$75,000/μL, carboplatin and paclitaxel were withheld until the myelosuppression resolved. If grade 3 dysphagia appeared, weekly carboplatin and paclitaxel were withheld and then readministered at 50% of the original dose at the discretion of the medical oncologist.

Neoadjuvant and adjuvant chemotherapy at systemic doses were allowed in either trial. The choice of chemotherapy type, dosing, and timing was at the discretion of the treating physicians. Only the chemotherapy given concurrently with the proton therapy was standardized.

Treatment Evaluation

Patients were evaluated at least weekly during treatment, at 4-6 weeks after treatment, and then every 3 months for 2 years and every 6 months thereafter. Adverse events were scored using Common Terminology Criteria version 3.0. The first follow-up visit included an interval medical history and physical examination, hematological studies, chest x-ray, and CT examination. A follow-up PET examination was conducted during the first 3 to 4 months after treatment. Thereafter, chest x-ray plus CT examinations were alternated with PET examinations.

Data on survival, time to progression, and failure patterns are being collected in the ongoing phase 2 trials. Early information on survival is reported here for completeness.

Comparison Groups

This report focuses on early toxicity of proton beam therapy and concurrent chemotherapy. The results are compared with historical results from 2 previously approved retrospective chart reviews of toxicity after x-ray (photon) RT (either IMRT[2,7] or 3D conformal RT [3D-CRT][8]) with concurrent chemotherapy as definitive treatment for locally advanced, unresectable NSCLC. Concurrent chemoradiation therapy has been the standard of care at the MD Anderson Cancer Center since the 1990s, although radiation delivery techniques evolved from 2-dimensional CRT to 3D-CRT in the late 1990s and then to IMRT in the early 2000s. We chose 2 comparison groups because the National Comprehensive Cancer Network still considers 3D-CRT with concurrent chemotherapy the standard of care for NSCLC (http://www.nccn.org/professionals/physician_gls/PDF/nscl.pdf) and because our institutional experience suggests that IMRT is associated with less pulmonary toxicity than 3D-CRT.[7] The median radiation dose in both comparison groups was 63 Gy; the survey periods were 2001-2003 for 3D-CRT and 2003-2005 for IMRT.[2,7,8]

Statistical Analyses

Stata/SE 11.1 (Stata Corp LP, College Station, Texas) was used for data analyses. Pearson's chi-square test was used to assess measures of association in frequency tables. Survival was calculated using the Kaplan-Meier method. The equality of means for continuous variables was assessed using t tests. $P \leq .05$ was considered statistically significant. Statistical tests were based on a 2-sided significance level. Mantel-Haenszel estimates were used to assess specific interactions between disease stage and toxicity grade by treatment group.

RESULTS

Patient characteristics, treatment characteristics, and follow-up information for all 3 groups are shown in Table 1. Thirty-seven patients were enrolled in the prospective trial of proton beam therapy for previously untreated stage 3 NSCLC, and 25 patients were enrolled in the trial that allowed disease at other stages. The median total proton dose was 74 Gy(RBE). Details of concurrent chemotherapy are also shown in Table 1. The median number of concurrent weekly chemotherapy cycles was 6; 23% of patients experienced treatment delays, 13% required chemotherapy dose reductions, and 10% did not complete the full course of concurrent chemotherapy. Twenty-six patients received neoadjuvant chemotherapy (median 3 cycles of systemic dose chemotherapy). Eight patients were known to proceed to adjuvant chemotherapy after a median 2 cycles of concurrent treatment.

Toxicity for all 3 patient groups is shown in Table 2. No differences in hematological toxicity (anemia, thrombocytopenia, neutropenia, and leukopenia) were found between groups (data not shown). The most common toxicity of concurrent proton therapy and chemotherapy (experienced by 60 patients [97%]) was dermatitis; in most cases this was mild, with only 15 patients (24%) experiencing grade 3 reactions. Esophageal reactions, usually odynophagia, were observed in 49 (79%) patients; 27 (43%) patients experienced grade 2 or higher reactions

Table 1. Baseline and Treatment Characteristics of Patients Treated With Photons Versus Protons

