

Comparison of intensity-modulated radiation therapy, adaptive radiation therapy, proton radiation therapy, and adaptive proton radiation therapy for small cell lung cancer

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Abstract

Background and Purpose: Proton radiation therapy for non-small cell lung cancer (NSCLC) can minimize dose to adjacent organs at risk (OARs) and potentially reduce morbidity, but limited proton data exist for small cell lung cancer (SCLC). This study compares nonadaptive intensity-modulated radiation therapy (IMRT), adaptive IMRT (AIMRT), nonadaptive proton therapy (PBT), and adaptive proton therapy (APBT) for SCLC.

Materials and Methods: Ten consecutive patients with limited-stage SCLC enrolled on an IRB-approved prospective adaptive imaging protocol treated with twice-daily photon radiation therapy to 45 Gy/30 fractions over 3 weeks were analyzed. Patients underwent repeat CT imaging after 10 and 20 fractions. Adaptive plans treated the initial CT scan to 15 Gy, second CT to 30 Gy, and third CT to 45 Gy. IMRT, AIMRT, PBT and APBT dosimetric differences were quantified (n = 40 plans).

Results: All plans provided comparable target coverage. From the simulation CT to second adaptive scan, primary and nodal GTVs decreased 54.6% and 51.9%, respectively. For photon plans, AIMRT lowered dose to lungs, esophagus, heart, and ipsilateral brachial plexus. For proton plans, APBT lowered dose to lungs, esophagus, heart, ipsilateral brachial plexus, and cord. PBT reduced dose to lungs and heart compared with IMRT and AIMRT. APBT further reduced doses to lungs, heart, and bilateral brachial plexuses compared with IMRT and AIMRT.

Conclusions: Proton therapy maintained optimal tumor coverage while significantly reducing OAR doses compared with photon plans. Adaptive planning provided dosimetric benefits for photons and protons. This study serves as the basis for a planned prospective phase II trial treating limit-staged SCLC patients with proton therapy using adaptive planning, as necessary, based on weekly verification scans.

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Table 1. Patient Clinical Characteristics and Treatment Course

Gender		
Female	8	(80%)
Male	2	(20%)
Race		
Caucasian	8	(80%)
African-American	2	(20%)
Clinical Stage		
Limited Stage	10	(100%)
Chemotherapy		
Cisplatin-Etoposide	9	(90%)
Carboplatin-Etoposide	1	(10%)
Radiation Therapy Start Timing		
Cycle 1	3	(30%)
Cycle 2	7	(70%)
Thoracic Radiation Therapy		
Twice Daily Irradiation	10	(100%)
Median Dose (Gy)	45	(100%)
Concurrent Chemotherapy	10	(100%)
3DCRT*	5	(50%)
IMRT*	5	(50%)

*Abbreviations: 3DCRT = three-dimensional conformal radiation therapy;
IMRT = intensity modulated radiotherapy

ing dose-volume histograms (DVHs) of target volumes and normal tissue structures in nonadaptive intensity-modulated radiation therapy (IMRT), adaptive IMRT, nonadaptive proton therapy, and adaptive proton therapy for SCLC to determine whether proton therapy is dosimetrically superior to photon therapy and to assess the benefit of adaptive planning.

Materials and Methods

Ten consecutive patients with limited-stage small cell lung cancer treated at the University of Pennsylvania, Philadelphia, with twice-daily photon radiation therapy were assessed in an Institutional Review Board-approved prospective study in which patients gave informed consent and underwent repeat imaging during radiation therapy. Patients were predominantly female and Caucasian (**Table 1**). All patients received concurrent chemotherapy and started radiation therapy with cycle 1 (30%) or cycle 2 (70%) of chemotherapy. All patients were treated to 45 Gy in 1.5 Gy twice-daily fractions (30 fractions) over 3 weeks with either 3-dimensional conformal radiation therapy (3DCRT) (50%) or IMRT (50%). Patients underwent replanning 4-dimensional CT scans after their 10th and 20th fractions of radiation therapy to evaluate treatment response.

