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Comparative Effectiveness of Proton vs Photon Therapy as Part of Concurrent Chemoradiotherapy for Locally Advanced Cancer

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IMPORTANCE Concurrent chemoradiotherapy is the standard-of-care curative treatment for many cancers but is associated with substantial morbidity. Concurrent chemoradiotherapy administered with proton therapy might reduce toxicity and achieve comparable cancer control outcomes compared with conventional photon radiotherapy by reducing the radiation dose to normal tissues.

OBJECTIVE To assess whether proton therapy in the setting of concurrent chemoradiotherapy is associated with fewer 90-day unplanned hospitalizations (Common Terminology Criteria for Adverse Events, version 4 [CTCAEv4], grade ≥3) or other adverse events and similar disease-free and overall survival compared with concurrent photon therapy and chemoradiotherapy.

DESIGN, SETTING, AND PARTICIPANTS This retrospective, nonrandomized comparative effectiveness study included 1483 adult patients with nonmetastatic, locally advanced cancer treated with concurrent chemoradiotherapy with curative intent from January 1, 2011, through December 31, 2016, at a large academic health system. Three hundred ninety-one patients received proton therapy and 1092, photon therapy. Data were analyzed from October 15, 2018, through February 1, 2019.

INTERVENTIONS Proton vs photon chemoradiotherapy.

MAIN OUTCOMES AND MEASURES The primary end point was 90-day adverse events associated with unplanned hospitalizations (CTCAEv4 grade ≥3). Secondary end points included Eastern Cooperative Oncology Group (ECOG) performance status decline during treatment, 90-day adverse events of at least CTCAEv4 grade 2 that limit instrumental activities of daily living, and disease-free and overall survival. Data on adverse events and survival were gathered prospectively. Modified Poisson regression models with inverse propensity score weighting were used to model adverse event outcomes, and Cox proportional hazards regression models with weighting were used for survival outcomes. Propensity scores were estimated using an ensemble machine-learning approach.

RESULTS Among the 1483 patients included in the analysis (935 men [63.0%]; median age, 62 [range, 18-93] years), those receiving proton therapy were significantly older (median age, 66 [range, 18-93] vs 61 [range, 19-91] years; $P < .01$), had less favorable Charlson-Deyo comorbidity scores (median, 3.0 vs 2.0; $P < .01$), and had lower integral radiation dose to tissues outside the target (mean [SD] volume, 14.1 [6.4] vs 19.1 [10.6] cGy/cc × 10^7; $P < .01$). Baseline grade ≥2 toxicity (22% vs 24%; $P = .37$) and ECOG performance status (mean [SD], 0.62 [0.74] vs 0.68 [0.80]; $P = .16$) were similar between the 2 cohorts. In propensity score weighted–analyses, proton chemoradiotherapy was associated with a significantly lower relative risk of 90-day adverse events of at least grade 3 (0.31; 95% CI, 0.15-0.66, $P = .002$), 90-day adverse events of at least grade 2 (0.78; 95% CI, 0.65-0.93, $P = .006$), and decline in performance status during treatment (0.51; 95% CI, 0.37-0.71; $P < .001$). There was no difference in disease-free or overall survival.

CONCLUSIONS AND RELEVANCE In this analysis, proton chemoradiotherapy was associated with significantly reduced acute adverse events that caused unplanned hospitalizations, with similar disease-free and overall survival. Prospective trials are warranted to validate these results.

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Invited Commentary
Supplemental content

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Concurrent chemoradiotherapy is a standard-of-care curative therapy for many locally advanced cancers, including lung cancer,[1] glioma,[2] head and neck cancer,[3] and esophageal cancer.[4,5] However, concurrent chemoradiotherapy is associated with substantial morbidity,[1,6] including oral mucositis, esophagitis, nausea, vomiting, significant weight loss, and radiation-induced lung injury that can result in unplanned hospitalizations, emergency department visits, treatment interruptions that can diminish the effectiveness of treatment, and decreased patient performance status.[1,2,7]

For decades, concurrent chemoradiotherapy has been administered using photon (ie, x-ray) radiation. Photon therapy, delivered as intensity-modulated radiotherapy or 3-dimensional conformal radiotherapy, uses multiple x-ray beams to irradiate a tumor target but unavoidably deposits radiation in normal tissues beyond the target. Proton radiation therapy is a US Food and Drug Administration–approved treatment that has emerged as an alternative radiation treatment modality that directs protons at the tumor target, where they deposit the bulk of their radiation dose to a finite depth in tissue with minimal residual radiation beyond the target (**Figure 1** and eFigure in the Supplement).[8] Although proton therapy has been in limited clinical use since the 1950s, clinical implementation has been slow owing to the high capital expenditure and maintenance costs required and challenges in dose computational modeling.[9] Advances in proton technology and decreasing equipment costs have increased patient access to proton therapy, and it is now often the preferred radiation modality for many pediatric,[10] base of skull,[11,12] and primary liver[13] cancers. Proton therapy as part of concurrent chemoradiotherapy may be able to reduce treatment toxicity, but limited data are available comparing results of proton chemoradiotherapy with chemoradiotherapy delivered with photon therapy, and proton therapy remains unproven in this setting.[9,14-18]