Characteristic	3D Conformal Concurrent Chemoradiation (n=74)	IMRT Concurrent Chemoradiation (n=66)	Proton Beam Concurrent Chemoradiation (n=62)	*P*
Treatment period	2001-2003	2003-2005	2006-2008	
Age, y, median (range)	61 (38-81)	62 (38-82)	67 (38-81)	.04[a]
Sex				
Men	37 (50%)	40 (61%)	34 (55%)	.453[b]
Women	37 (50%)	26 (39%)	28 (45%)	
Karnofsky performance score				
100	0	2 (3%)	1 (2%)	.05[b]
90	22 (30%)	9 (13%)	22 (35%)	
80	44 (59%)	39 (59%)	29 (47%)	
70	4 (5%)	13 (20%)	7 (11%)	
60	4 (5%)	3 (5%)	3 (5%)	
Weight loss				
<5%	71 (96%)	58 (88%)	48 (77%)	.005[b]
≥5%	3 (4%)	8 (12%)	14 (23%)	
Tumor histology				
Squamous	27 (36%)	17 (26%)	25 (40%)	.19[b]
Nonsquamous	47 (64%)	49 (74%)	37 (60%)	
Ethnicity				
White	65 (88%)	46 (70%)	37 (60%)	.001[b]
Nonwhite	9 (12%)	20 (30%)	25 (40%)	
Prior malignancy				
Yes	10 (14%)	18 (27%)	17 (27%)	.13[b]
No	64 (86%)	48 (73%)	45 (73%)	
Clinical disease stage				
1B	0	0	2 (3%)	.002[b]
2A	2 (3%)	0	0	
2B	2 (3%)	3 (5%)	5 (8%)	
3A	30 (41%)	15 (23%)	25 (40%)	
3B	34 (46%)	38 (58%)	17 (27%)	
4	6 (8%)	7 (11%)	5 (8%)	
Recurrent	0	3 (4%)	8 (13%)	
Lymph node involvement				
Yes	59 (80%)	60 (91%)	50 (81%)	.151[b]
No	15 (20%)	6 (9%)	12 (19%)	
Tumor location				
Left lung	30 (41%)	22 (33%)	28 (45%)	.68[b]
Right lung	43 (58%)	42 (64%)	33 (53%)	
Mediastinum	1 (1%)	2 (3%)	1 (2%)	
Total radiation dose, median (range)	63 Gy (60-69.9)	63 Gy (60-76)	74 Gy(RBE) (63-80.95)	<.001[a]
Gross tumor volume, cm^3, median (range)	141.1 (6.2-1186.1)	203.1 (20.9-817.9)	67.45 (4.1-753.2)	.04[a]
Radiation therapy completed				
Yes	74	63	61	.151[b]
No	0	3	1	
Delay until completion of radiation, d				
≤5	4	22	6	.442[b]
>5	1	2	2	
Induction chemotherapy				
Yes	42 (57%)	22 (33%)	23 (37%)	.01[b]
No	32 (43%)	44 (67%)	39 (63%)	

(Continued)

Table 1. (Continued)

Characteristic	3D Conformal Concurrent Chemoradiation (n=74)	IMRT Concurrent Chemoradiation (n=66)	Proton Beam Concurrent Chemoradiation (n=62)	*P*
No. of induction chemotherapy cycles				
0	32	44	39	
1	1	5	1	
2	24	9	8	
3	12	5	4	
4+	3	0	6	
Unknown	2	3	4	
Concurrent chemotherapy				
Yes	74	66	62	
No	0	0	0	
No. of concurrent chemotherapy cycles				
1	1	0	0	
2	2	1	2	
3	1	6	2	
4	2	2	1	
5	0	5	1	
6	67	43	54	
7	0	0	2	
Unknown	1	9	0	
Adjuvant chemotherapy				
Yes	15 (20%)	32 (48%)	9 (14%)	<.001[b]
No	59 (80%)	34 (52%)	53 (86%)	
No. adjuvant chemotherapy cycles				
1	0	0	4	
2	4	11	2	
3	3	11	2	
4+	5	0	1	
Unknown	3	10	0	
Vital status at last follow-up				<.001[b]
Alive with disease	4	4	20	
Alive without disease	9	11	20	
Alive, disease status unknown	1	0	0	
Dead of disease	40	38	18	
Dead of intercurrent disease	0	5	1	
Dead of unknown causes	20	8	3	
Follow-up time, mo, median (range)				<.001[a]
All patients	17.9 (2.3-76.1)	17.4 (1.8-65.5)	15.2 (3.3-27.4)	
Patients alive at last follow-up	63.3 (24.0-79.1)	45.6 (1.8-65.5)	15.2 (5.2-27.4)	

3D indicates 3-dimensional; IMRT, intensity-modulated radiation therapy.
[a] Analysis of variance.
[b] Chi-square test.