CT data were attained with a slice thickness of 3 mm. To define target and nontarget structures, CT images were imported into photon and proton commercial treatment planning systems (Eclipse Treatment Planning Version 13.0, Varian Medical Systems, Palo Alto, California). OARs and target volumes were contoured on the initial CT data set and each subsequent re-imaging CT data set. Assessed OARs included the spinal cord, lungs, brachial plexus, esophagus, and heart.

Gross tumor volume (GTV) was defined as all gross disease determined from bronchoscopy, CT scan (nodes > 1 cm

Twice-daily radiation therapy with concurrent cisplatin and etoposide is standard treatment for patients with limited-stage small cell lung cancer (SCLC).^{1,2} However, concurrent therapy is associated with increased toxicity, particularly when radiation therapy is administered twice daily.³ Turrisi et al reported that among 417 patients randomized to receive twice-daily or once-daily thoracic radiation therapy with concurrent chemotherapy for SCLC, 90% of patients receiving twice-daily radiation therapy experienced grade 3 or higher toxicity, including 3% with grade 5 toxicity. Grade 3 or higher toxicities included esophagitis in 32% and pulmonary in 6%.⁴

Proton radiation therapy for non-small cell lung cancer (NSCLC) can minimize radiation dose to adjacent organs at risk (OARs), which can potentially reduce toxicities and patient morbidity.⁵⁻¹⁰ In single-arm studies assessing survival outcomes for proton therapy to treat NSCLC, proton therapy has been reported to improve 2- and 3-year survival rates compared to historically reported

rates for photon therapy.^{11,12} Although early data suggest promising outcomes with protons for NSCLC, data on proton therapy for SCLC is lacking and limited to a single case series,¹³ likely due to concerns that rapid tumor volume changes during proton therapy could lead to loss of plan validity and overdosing of OARs. Such changes, therefore, might require adaptive planning if proton therapy were delivered for SCLC.

Studies in NSCLC have shown adaptive proton therapy can reduce dose to OARs. Adaptive proton therapy for NSCLC can allow for dose escalation while limiting side effects.¹⁴ In a comparison of non-adaptive proton therapy to adaptive proton radiation therapy for NSCLC, adaptive planning showed less toxicity and more OAR sparing.¹⁵

To date, only limited data directly compare different radiation therapy modalities and treatment strategies for SCLC, including the use of proton and particle therapy for SCLC. Additionally, no existing reports assess adaptive photon or proton radiation therapy for SCLC. This is the first study compar-

Table 2. Changes in Gross Tumor Volumes (GTV)* and Planning Target Volumes (PTV)* During Treatment

Patient	Primary GTV ₁	Primary GTV ₂	Primary GTV ₃	Primary PTV ₁	Primary PTV ₂	Primary PTV ₃	Nodal GTV ₁	Nodal GTV ₂	Nodal GTV ₃	Nodal PTV ₁	Nodal PTV ₂	Nodal PTV ₃
1	70.4	46.0	27.9	350.1	285.6	229.4	9.9	5.6	2.5	106.8	82.9	62.7
2	0.6	0.3	0.1	42.7	34.4	29.9	36.8	21.7	15.5	170.2	140.3	126.0
3	35.8	9.7	5.3	240.4	125.3	96.0	38.9	19.2	14.9	188.8	135.5	103.1
4	5.3	2.6	2.2	82.8	62.2	58.9	110.3	92.4	68.4	378.7	351.8	308.4
5	14.5	10.2	7.6	159.0	148.6	122.5	111.2	94.5	79.3	338.3	307.7	250.2
6	162.5	114.3	92.9	607.8	480.1	407.7	26.5	15.8	13.3	131.7	109.3	101.4
7	11.1	7.0	4.5	198.9	173.3	144.2	19.5	13.5	9.3	122.8	98.5	84.3
8	34.0	27.3	22.7	302.5	281.3	268.8	58.8	40.6	30.9	314.1	266.4	223.2
9	19.3	4.4	2.2	178.3	104.2	91.4	320.1	154.7	118.1	756.8	472.1	385.8
10	18.1	5.7	3.3	162.6	96.8	91.4	26.6	15.7	12.8	214.2	180.6	143.9
Mean	37.2	22.7	16.9	232.5	179.2	154.0	75.9	47.4	36.5	272.2	214.5	178.9