Key Points

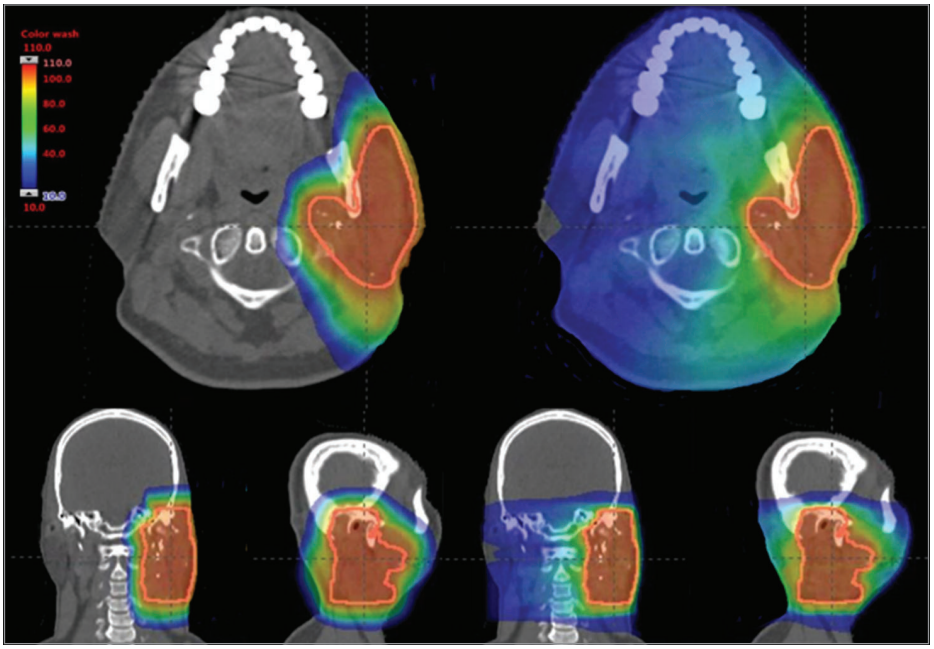
Question Can proton therapy reduce the risk of severe adverse events associated with unplanned hospitalizations compared with photon therapy for patients undergoing concurrent chemoradiotherapy?

Findings In this comparative effectiveness study of 1483 adults with nonmetastatic cancer and treated with curative intent, proton therapy was associated with a two-thirds reduction in adverse events associated with unplanned hospitalizations, with no difference in disease-free or overall survival.

Meaning These findings suggest that, in adults with locally advanced cancer, proton therapy with concurrent chemoradiotherapy may significantly reduce severe adverse events compared with photon therapy, with comparable oncologic outcomes.

In this comparative effectiveness cohort study, we compared the rate of severe 90-day adverse events associated with unplanned hospitalizations (defined as Common Terminology Criteria for Adverse Events, version 4 [CTCAEv4], grade ≥3) ([range, 0 [no toxicity] to 5 [death]) for patients treated with proton vs photon chemoradiotherapy. Secondary end points included a decline in the Eastern Cooperative Oncology Group (ECOG) performance status scores from the start to the completion of radiotherapy for patients treated with proton vs photon chemoradiotherapy and the rate of acute 90-day adverse

Figure 1. Representative Proton and Photon Treatment Plan for a Patient With Head and Neck Cancer



Proton Therapy Photon Therapy

Radiation dose is represented as a color wash, with blue indicating the region receiving the lowest radiation dose and red indicating the region receiving the highest radiation dose.

events that limit the patient's instrumental activities of daily living (CTCAEv4 grade ≥2).[19,20] Decline in ECOG performance status is associated with worse outcomes, including inability to undergo additional planned therapies, decreased survival, decreased quality of life, and inability to perform work activities.[21] We hypothesized that, in the setting of chemoradiotherapy, proton therapy compared with photon therapy is associated with reduced 90-day severe adverse events that result in unplanned hospitalizations and less decline in ECOG performance status during chemoradiotherapy, without a reduction in cancer control outcomes.