(ie, symptomatic and affecting eating or swallowing, with intravenous fluids indicated for <24 hours), but only 3 (5%) patients experienced grade 3 reactions (ie, symptomatic and severely affecting eating/swallowing, with intravenous fluids, tube feedings, or total parenteral nutrition indicated for ≥24 hours). Treatment-related pneumonitis was noted in 49 patients (79%), but only 1 (2%) patient experienced pneumonitis of grade 3 or higher (ie, symptomatic [rather than only visible on radiography], interfering with activities of daily living, and requiring supplemental oxygen) (Table 2). Because differences in tumor volume (67 cm^3 for the proton group, 141 cm^3 for the 3D-CRT group, and 203 cm^3 for the IMRT group [Table 1]) could have influenced these results, we

Table 2. Acute Nonhematologic Toxicity After Photon Versus Proton Therapy for Nonsmall Cell Lung Cancer

Toxicity and Treatment	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Unknown	*P*
Esophagitis								<.001
Chemotherapy+3D-CRT	3 (4)	25 (34)	33 (45)	13 (18)	0	0	0	
Chemotherapy+IMRT	4 (6)	9 (14)	24 (36)	26 (39)	3 (4.5)	0	0	
Chemotherapy+PBT	13 (21)	22 (35.5)	24 (39)	3 (5)	0	0	0	
Pneumonitis								<.001
Chemotherapy+3D-CRT	23 (31)	9 (12)	20 (27)	22 (30)	0	0	0	
Chemotherapy+IMRT	19 (29)	24 (36)	17 (26)	4 (6)	0	2 (3)	0	
Chemotherapy+PBT	13 (21)	30 (48)	18 (29)	1 (2)	0	0	0	
Dermatitis								<.001
Chemotherapy+3D-CRT	6 (8)	54 (73)	9 (12)	5 (7)	0	0	0	
Chemotherapy+IMRT	5 (8)	33 (50)	17 (26)	11 (17)	0	0	0	
Chemotherapy+PBT	2 (3)	22 (35.5)	23 (37)	15 (24)	0	0	0	
Fatigue								.002
Chemotherapy+3D-CRT	0	20 (24)	28 (34)	24 (29)	2 (2)	0	0	
Chemotherapy+IMRT	12 (18)	16 (24)	27 (41)	10 (15)	1 (1.5)	0	0	
Chemotherapy+PBT	3 (5)	12 (19)	32 (52)	12 (19)	3 (5)	0	0	

All data are expressed as No. of patients (%).
3D-CRT indicates 3-dimensional conformal radiation therapy; IMRT, intensity-modulated radiation therapy; PBT, proton beam therapy.

Table 3. Acute Grade ≥2 Nonhematologic Toxicity After Photon Versus Proton Therapy for Nonsmall Cell Lung Cancer According to Gross Tumor Volume

Toxicity and Treatment	Gross Tumor Volume											
	≤50 cm^3		≤100 cm^3		≤200 cm^3		≤300 cm^3		≤400 cm^3		≤500 cm^3	
	Events (%)	*P*	Events (%)	*P*	Events (%)	*P*	Events (%)	*P*	Events (%)	*P*	Events (%)	*P*
Esophagitis												
Chemotherapy+3D-CRT	6 (67)	.160	16 (62)	.013	27 (55)	<.001	32 (57)	<.001	38 (61)	<.001	41 (60)	<.001
Chemotherapy+IMRT	3 (100)		6 (75)		22 (79)		33 (80)		35 (80)		43 (83)	
Chemotherapy+PBT	11 (48)		19 (45)		24 (44)		25 (44)		25 (42)		26 (43)	
Pneumonitis												
Chemotherapy+3D-CRT	7 (78)	.017	17 (65)	<.001	31 (63)	<.001	36 (64)	<.001	37 (60)	<.001	38 (56)	<.001
Chemotherapy+IMRT	1 (33)		3 (38)		11 (39)		17 (41)		18 (41)		19 (37)	
Chemotherapy+PBT	4 (17)		10 (24)		17 (31)		17 (30)		18 (31)		18 (30)	
Dermatitis												
Chemotherapy+3D-CRT	0 (0)	.035	5 (19)	.03	8 (16)	.001	10 (18)	<.001	12 (19)	<.001	13 (19)	<.001
Chemotherapy+IMRT	1 (33)		3 (38)		10 (36)		16 (39)		17 (39)		21 (40)	
Chemotherapy+PBT	14 (61)		16 (38)		33 (60)		35 (61)		37 (63)		37 (62)	
Fatigue												
Chemotherapy+3D-CRT	5 (56)	.671	16 (62)	.227	33 (67)	.001	37 (66)	.001	43 (69)	<.001	49 (72)	.001
Chemotherapy+IMRT	2 (67)		6 (75)		16 (57)		23 (56)		24 (55)		29 (56)	
Chemotherapy+PBT	18 (78)		30 (71)		40 (73)		42 (74)		44 (75)		45 (75)	