*GTV₁ and PTV₁ calculated at the time of treatment planning simulation scan prior to beginning radiation therapy, GTV₂ and PTV₂ calculated at the time of replanning scan at the end of the first week of radiation therapy, GTV₃ and PTV₃ calculated at the time of replanning scan at the end of the third week of radiation therapy; volumes in cm³

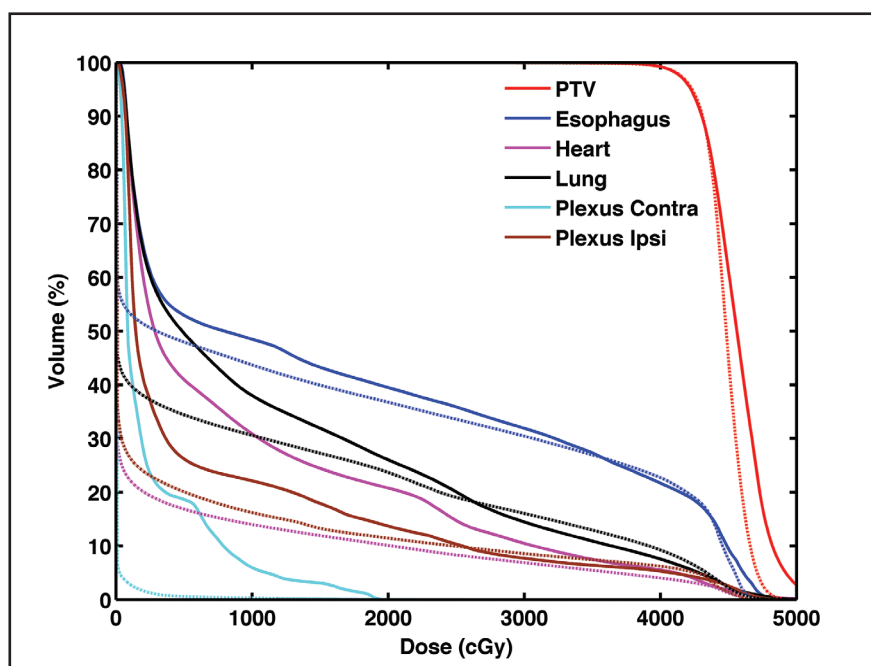


FIGURE 1. Composite dose-volume histograms. Comparison of the mean dose-volume histograms for all nonadaptive photon ($n = 10$, solid lines) and nonadaptive proton ($n = 10$, dashed lines) treatment plans for all patients with limited-stage SCLC. Structures include PTV (red), esophagus (blue), heart (magenta), total lung minus GTV (black), contralateral brachial plexus (cyan), and ipsilateral brachial plexus (brown).

short axis diameter), positron emission tomography (PET) scan ($SUV > 3$), or pathologic nodal sampling or dissection. Separate GTVs were contoured for primary tumor, designated GTV_{Primary}, and

nodal metastasis, designated GTV_{Nodal}. To account for intrafractional motion, an internal GTV was created for each GTV, designated iGTV, by expanding the GTV based on tumor excursion seen

on 4D imaging. A 10 mm expansion was added to iGTV_{Primary} to account for microscopic disease to create clinical target volumes (CTV). For nodal stations involved with tumor, the entire nodal level was included in the CTV, and an additional 3–5 mm margin was added to the involved nodal station.

To account for set-up variation and organ and patient motion, a uniform 5 mm margin in all directions was added to each CTV to define planning target volumes (PTVs) PTV_{Primary} and PTV_{Nodal}. PTV_{Primary} and PTV_{Nodal} were combined to PTV_{Total} and planned to 45 Gy for photon plans or 45 cobalt Gray equivalents (CGE) for proton plans, with proton doses corrected with the accepted relative biologic effectiveness value of 1.1.¹⁶

For proton plans, beam range compensators were designed to account for properties of the proton beam and range uncertainties by providing proximal and distal margins relative to each PTV. Blocking was designed to create a lateral margin relative to each PTV, with margins individualized for each patient based on formulas by Moyers et al.¹⁷ For the IMRT plan, dose objectives were created for PTVs and OARs. Helios Inverse Treatment Planning