Methods

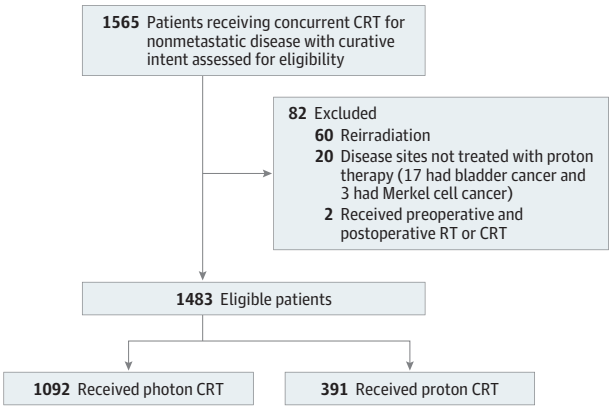
Cohort

This retrospective, nonrandomized comparative effectiveness study was approved by the institutional review board of the University of Pennsylvania, which waived the need for informed consent for the use of medical records. Adult patients (aged ≥18 years) treated with concurrent chemoradiotherapy with curative intent for nonmetastatic cancer using proton or photon radiotherapy in the University of Pennsylvania Health System from January 1, 2011, through December 31, 2016, were included. Patients treated with salvage reirradiation overlapping with prior radiotherapy portals or those treated with stereotactic body radiotherapy were excluded. Diseases treated at our institution with only photon and not proton chemoradiotherapy (bladder and Merkel cell cancer) were excluded (**Figure 2**). We classified patients as having received proton therapy if any part of their treatment consisted of proton therapy; otherwise, patients were classified as having been treated with photon therapy. All patients were treated using the same treatment planning system, standard procedures, and radiation dose constraints; all radiation treatment plans were centrally reviewed at a weekly patient management conference.

Variables

The research question, study design, and plan for the analysis followed a prospectively defined protocol (eMethods 1 in the Supplement). Detailed demographic, clinical, pathologic, and treatment-related factors and oncologic outcomes were extracted from Penn's Oncology Research and Quality Improvement Datamart, a clinical data repository that sources data from multiple databases, including the Epic electronic medical record, the Penn Medicine Cancer Registry, and the ARIA radiation oncology information and treatment planning system (Varian Medical Systems).[22] Manual medical record review was used when needed to fill in absent values. Demographic variables included age, race, sex, ECOG performance status (range, 0-5, with 0 meaning no functional impairment and 5 meaning death), body mass index, and Charlson-Deyo comorbidity score (for patients with solid tumor, scores range from 2-33, with higher scores indicating greater comorbidities)[23]; socioeconomic variables included insurance status, insurance provider, and treatment location (main site vs satellite facility). Complete clinical, pathologic, and surgical variables were obtained, and information on chemotherapeutic agents were also collected. Radiotherapy-specific variables included treatment modality, delivered dose, fractionation, elapsed days for radiotherapy, treatment site, the integral dose to the planning target volume, the integral dose delivered outside of the target volume, and the treating physician. The integral dose delivered outside the target volume is a measure of the total amount of radiation absorbed by normal tissues that are outside of the radiation target volume. We used 131 clinically relevant variables in the development and construction of the model (eMethods 2 in the Supplement).

Figure 2. Consort Diagram



CRT indicates chemoradiotherapy; RT, radiotherapy.

The only missing covariate data included integral dose delivered outside the target volume (57 [3.8%] missing), starting ECOG score (91 [6.1%] missing), ending ECOG score (68 [4.6%] missing), and body mass index (15 [1.0%] missing). All other variables were complete for all patients.

Outcomes

Adverse events were defined using the National Cancer Institute's CTCAEv4 grading system, the criterion standard for assessing adverse events in oncology trials. Patient functional status was defined using the ECOG performance status score.[24] We scored CTCAEv4 adverse events and ECOG performance status prospectively using standardized templates at each weekly visit during treatment and all subsequent follow-ups. End points were chosen a priori. Assessment and documentation of adverse events was the same regardless of treatment modality. Hematologic adverse events were not scored prospectively and were not considered in the analysis. A CTCAEv4 grade of at least 3 within the first 90 days of treatment was the primary end point, which is defined as severe adverse events for which unplanned hospitalization is indicated. These adverse events of at least grade 3 are disabling and limit the patient's ability to perform basic self-care activities. We chose 90-day adverse events of at least grade 3 because (1) most early adverse events for chemoradiotherapy occur within the first 90 days, with many of these events resolved or improved later[25,26]; (2) acute events after radiotherapy are commonly defined as occurring during this period[25,27]; and