3D-CRT indicates 3-dimensional conformal radiation therapy; IMRT, intensity-modulated radiation therapy; PBT, proton beam therapy.

compared toxicity according to tumor volume and found that rates of grade ≥2 pneumonitis were lower after proton therapy at every tumor volume (Table 3). We further found that disease stage was related to the severity of esophagitis in the 3D-CRT group, but not to the severity of pneumonitis, dermatitis, or fatigue in any treatment group (Table 4). Finally, we found that toxicity from concurrent proton therapy and chemotherapy was not affected by receipt of neoadjuvant therapy, with no differences observed in the incidence or severity of esophagitis, pneumonitis, fatigue, dermatitis, or hematological variables (data not shown).

Table 4. Disease Stage and Acute Toxicity After Photon Versus Proton Therapy for Nonsmall Cell Lung Cancer

Toxicity and Disease Stage	Treatment and Toxicity Grade																	
	3D-CRT						IMRT						PBT					
	0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5
Esophagitis[a]																		
1B	—	—	—	—	—	—	—	—	—	—	—	—	0	1	1	0	0	0
2A	0	0	2	0	0	0	—	—	—	—	—	—	—	—	—	—	—	—
2B	1	0	0	1	0	0	1	0	1	1	0	0	3	2	0	0	0	0
3A	0	14	13	3	0	0	1	5	5	4	0	0	4	11	10	0	0	0
3B	2	9	16	7	0	0	2	3	15	16	2	0	3	3	9	2	0	0
4	0	2	2	2	0	0	0	1	3	2	1	0	2	0	2	1	0	0
Recurrent	—	—	—	—	—	—	0	0	0	3	0	0	1	5	2	0	0	0
Pneumonitis[b]																		
1B	—	—	—	—	—	—	—	—	—	—	—	—	0	1	1	0	0	0
2A	0	0	1	1	0	0	—	—	—	—	—	—	—	—	—	—	—	—
2B	1	0	1	0	0	0	0	1	1	1	0	0	0	3	2	0	0	0
3A	8	5	9	8	0	0	6	2	6	1	0	0	2	15	7	1	0	0
3B	9	4	9	12	0	0	12	15	7	2	0	2	5	7	5	0	0	0
4	5	0	0	1	0	0	0	4	3	0	0	0	2	2	1	0	0	0
Recurrent	—	—	—	—	—	—	1	2	0	0	0	0	4	2	2	0	0	0
Dermatitis[c]																		
1B	—	—	—	—	—	—	—	—	—	—	—	—	0	2	0	0	0	0
2A	0	2	0	0	0	0	—	—	—	—	—	—	—	—	—	—	—	—
2B	0	2	0	0	0	0	1	1	1	0	0	0	0	2	1	2	0	0
3A	3	22	3	2	0	0	0	10	2	3	0	0	1	9	12	3	0	0
3B	3	24	4	3	0	0	3	16	12	7	0	0	1	4	7	5	0	0
4	0	4	2	0	0	0	1	3	2	1	0	0	0	0	3	2	0	0
Recurrent	—	—	—	—	—	—	0	3	0	0	0	0	0	5	0	3	0	0
Fatigue[d]																		
1B	—	—	—	—	—	—	—	—	—	—	—	—	0	0	1	0	1	0
2A	0	1	0	1	0	0	—	—	—	—	—	—	—	—	—	—	—	—
2B	0	0	0	2	0	0	2	1	0	0	0	0	0	1	3	1	0	0
3A	0	10	13	7	0	0	3	3	7	2	0	0	2	5	15	3	0	0
3B	0	8	12	13	1	0	6	10	15	6	1	0	0	3	9	4	1	0
4	0	1	3	1	1	0	1	1	4	1	0	0	0	0	2	3	0	0
Recurrent	—	—	—	—	—	—	0	1	1	1	0	0	1	3	2	1	1	0