Table 3. Comparison of the Average Doses to Normal Tissues Between IMRT, Adaptive IMRT, Proton Therapy, and Adaptive Proton Therapy

	Spinal Cord	Lung			Ipsilateral Brachial Plexus	Contralateral Brachial Plexus	Esophagus		Heart		
	Max	V5	V20	Mean	Max	Max	V30	Mean	1/3	2/3	Mean
IMRT	33.6	49.6	26.0	12.1	18.6	6.0	32.0	17.6	9.0	4.1	10.0
Adaptive IMRT	33.0	48.9	23.9	11.3	16.4	6.1	28.1	16.2	8.7	2.9	9.2
Proton	29.4	34.9	24.4	10.2	17.6	3.7	30.5	16.0	1.2	0.2	4.7
Adaptive Proton	27.1	33.6	21.9	9.1	15.1	2.5	26.8	14.5	0.7	0.2	4.0

Max = average maximum point dose (Gy)

V5/20/30 = volume receiving 5/20/30 Gy (percentage)

(Varian Medical Systems) was used to optimize plans to minimize dose to critical structure by increasing OAR constraints, while maintaining optimal coverage on target volumes and dose homogeneity.

Four treatment plans were created for each patient ($n = 40$ plans): (1) photon IMRT, with treatment planned to the target volumes and normal structures from the initial CT image set to 45 Gy; (2) adaptive photon IMRT, with treatment planned to target volumes and normal structures from the initial CT image set to 15 Gy, second CT obtained after 10 fractions of treatment to 30 Gy, and third CT obtained after 20 fractions of treatment to 45 Gy; (3) passively scattered proton therapy, with treatment planned from the initial CT image set to 45 CGE; and (4) adaptive passively scattered proton therapy, with treatment planned from the initial CT image set to 15 CGE, second CT to 30 CGE, and third CT to 45 CGE. For adaptive IMRT and proton plans, the second and third CTs were fused to the initial CT image set using deformable registration, and new OARs and target volumes were contoured on each of the successive re-planning CT scans. The same expansions to CTVs, PTVs and planning objectives were employed, and plan sums and composite DVHs were generated.

Planning was performed to achieve maximum doses (D_{max}) to the spinal

cord < 36 Gy and brachial plexus < 45 Gy, and the doses to 2/3 of the heart < 20 Gy and 1/3 of the heart < 35 Gy. Lung constraints were mean < 20 Gy, V5 (volume receiving 5 Gy) $< 60\%$, and V20 $< 35\%$, whereas esophageal constraints were mean < 20 Gy and V30 $< 50\%$.

Statistics

The Friedman test, a nonparametric small sample test for comparing multiple treatments across dependent repeated measures, was used to compare the four treatment plans across patients. The Wilcoxon signed rank sum test was subsequently used to conduct post-hoc pairwise comparisons. No multiple testing correction was applied since these were exploratory analyses with small sample sizes. All tests were two-tailed, and results were considered to be statistically significant when $p < 0.05$.

Results

Patient statistics

The cohort mean GTV_{Nodal} from the initial CT image set obtained before concurrent chemoradiation was 75.9cm^3 (range $9.9\text{--}320.1\text{cm}^3$) (Table 2). The mean GTV_{Nodal} from the second CT image set decreased by 37.6% to 47.4cm^3 ($5.6\text{--}154.7\text{cm}^3$). The mean GTV_{Nodal} from the third CT image set decreased an additional 22.9% to 36.5cm^3 ($2.5\text{--}118.1\text{cm}^3$), for an overall reduction of 51.9%. The corresponding

mean PTV_{Nodal} were 272.2cm^3 ($106.8\text{--}756.8\text{cm}^3$), 214.5cm^3 ($82.9\text{--}472.1\text{cm}^3$; 21.2% reduction), and 178.9cm^3 ($62.7\text{--}385.8\text{cm}^3$; 16.6% additional reduction, 34.3% total reduction).