(3) the 90-day interval is an accepted interval for assessing early morbidity and mortality after oncologic surgery.[28,29] Patients with any adverse events of grade 3 or greater that were not present at baseline or that had increased in severity from baseline were scored as having the outcome of interest. Patients who did not have the event of interest and had less than 90 days of follow-up were excluded. Change in ECOG status from the start to the completion of radiotherapy was assessed as a binary outcome, with deterioration in ECOG status as the outcome of interest. Less severe acute adverse events that cause significant impairment of the patient's ability to perform their instrumental activities of daily living (eg, shopping, cleaning) were also assessed (90-day CTCAEv4 grade ≥2). We also assessed disease-free survival (DFS) and overall survival (OS). Events of interest for DFS included death due to any cause or relapse, whichever occurred first. Oncologic outcomes data were obtained from the Penn Medicine Cancer Registry, which is prospectively maintained. All oncologic outcomes data were reviewed, confirmed, and updated by a radiation oncologist (B.C.B.). Survival was measured from the start of treatment to events of interest; otherwise, patients were censored.

Statistical Analysis

Data were analyzed from October 15, 2018, through February 1, 2019. Confounding is an important concern in any observational study but particularly in this study, given the heterogeneity of the patient population and the multiple factors that could affect patient selection for proton vs photon therapy. We used propensity score weighting to account for bias due to measured confounding and conducted an extensive sensitivity analysis to assess the effects of unmeasured confounders. For example, although Medicare generally covers proton therapy for most malignant neoplasms, most commercial payers and Medicaid do not.[30] Thus, in general, we expected to find that patients 65 years or older were more likely to receive proton therapy than photon therapy.

We first estimated propensity scores using an ensemble machine-learning algorithm called Super Learner.[31] The algorithm combines weighted estimates across several parametric and nonparametric approaches based on the accuracy of the estimations from the models to create an overall propensity score estimate, which increases the robustness of the analysis. All covariates that were deemed clinically relevant a priori were included in the propensity score model, and no further filtering or selection was conducted. These covariates included age, sex, race, comorbidity score, cancer site, clinical tumor stage, clinical nodal stage, chemoradiotherapy timing, delivered radiation dose, and ECOG score before starting radiotherapy. We used standardized mean differences to assess the covariate balance before and after propensity score weighting.[32] We used these estimated propensity scores to calculate each patient's inverse probability of being treated with protons.[33] The inverse probability treatment weights were the inverse of the propensity score for the patients in the proton cohort and were the inverse of 1 minus the propensity score for the patients in the photon cohort. These weights were then included in a modified Poisson regression model with robust standard errors to estimate relative risks and corresponding 95% CIs for each of the binary outcomes.[34] Overlap of propensity score distributions between treatment groups was assessed graphically, and balance on all confounders was assessed using balance diagnostics.[35] Using a more traditional approach, we also estimated propensity scores using logistic regression and found nearly identical results; however, Super Learner results demonstrated efficiency gains. Missing covariate data were imputed using multiple imputation before propensity score estimation (6.1% missing starting ECOG score and 3.8% missing integral dose). We assessed DFS and OS using a propensity score–weighted Cox proportional hazards regression model. The proportional hazards regression assumption was evaluated using Schoenfeld residuals.

To assess the potential effect of unmeasured confounding, we conducted a regression-based sensitivity analysis in which we evaluated the sensitivity of our relative risk (RR) estimates to the presence of a binary unmeasured confounder (such as physical frailty, which was not collected in our data). The presence of physical frailty could increase the risk of severe adverse events and may also be independently associated with worse survival.[36] We varied the prevalence and strength of the unmeasured confounder to assess whether our primary findings would have been altered if we had been able to adjust for the unmeasured confounder.[37]

All analyses were conducted in R, version 3.5 (R Foundation for Statistical Computing). All tests were 2 sided. We used a Bonferroni correction given the 5 analytic approaches used, such that $P < .01$ (0.05/5.0) was considered statistically significant. Analysis was based on intention to treat; all patients who started radiotherapy with either modality were included.

Results

We identified 1483 consecutive adult patients undergoing chemoradiotherapy (935 men [63.0%] and 548 women [37.0%]; median age, 62 [range, 18-93] years), including 391 in the proton cohort and 1092 in the photon cohort. Common tumor sites included head and neck, lung, brain, esophagus/gastric tract, rectum, and pancreas (**Table**). Patients treated with protons were significantly older (median age, 66 [range, 18-93] vs 61 [range, 19-91] years; mean [SD] age, 63.3 [14.9] vs 60.2 [11.1] years; $P < .01$) and had higher age-unadjusted Charlson-Deyo comorbidity index scores (median, 3.0 [range, 2-16] vs 2.0 [range, 2-13]; mean [SD], 3.2 [1.5] vs 3.0 [1.6]; $P < .01$). The proton therapy group had a lower integral radiation dose to tissues outside the target (mean [SD], 14.1 [6.4] vs 19.1 [10.6] cGy/cc × 10^6; $P < .01$). There was no statistically significant difference in the integral dose to the planning target volume, which is a measure of the mean dose delivered to the treatment volume (mean [SD], 32.9 [25.6] vs 33.5 [31.1] cGy/cc × 10^7; $P = .72$). One thousand sixteen patients (93.0%) in the photon therapy group were treated with intensity-modulated radiotherapy. Baseline toxicity of at least grade 2 (24% vs 22%; $P = .37$) and baseline ECOG performance status (median, 0 [range, 0-3] vs 1 [range, 0-3]; mean [SD], 0.62 [0.74] vs 0.68 [0.80]; $P = .16$) were similar between the 2 cohorts.