3D-CRT indicates 3-dimensional conformal radiation therapy; IMRT, intensity-modulated radiation therapy; PBT, proton beam therapy.
[a] $P = .042$ for 3D-CRT, .333 for IMRT, and .155 for PBT (Mantel-Haenszel, not significant).
[b] $P = .412$ for 3D-CRT, .388 for IMRT, and .655 for PBT (Mantel-Haenszel, not significant).
[c] $P = .953$ for 3D-CRT, .537 for IMRT, and .315 for PBT.
[d] $P = .324$ for 3D-CRT, .911 for IMRT, and .237 for PBT.

Preliminary findings on survival are as follows. Median overall survival times were 17.7 months for the 3D-CRT group, 17.6 months for the IMRT group, and 24.4 months for the proton therapy group (log-rank $P = 0.1061$ [not significant]).

DISCUSSION

This is the first report of proton beam therapy with concurrent chemotherapy for NSCLC that permits evaluation of acute and subacute toxicity. We recognize that any comparison of treatment outcomes that involves 1 or more retrospective components will be associated with selection bias; nevertheless, we believe that historical comparisons such as the ones made here are important.

Unresectable NSCLC is far more common and lethal than the other diseases treated with proton therapy to date. Concurrent chemoradiation therapy has emerged as the treatment of choice for unresectable NSCLC, but the sensitivity of the normal lung limits the radiation doses that can be delivered. Local control rates at conventional radiation doses are poor, ranging from 20% to 50%, depending on the method of evaluation.[9] Findings from a phase 1/2 trial by the Radiation Therapy Oncology Group (RTOG),[10] a phase 1 trial by the North Central Cancer Treatment Group,[11] and a phase 2 trial by the

Table 5. Pneumonitis and Esophagitis in Other Trials of Chemoradiation Therapy for Locally Advanced Nonsmall Cell Lung Cancer

Study	No. of Patients	Esophagitis, %	Pneumonitis, %
Bradley et al[10]	53	40[a]	23
Socinski et al[12]	37	16	11
Antonadou et al[15]	73	84	56
Komaki et al[16]	62	35	16
Leong et al[17]	60	15	NR
Senzer[18]	100	21	NR
Movsas et al[19]	243	34	16.7
Wei et al[20]	215	20.5	NR
Current study	62	5	2

All toxicities are grade ≥3 unless noted otherwise.
NR indicates not reported.
[a] Grade ≥2 esophagitis; grade ≥3 esophagitis not reported.

Cancer and Leukemia Group B[12] confirm that the maximum tolerated dose of x-ray (photon) therapy, given as 3D-CRT with paclitaxel- and carboplatin-based chemotherapy, is 74 Gy. If the use of protons allowed the radiation dose to the tumor to be increased without increasing the toxicity of the concurrent treatment, this could be an important factor in improving outcome.

Concurrent chemoradiation therapy has been the standard of care for locally advanced NSCLC at the MD Anderson Cancer Center since the 1990s. The transition from 2D-RT to 3D-CRT took place in 1997.[13,14] The transition from 3D-CRT to IMRT occurred in 2004, and results comparing these 2 techniques have been reported elsewhere.[2,7] Studies of tumor motion and methods of managing it also took place during 2003-2005[6] and were used as the basis for addressing tumor motion with IMRT and with proton therapy. Nevertheless, when this report was written, IMRT was not considered standard throughout the United States, which led to our including a comparison group treated with 3D-CRT as well as another group treated with IMRT during the past decade.

This report focuses only on acute and subacute toxicity, because our follow-up time is too short to evaluate tumor control and survival. Findings from other trials of concurrent chemoradiation therapy for NSCLC are shown in Table 5.[10,12,15-20] Notably, our median total dose from proton therapy as reported here was 74 Gy(RBE), which is more than 15% higher than the standard 63-Gy dose used in most NSCLC trials such as RTOG 9410.[21] Both phase 2 trials that used 74 Gy (photons) with carboplatin and paclitaxel[10,12] have shown substantially higher rates of severe (grade ≥3) pneumonitis than the current experience (Table 5). Rates of severe esophagitis are more difficult to compare directly, because the RTOG report[10] included only grade ≥2 esophagitis. Nevertheless, the rate of grade ≥2 esophagitis in that study (40%) compared favorably with the rate in the current study (43%).