Similarly, the mean $GTV_{Primary}$ from the initial CT image set was 37.2cm^3 ($0.6\text{--}162.5\text{cm}^3$), decreased 38.8% to 22.7cm^3 ($0.3\text{--}114.3\text{cm}^3$) at the second CT, and decreased an additional 25.9% to 16.9cm^3 ($0.1\text{--}92.9\text{cm}^3$) at the third CT, for an overall 54.6% decrease. The corresponding $PTV_{Primary}$ were 232.5cm^3 ($42.7\text{--}607.8\text{cm}^3$), 179.2cm^3 ($34.4\text{--}480.1\text{cm}^3$; 22.7% reduction), and 154.0cm^3 ($29.9\text{--}407.7\text{cm}^3$; 14.3% additional reduction, 33.8% total reduction).

Dose Coverage

IMRT, adaptive IMRT, proton therapy, and adaptive proton therapy plans all provided comparable and acceptable target volume coverage, with no significant difference in coverage to PTV_{Nodal} ($p = 0.32$ to $p = 0.92$ for all 6 plan comparisons), $PTV_{Primary}$ ($p = 0.44\text{--}0.92$), and PTV_{Total} ($p = 0.56\text{--}0.95$) (Figure 1). In all cases, 95% of the PTV_{Total} was covered by at least 99% of the prescription dose, 99% of the CTVs were covered by the prescription dose, and no point dose exceeded 120% of the prescription dose.

IMRT vs. Adaptive IMRT

Compared with IMRT plans, adaptive IMRT statistically significantly

decreased esophagus mean dose and V30 (both $p < 0.01$), lung mean ($p = 0.04$) and V20 ($p = 0.04$), and dose received by 2/3 of the heart ($p = 0.03$) (Table 3). Adaptive IMRT also trended to lower the mean heart dose ($p = 0.06$) and significantly lowered the Dmax to the ipsilateral brachial plexus ($p = 0.01$), but not the contralateral brachial plexus ($p = 0.14$). There was no statistically significant difference in spinal cord Dmax ($p = 0.22$), dose received by 1/3 of the heart ($p = 0.51$), and lung V5 ($p = 0.36$).

IMRT vs. Proton Therapy

Compared with IMRT, proton therapy significantly reduced lung mean ($p = 0.03$) and V5 ($p < 0.01$), as well as heart mean and doses to 1/3 and 2/3 of the heart (all $p < 0.01$) (Figure 1). Proton therapy trended to lower the contralateral brachial plexus Dmax ($p = 0.06$) but did not significantly reduce the ipsilateral brachial plexus Dmax ($p = 0.14$). The spinal cord Dmax ($p = 0.20$), lung V20 ($p = 0.44$), and esophagus mean ($p = 0.39$) and V30 ($p = 0.84$) were not significantly decreased with proton therapy.

Adaptive IMRT vs. Proton Therapy

Compared with adaptive IMRT plans, proton therapy significantly lowered lung V5, heart mean, and doses received by 1/3 and 2/3 of the heart (all $p < 0.01$). The contralateral brachial plexus Dmax ($p = 0.06$) and lung mean ($p = 0.11$) trended lower with protons. Ipsilateral brachial plexus ($p = 0.58$) and spinal cord ($p = 0.14$) Dmax and esophagus mean ($p = 0.96$) and V30 ($p = 0.28$) were not improved with proton therapy.

IMRT vs. Adaptive Proton Therapy

Adaptive proton therapy significantly lowered lung mean and V5, heart mean, and doses received by 1/3 and 2/3 of the heart (all $p < 0.01$) compared with IMRT. Adaptive proton therapy also significantly reduced the ipsilateral ($p < 0.01$)

and contralateral ($p = 0.02$) brachial plexus Dmax and trended to lower spinal cord Dmax ($p = 0.07$), esophagus mean ($p = 0.09$) and V30 ($p = 0.11$), and lung V20 ($p = 0.06$).