Table. Baseline Characteristics of the Entire Cohort

Characteristic	CRT Cohort[a]		P Value
	Proton (n = 391)	Photon (n = 1092)	
Age, mean (SD), y	63.3 (14.9)	60.2 (11.1)	<.01
Sex			
Male	230 (58.8)	705 (64.6)	.05
Female	161 (41.2)	387 (35.4)	
Race			
White	327 (83.6)	842 (77.1)	<.01
Black	46 (11.8)	206 (18.9)	
Asian or other	18 (4.6)	44 (4.0)	
Insurance status			
Medicare	207 (52.9)	305 (27.9)	<.01
Private insurance	178 (45.5)	742 (67.9)	
Medicaid	2 (0.5)	40 (3.7)	
Other	4 (1.0)	5 (0.5)	
BMI, mean (SD)	27.3 (5.5)[b]	27.4 (5.6)[c]	.89
Charlson-Deyo comorbidity score, mean (SD)[d]	3.2 (1.5)	3.0 (1.6)	<.01
Starting ECOG performance status score, mean (SD)[e]	0.62 (0.74)	0.68 (0.80)	.16
Treatment facility			
Main site	391 (100)	874 (80.0)	<.01
Satellite facility	0	218 (20.0)	
Year of treatment			
2011-2012	53 (13.6)	483 (44.2)	<.01
2013-2014	195 (49.9)	364 (33.3)	
2015-2016	143 (36.6)	245 (22.4)	
Disease site			
Head and neck	40 (10.2)	397 (36.4)	<.01
Lung	132 (33.8)	195 (17.9)	
Brain	57 (14.6)	183 (16.8)	
Esophagus/gastric tract	55 (14.1)	95 (8.7)	
Pancreas, duodenum, or hepatobiliary	44 (11.3)	47 (4.3)	
Rectal	41 (10.5)	83 (7.6)	
Anal	18 (4.6)	62 (5.7)	
Gynecologic	4 (1.0)	30 (2.7)	
Clinical tumor stage			
T1	58 (14.8)	153 (14.0)	<.01
T2	97 (24.8)	281 (25.7)	
T3	130 (33.2)	275 (25.2)	
T4	49 (12.5)	200 (18.3)	
NA[f]	57 (14.6)	183 (16.8)	
Clinical nodal stage			
N0	110 (28.1)	230 (21.1)	<.01
N1	87 (22.3)	229 (21.0)	
N2	112 (28.6)	397 (36.4)	
N3	25 (6.4)	53 (4.9)	
NA[f]	57 (14.6)	183 (16.8)	
Timing of CRT			
Preoperative	86 (22.0)	135 (12.4)	<.01
Definitive	103 (26.3)	372 (34.1)	
Postoperative	202 (51.7)	585 (53.6)	
Delivered radiation dose, mean (SD), Gy	58.5 (7.6)	60.3 (10.5)	<.01
Integrated radiation dose delivered to the target volume, mean (SD), cGy/cc × 10^6	32.9 (25.6)[g]	33.5 (31.1)[h]	.72
Integral radiation dose outside of the target volume, mean (SD), cGy/cc × 10^7	14.1 (6.4)[g]	19.1 (10.6)[h]	<.01

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by square of height in meters); CRT, concurrent chemoradiotherapy; ECOG, Eastern Cooperative Oncology Group; NA, not applicable.

[a] Unless otherwise indicated, data are expressed as number (percentage) of patients. Percentages have been rounded and may not total 100.

[b] Values available for 387 of 391 patients.

[c] Values available for 1081 of 1092 patients.

[d] Patient scores ranged from 2 to 16, with higher scores indicating higher burden of comorbid disease.

[e] Patient scores ranged from 0 to 3, with higher scores indicating worse performance status.