Treatment-related pneumonitis is the most serious adverse effect of radiation or chemoradiation in NSCLC. It occurs predominantly within 6 months of treatment[22] and can contribute to the death of patients. In the MD Anderson Cancer Center experience with 3D-CRT given at a median total dose of 63 Gy, 32% of patients had treatment-related pneumonitis of grade 3 or higher.[2] Pneumonitis is well known to be related to the volume of normal lung irradiated[22-25]; hence in cooperative group studies, a limit is placed on the volume of normal lung that can receive a total dose of 20 Gy or more. Findings from treatment planning studies[3] suggest that proton beam therapy could decrease the volume of normal lung irradiated compared with x-ray treatments (3D-CRT and IMRT) even while delivering higher total radiation doses to the tumor. Our experience to date supports this hypothesis.

Esophageal reactions are rarely life-threatening, but the odynophagia resulting from concurrent chemoradiation therapy can profoundly hinder quality of life during treatment and for weeks thereafter. Such reactions are relatively common (Tables 2, 4, 5); in an RTOG study of the cytoprotectant amifostine to reduce dysphagia and odynophagia from concurrent chemoradiation for NSCLC,[19] the rate of severe (≥grade 3) esophageal reactions was 34% in the control (no-amifostine) group (n = 122). In the present study, we found that proton beam therapy produced severe esophagitis in only 5% of patients.

The relatively high rate of dermatitis in the proton group probably reflects the higher surface dose of protons versus photons and the use of relatively few proton beams (2-4 per patient) to minimize the exposure of normal lung tissue. In any event, dermatitis associated with proton therapy was rarely severe (24% grade 3 and no grade 4-5 [Table 2]) and was effectively treated with supportive measures without the need to delay therapy.

Our study did have several shortcomings related to the use of retrospective data for comparison, including substantial differences in pretreatment assessments (especially imaging) and treatment-planning capabilities[7] over the periods of study and the heterogeneity of the patient populations. The difference in baseline GTV between the 3 groups in particular could be attributable to heterogeneity of disease stage, but also to the increasing use of more rigorous evaluations of nodal disease (eg, PET, endoscopic ultrasonography) and the development of highly

conformal planning and delivery techniques over the periods of study, both of which might be expected to lead to smaller GTVs. The proton therapy group was itself somewhat heterogeneous because of the inclusion of 25 patients with any stage (including recurrent) disease; however, a separate analysis of only those patients with previously untreated stage 3 disease showed similar rates of grade 3 toxicity (dermatitis 13.3%, esophagitis 6.7%, pneumonitis 3.3%) and no grade 4-5 toxicity.[26] Moreover, our analysis of toxicity according to GTV revealed that most toxicities were independent of tumor size within the groups and that the rate of pneumonitis was lower in the proton group regardless of tumor size (Table 3) and disease stage (Table 4). Despite these acknowledged shortcomings, it seemed important nevertheless to have clinical data on the potential toxicity of proton therapy before proceeding to a randomized trial, particularly one involving a higher total radiation dose. Some strengths that may warrant such comparisons include the consistency of normal-tissue dose constraints over the 3 treatment periods (2001-2003 for 3D-CRT, 2003-2005 for IMRT, and 2006-2008 for proton therapy). These dose constraints were derived from those used by the RTOG, of which MD Anderson Cancer Center has been a participating member for more than 2 decades. Moreover, tumor motion has been accounted for in the same way since 2004; specifically, 4-dimensional CT scanning is used during treatment simulation and planning to develop individualized GTVs and clinical target volumes.

This promising early experience with concurrent chemotherapy and proton therapy has led us to design a prospective randomized comparative trial of proton therapy versus IMRT, both with concurrent chemotherapy, for stage 2/3 NSCLC (ClinicalTrials.gov identifier NCT00495040). In that trial, patients are randomly assigned to receive IMRT+chemotherapy or proton beam therapy+chemotherapy. Both arms require that the GTV be treated to the same total dose [74 Gy of IMRT; 74 Gy(RBE) of proton therapy] in the same fractionation [2 Gy or 2 Gy(RBE) per fraction]. Primary endpoints are local tumor control and severe (≥grade 3) treatment-related pneumonitis. This trial, a joint effort between Massachusetts General Hospital and MD Anderson Cancer Center, is supported in part by a grant from the National Cancer Institute (P01CA021239).

CONFLICT OF INTEREST DISCLOSURES

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