Adaptive IMRT vs. Adaptive Proton Therapy

When compared to adaptive IMRT, adaptive proton therapy significantly reduced spinal cord Dmax ($p = 0.02$), heart mean and doses to 1/3 and 2/3 of the heart (all $p < 0.01$), and lung mean ($p = 0.03$) and V5 ($p = 0.01$). Adaptive proton therapy also significantly lowered the ipsilateral and contralateral brachial plexus Dmax (both $p < 0.01$). Esophagus mean ($p = 0.28$) and V30 ($p = 0.88$) doses did not differ.

Proton Therapy vs. Adaptive Proton Therapy

Adaptive proton therapy improved the esophagus mean and V30, ipsilateral brachial plexus Dmax, heart mean, and lung mean and V20 (all $p < 0.01$) compared with nonadaptive proton therapy. Adaptive proton therapy also significantly reduced the lung V5 ($p = 0.02$) and cord Dmax ($p = 0.04$) and trended to lower the contralateral brachial plexus Dmax ($p = 0.12$) and dose received by 2/3 of the heart ($p = 0.07$). There was no difference in dose received by 1/2 of the heart ($p = 0.14$).

Discussion

This study showed significant differences in doses to OARs when comparing nonadaptive IMRT, adaptive IMRT, nonadaptive proton therapy, and adaptive proton therapy for treatment of SCLC. Proton therapy significantly reduced dose to the lungs and heart compared with IMRT or adaptive IMRT. Adaptive proton therapy further reduced the doses to the heart and lungs compared with IMRT and adaptive IMRT, and also significantly reduced maximum doses to the bilateral brachial plexuses. When looking at the benefits of adap-

tive therapy within a radiation particle type, adaptive IMRT improved doses to the lung, esophagus, heart, and ipsilateral brachial plexus compared with nonadaptive IMRT, whereas adaptive proton therapy reduced doses to the lung, esophagus, heart, ipsilateral brachial plexus, and cord compared with nonadaptive proton therapy. This study also demonstrated significant shrinkage of tumor volumes during the course of radiation therapy, including $> 50\%$ reductions in GTVs and $> 30\%$ reduction in PTVs, with similar magnitude of nodal and primary tumor reductions achieved.

Colaco et al previously reported on a retrospective case series of 6 patients with SCLC who were treated with proton therapy. In that report, no acute grade ≥ 3 esophagitis or acute grade ≥ 2 pneumonitis were observed, and dosimetric comparisons with IMRT showed better sparing of lungs and esophagus with proton therapy.¹³ Although the data describing the use of proton therapy to treat SCLC are extremely limited, numerous reports have demonstrated excellent survival outcomes with proton therapy for NSCLC. Xiang et al reported a median survival of 29.9 months across two prospective trials of 84 patients treated with concurrent proton therapy and chemotherapy for stage III NSCLC and found a 34.8% local recurrence-free survival, 35.4% distant metastasis-free survival, 31.2% progression-free survival, and 37.2% overall survival at 3 years.¹¹ Among 35 patients treated with inoperable locally advanced NSCLC with proton radiation therapy alone without chemotherapy, no grade 3 or higher toxicity was observed. The overall survival rate was 81.8% at 1 year and 58.9% at 2 years, and local progression-free survival was 93.3% at 1 year and 65.9% at 2 years.¹²

Proton therapy has also been reported in multiple studies to improve dosimetric parameters compared with photon therapy for NSCLC,^{6,8,18,19} consistent with the current study findings for SCLC. Re-

duced OAR doses with proton therapy for lung cancer may reduce treatment-related toxicities for lung cancer. Sejjal et al investigated the toxicity associated with proton therapy to a median of 74 CGE with concurrent chemotherapy for NSCLC compared with toxicity for disease-stage matched patients treated with 3D-CRT or IMRT to a median of 63Gy with concurrent chemotherapy. While proton radiation therapy allows for higher radiation doses, it also significantly lowers rates of grade ≥ 3 pneumonitis (2% vs. 30% vs. 9%, $p < 0.001$) and esophagitis (5% vs. 18% vs. 44%, $p < 0.001$) compared with 3D-CRT and IMRT, respectively.¹⁰