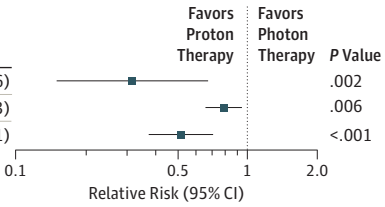
[f] Denotes central nervous system cancers without TNM staging.

[g] Values available for 364 of 391 patients.

[h] Values available for 1062 of 1092 patients.

Figure 3. Adverse Events and Decline in Eastern Cooperative Oncology Group (ECOG) Performance Status for Proton vs Photon Chemoradiotherapy (CRT) and Propensity Analysis Results

Outcome	Proton CRT Group (n = 391) No. of Events	Proton CRT Group (n = 391) Percentage (95% CI)	Photon CRT Group (n = 1092) No. of Events	Photon CRT Group (n = 1092) Percentage (95% CI)	Relative Risk (95% CI)	P Value
90-day Grade ≥3 adverse events	45	11.5% (8.3%-14.7%)	301	27.6% (24.9%-30.2%)	0.31 (0.15-0.66)	.002
90-day Grade ≥2 adverse events	290	74.2% (69.8%-78.5%)	926	84.8% (82.7%-86.9%)	0.78 (0.65-0.93)	.006
ECOG performance status decline	145	37.1% (32.3%-41.9%)	434	42.4% (39.4%-45.4%)	0.51 (0.37-0.71)	<.001



Ninety-day adverse events are measured using Common Terminology Criteria for Adverse Events, version 4 (CTCAEv4). Patients were identified with CTCAEv4 grades of at least 3 and at least 2. ECOG performance status scores range from 0 to 5, with higher scores indicating worse performance status.

Forty-five 90-day adverse events of at least grade 3 occurred in the proton cohort (11.5%; 95% CI, 8.3%-14.7%) vs 301 in the photon cohort (27.6%; 95% CI, 24.9%-30.2%; $P < .001$). Adverse event outcomes are summarized in **Figure 3**.

In propensity score–weighted analyses, proton chemoradiotherapy was associated with statistically significantly lower acute 90-day adverse events of at least grade 3 compared with photon chemoradiotherapy (RR, 0.31; 95% CI, 0.15-0.66; $P = .002$) (Figure 3). Proton chemoradiotherapy was associated with significantly less decline in ECOG performance status scores during chemoradiotherapy (RR, 0.51; 95% CI, 0.37-0.71; $P < .001$). Proton chemoradiotherapy was also associated with a significantly lower risk of acute 90-day adverse events of at least grade 2 (RR, 0.78; 95% CI, 0.65-0.93; $P = .006$).

Median follow-up for the proton cohort was 3.7 (range, 0.1-6.5) years; for the photon cohort, 4.2 (range, 0.1-5.9) years. One- and 3-year adjusted DFS for the proton cohort was 70.0% (95% CI, 65.5%-74.7%) and 45.9% (95% CI, 40.8%-51.8%), respectively; for the photon cohort, 67.3% (95% CI, 64.6%-79.2%) and 48.5% (95% CI, 45.5%-51.7%), respectively. We found no significant difference in DFS for proton chemoradiotherapy compared with photon chemoradiotherapy in our propensity score–weighted Cox proportional hazards regression model (hazard ratio, 0.84; 95% CI, 0.48-1.48; $P = .55$). One- and 3-year adjusted OS for the proton cohort was 83.0% (95% CI, 79.3%-86.8%) and 56.2% (95% CI, 50.7%-62.2%), respectively; for the photon cohort, 81.1% (95% CI, 78.8%-83.4%) and 57.9% (95% CI, 54.8%-61.1%), respectively. There was no significant difference in OS (hazard ratio, 0.73; 95% CI, 0.38-1.39; $P = .34$) (**Figure 4**).

Sensitivity Analysis

We performed an extensive sensitivity analysis to assess the potential effect of an unmeasured confounder, such as physical frailty, on the primary outcome of 90-day toxicity of at least grade 3. We found that a substantial imbalance in physical frailty would be needed to significantly alter the overall results of the study (eTable in the Supplement). For instance, assuming an RR of 2.00 for unplanned hospitalizations for physical frailty, the prevalence of the unmeasured confounder would need to be 200% higher in the photon group than the proton group for our RR estimates to no longer be statistically significant.

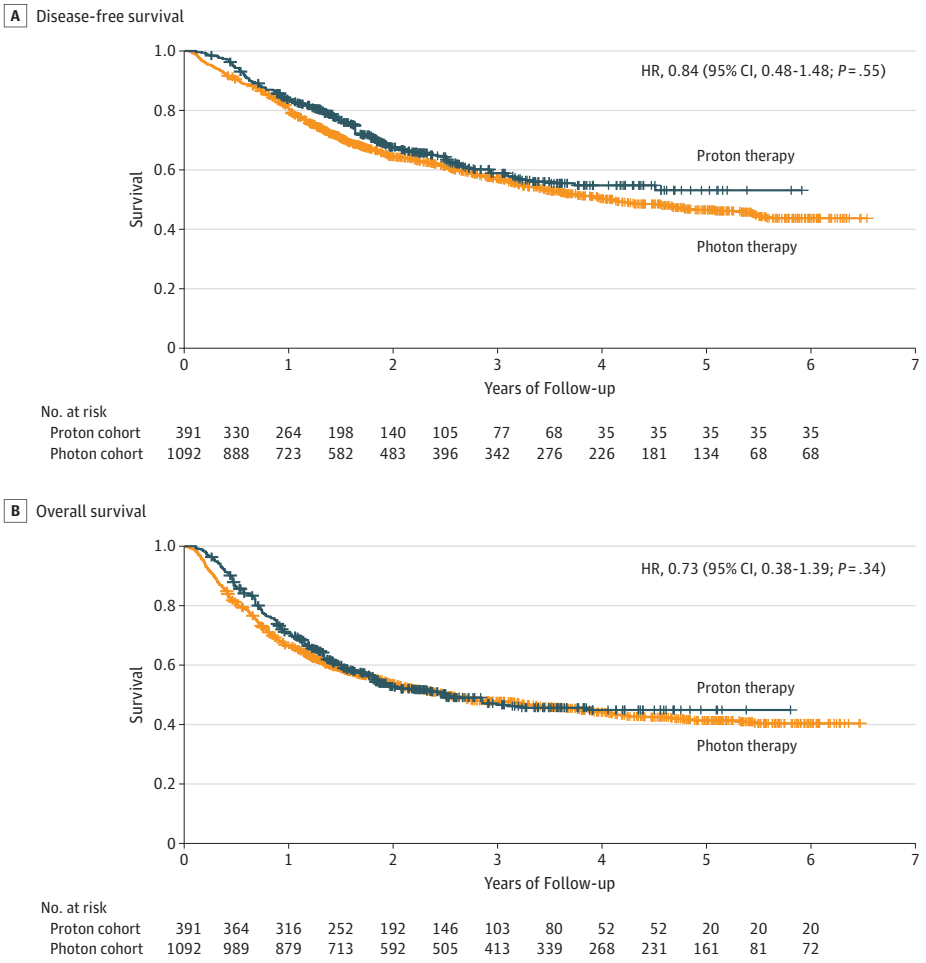
Discussion

We conducted a study of 1483 adult patients with locally advanced cancer treated with chemoradiotherapy to assess the comparative effectiveness of photon vs proton therapy using prospectively gathered data on adverse events and oncologic outcomes. We found that, compared with photon therapy, proton therapy was associated with a nearly two-thirds reduction in 90-day severe adverse events associated with unplanned hospitalizations. Proton therapy was also associated with significantly lower risk of a decline in ECOG performance status and significantly less risk of adverse events causing impairment in patient's instrumental activities of daily living. There were no statistically significant differences in DFS or OS between treatment groups.

We observed substantial morbidity associated with conventional photon chemoradiotherapy; 27.6% of patients developed severe 90-day adverse events associated with unplanned hospitalizations (CTCAEv4 grade ≥3), whereas in the proton group, 11.5% of patients had severe 90-day adverse events. Previous research has demonstrated that proton chemoradiotherapy is associated with significant morbidity.[38] One study[39] found that one-third of patients undergoing definitive radiotherapy with or without chemotherapy had an unplanned emergency department visit or hospitalization within 30 days. In a pooled analysis, patients receiving chemoradiotherapy accounted for 6% of all intensive care unit admissions and 26% of all cancer-related intensive care unit admissions.[40]

Our results demonstrating significant reduction in toxicity with the use of proton chemoradiotherapy are consistent with and extend previous research,[11,41-48] although this outcome remains an area of controversy. Before this study, data on the toxicity differences between proton vs photon chemoradiotherapy have been limited, with relatively small patient numbers, although most studies[11,41-48] have found a toxicity advantage and/or dosimetric advantage in favor of proton chemoradiotherapy. To our knowledge, only 1 randomized trial of chemoradiotherapy with proton vs photon therapy[16] has been reported in locally advanced non–small cell lung cancer. There was no difference in the primary end point (grade ≥3 radiation pneumonitis). Other toxicity end points have not yet been reported. Exploratory subset analysis of the patients with non-

Figure 4. Adjusted Disease-Free and Overall Survival for the Proton vs Photon Chemoradiotherapy Cohorts



HR indicates hazard ratio.