In efforts to decrease dose to adjacent normal tissues while maintaining optimal target volume coverage, adaptive radiation planning has been increasingly investigated. Although no published data on adaptive radiation therapy for small cell lung cancer currently exist prior to this report, adaptive radiation therapy for NSCLC has previously been evaluated. By assessing the effects of a 20-28 Gy boost to a shrunken PTV after 40 Gy in 66 patients with stage III NSCLC, Ding et al reported significant sparing of OARs compared to nonadaptive radiation therapy, which the authors reported may allow for dose escalation and an improvement in local control.²⁰ Similar significant reductions in lung doses and an ability to dose escalate were reported in another study of 13 patients with locally advanced NSCLC. This investigation also demonstrated a reduction in mean lung dose of 5.0% with single-plan adaptation in week 3, 5.6% with single-plan adaption in week 5, and 7.9% with adapting the plan after both weeks 3 and 5.^{21,22} This benefit is in keeping with the even greater benefit seen in our study, in which the mean lung dose was reduced by 5.5% with IMRT and 11.9% with proton therapy with a single-plan adaption after 15 Gy, and by 14.7% with IMRT and 17.6%

with proton therapy with a single-plan adaption after 30 Gy.

Another study that utilized PET rescanning during the course of treatment to design boost fields for NSCLC demonstrated the potential for significantly escalating doses while sparing OARs.²³ Still another study showed that adaptive image-guided radiation therapy methods for NSCLC were optimal in improving PTV coverage and decreasing dose to normal tissues, including significantly reducing the mean lung dose.²⁴ Other studies, however, have showed less benefit to adaptive radiation therapy, including its use for the treatment of stage I NSCLC with stereotactic body radiation therapy (SBRT).²⁵ However, unlike the dramatic reduction in tumor volume demonstrated during the course of treatment for SCLC in the current study, a significant tumor volume reduction would not be expected during the short course of SBRT.

More limited data exist assessing adaptive radiation therapy when delivering proton therapy. A dosimetric study that compared IMRT, adaptive IMRT, proton therapy, and adaptive proton therapy for squamous cell carcinoma of the head and neck found that proton therapy decreased doses to OARs compared to IMRT, and that adaptive proton therapy further reduced doses to OARs compared to nonadaptive proton therapy.²⁶ Another study of 18 patients assessing the toxicity and patterns of failure associated with adaptive proton therapy for NSCLC showed that proton therapy is well-tolerated and a promising approach to allow for higher doses while limiting side effects. No patient experienced Grade 4 or 5 toxicity, and patients most commonly experienced dermatitis (Grade 2, 67%; Grade 3, 17%), Grade 2 fatigue (44%), and Grade 2 pneumonitis (11%).¹⁴ A third study examining the outcomes of adaptive proton therapy compared to nonadaptive proton therapy for NSCLC found less toxicity and greater OAR

sparing with adaptive planning. Koay et al found adaptive planning significantly reduced NSCLC tumor volume size ($p < 0.01$) and improved sparing to the esophagus and spinal cord. However, unlike the current study, no significant reduction to the heart or lungs was observed.¹⁵

Although no appreciable data on adaptive radiation therapy for SCLC exist to date, to account for the rapid tumor response to therapy and to attempt to minimize radiation dose to OARs, modification of plans during SCLC treatment are being studied in Alberta, Canada, in a prospective trial. Clinical trials in Ontario, Canada, and Limburg, Netherlands, are also enrolling patients to examine adaptive radiation therapy for NSCLC. Image-guided adaptive proton therapy is being compared to photon therapy in a collaboration between Massachusetts General Hospital and UT MD Anderson Cancer Center, whereas a Stanford University trial is evaluating differences in 4DCT-based ventilation imaging during simulation and treatment. The Radiation Therapy Oncology Group (RTOG) and American College of Radiology Imaging Network (ACRIN) are investigating whether tumor dose can be escalated to improve local control when an individualized adaptive radiation treatment plan is applied by using FDG-PET/CT scans acquired at 40-46 Gy in patients with inoperable or unresectable stage III NSCLC (RTOG 1106/ACRIN 6697).²⁷

Limitations

Although some radiation oncologists continue to treat SCLC with 3D-CRT, as was done in Intergroup 0096,⁴ IMRT-based radiation therapy with concurrent chemotherapy for limited-stage SCLC has become increasingly utilized to decrease dose to OARs compared to 3DCRT, and IMRT is being prospectively evaluated for SCLC in the Netherlands.²⁷ In this study, photon plans were delivered with IMRT to maximize tumor coverage and minimize OAR

dose. It is possible that the magnitude of benefit demonstrated in this study with proton therapy over photon therapy would have been even greater had the photon plans employed 3DCRT. Furthermore, as the entire treatment course with twice daily radiation therapy was completed in 3 weeks, it is possible that greater target volume shrinkage and further reductions of dose to OARs would have been demonstrated if radiation therapy was administered once daily over 6-8 weeks instead of twice daily. Also, as 7 of the 10 patients received one cycle of chemotherapy prior to beginning radiation therapy, the magnitude of tumor volume reduction and OAR sparing may have been even greater if only chemotherapy-naïve patients were assessed. As patients treated with once-daily radiation therapy or starting radiation therapy with cycle 1 of chemotherapy may have an even greater magnitude of benefit for adaptive therapy, adaptive planning may be even more imperative when treating such patients with proton therapy.

Furthermore, all proton plans were performed using passively scattered proton therapy. It is possible that the benefit demonstrated in this study with proton therapy over photon therapy would have been even greater had the proton plans employed pencil-beam scanning proton therapy instead of passively scattered proton therapy. Additionally, all doses reported for tumor and OARs were based on the clinical proton treatment planning system. The accuracy of proton dose in a heterogeneous environment like the lung is limited due, in part, to degradation of the lateral penumbra.²⁸⁻³⁰ As a result, the reported values may be overestimated for target dose and underestimated for dose to normal lung, and reanalysis with Monte Carlo-based dose calculation might more accurately describe the true doses to these volumes.^{28,31} However, the magnitude of the effects seen in this study, including the benefit of pro-

ton therapy over IMRT and the benefit of adaptive therapy over nonadaptive therapy, would be expected to remain significant and largely proportional regardless of the dose calculation method used and out-of-field dose inaccuracies.

Additionally, given the limited data on adaptive planning in lung cancer, caution must be taken when clinically performing adaptive therapy by shrinking the target volumes, as viable microscopic disease might remain in the original treatment volume despite a strong initial response to chemoradiation. We mitigated this concern, in part, by using the same expansions to CTVs and PTVs in the adaptive plans that were used in the initial plans and by using the same field arrangements in the adaptive plans that were used in the initial plans to allow for dose delivery via beams already traversing these areas of potential microscopic residual disease. Furthermore, findings from two large studies, including a 494-patient cooperative group study, suggest that the radiation therapy treatment of smaller volumes of disease following an initial response to therapy for SCLC is not associated with reduced local control or overall survival.³²⁻³³ Lastly, the statistical results in this study should be interpreted with caution since the sample size was limited, as this was an exploratory analysis intended to provide evidence supporting the initiation of a planned prospective clinical trial.

Conclusions

This study demonstrated a rapid shrinkage of tumor volumes during the course of radiation therapy for SCLC, which allowed for adaptive plans to be dosimetrically superior to nonadaptive plans for both photons and protons. Adaptive plans may be of more critical importance for proton therapy, and verification scans should be performed during treatment to ensure continued plan validity. Adaptive planning for proton therapy may be further facilitated using cone-

beam computed tomography and deformable registration.³⁴ When compared with photon therapy, proton therapy allowed for the maintenance of optimal tumor coverage while significantly reducing dose to critical normal structures like lungs and heart. With decreased doses delivered to OARs, patients receiving proton therapy may experience fewer radiation-induced side effects. Prospective clinical trials are needed to determine if the dosimetric superiority of proton therapy can result in less toxicity for patients with limited-stage SCLC. Future studies should also focus on the feasibility and benefit of pencil-beam scanning and intensity-modulated proton therapy (IMPT) for SCLC to further reduce dose to OARs, including the esophagus.^{35,36} The findings in this study serve as the basis for a planned phase II trial assessing toxicities in limit-staged SCLC patients treated with proton therapy using adaptive planning, as necessary, based on weekly verification scans.

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