small cell lung cancer in our cohort revealed a reduction in overall toxicity of at least grade 3 with proton therapy that was comparable to the reduction seen in the entire cohort. Although several cooperative group trials randomizing patients to proton vs photon chemoradiotherapy are in progress, including NRG BN-005 in glioma and RTOG 1308 in lung cancer,[14,49] results will not be available for years, and accrual is challenging.[30]

The significant reduction in adverse events that we observed with proton therapy was not accompanied by a reduction in treatment efficacy. We compared DFS and OS between the 2 cohorts and found that survival outcomes were comparable. This finding is noteworthy because it suggests that, with careful delineation of the target volume, proton therapy is not associated with worse cancer control outcomes that could occur due to a marginal miss if the proton beam stops short of covering the full extent of the subclinical disease.[11]

Our finding that proton therapy is not associated with worse cancer control outcomes is also consistent with and extends the existing literature. Preliminary results from the lung cancer trial found no difference in local control at 12 months.[16] Similarly, retrospective studies have not shown worse oncologic outcomes with proton chemoradiotherapy, with some studies showing improvement in survival with proton therapy.[17,42] These studies were smaller and/or relied on the National Cancer Database, which is missing key variables and has no cancer-specific outcomes data.[50]

Limitations

This study has several limitations. First, this observational study cannot draw causal inferences. However, we used several approaches to adjust for measured confounding and consider unmeasured confounding. The database included 131 relevant demographic, socioeconomic, clinical, pathologic, and treatment variables. We used robust statistical approaches to try to account for measured confounding, including a modern ensemble machine-learning approach for propensity score estimation that may better reduce residual bias.[33-35] This analysis helps us to account for the heterogeneity of the proton and photon cohorts, although we acknowledge that these statistical techniques to reduce residual bias have limitations. At our institution, 80% of patients receiving photon therapy were treated at the same hospital by the same physicians as those receiving proton therapy; radiation target volumes were not significantly different; and the choice of proton therapy was usually determined not by clinical or disease-specific factors but by whether the patient's insurance approves proton therapy.[51] In addition, the sensitivity analysis suggests—although it does not confirm—that a very large imbalance in an unmeasured

confounder, such as physical frailty or socioeconomic status, with effects on unplanned hospitalizations would be required to alter the findings of the study.

Second, the study involved nonblinded outcomes assessment and is subject to possible observer bias. However, the National Cancer Institute cooperative group studies of radiotherapy use similar approaches to outcome assessment. Moreover, our primary end point of adverse events associated with unplanned hospitalizations and survival outcomes is not subtle, and the likelihood of systematic bias in the reporting of these events is quite low. Although there was some difference in median follow-up between the 2 cohorts, our primary end point was short term, and patients with insufficient follow-up for the primary end point were excluded.

Last, hematologic adverse events and detailed data on chemotherapy administration, including number of cycles and doses, were not included in the analysis; however, choice of chemotherapy agent(s) is standardized by disease site at our institution and did not vary based on radiation modality. Hematologic adverse events are far more likely to be chemotherapy related and would be unlikely to favor the photon cohort because photon therapy would be expected to expose more bone marrow to clinically meaningful doses of radiation owing to the higher integral dose of photon therapy.

Conclusions

This study has 3 important implications for future research. First, proton therapy's lower observed toxicity and its more favorable association with performance status at least raises the tantalizing possibility that the higher up-front cost of proton therapy may be offset by cost savings from reduced hospitalizations[52] and enhanced productivity from patients and caregivers.[53] Second, the lower observed toxicity of proton therapy offers an opportunity to explore clinical trials combining proton therapy with intensified systemic therapy and/or dose-escalated radiotherapy, which may, in turn, improve survival outcomes.[54-56] Third, in our study, older patients with more comorbid disease were more likely to receive proton therapy and experienced less toxicity; thus, proton therapy may allow older patients with more comorbidities to receive the most effective combined-modality treatments. Inclusion criteria for clinical trials of proton chemoradiotherapy may be liberalized to include older, sicker patients who have been excluded from combined modality trials in the past.[57-60]

In adults with locally advanced cancer treated at the University of Pennsylvania, proton chemoradiotherapy compared with photon chemoradiotherapy was associated with a significant reduction in 90-day adverse events associated with unplanned hospitalizations (CTCAEv4 grade ≥3), less decline in ECOG performance status, and fewer 90-day adverse events of at least grade 2. We found no difference in DFS and OS. Reduced adverse events associated with proton therapy could offer an opportunity to intensify chemoradiotherapy treatments and/or broaden inclusion criteria on clinical trials to include older, sicker patients, which may improve oncologic outcomes. Prospective clinical trials of proton vs photon chemoradiotherapy are warranted to validate these results.

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