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ORIGINAL REPORT

Dose-Limiting Toxicity After Hypofractionated Dose-Escalated Radiotherapy in Non–Small-Cell Lung Cancer

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ABSTRACT

Purpose
Local failure rates after radiation therapy (RT) for locally advanced non–small-cell lung cancer (NSCLC) remain high. Consequently, RT dose intensification strategies continue to be explored, including hypofractionation, which allows for RT acceleration that could potentially improve outcomes. The maximum-tolerated dose (MTD) with dose-escalated hypofractionation has not been adequately defined.

Patients and Methods
Seventy-nine patients with NSCLC were enrolled on a prospective single-institution phase I trial of dose-escalated hypofractionated RT without concurrent chemotherapy. Escalation of dose per fraction was performed according to patients' stratified risk for radiation pneumonitis with total RT doses ranging from 57 to 85.5 Gy in 25 daily fractions over 5 weeks using intensity-modulated radiotherapy. The MTD was defined as the maximum dose with ≤ 20% risk of severe toxicity.

Results
No grade 3 pneumonitis was observed and an MTD for acute toxicity was not identified during patient accrual. However, with a longer follow-up period, grade 4 to 5 toxicity occurred in six patients and was correlated with total dose ($P = .004$). An MTD was identified at 63.25 Gy in 25 fractions. Late grade 4 to 5 toxicities were attributable to damage to central and perihilar structures and correlated with dose to the proximal bronchial tree.

Conclusion
Although this dose-escalation model limited the rates of clinically significant pneumonitis, dose-limiting toxicity occurred and was dominated by late radiation toxicity involving central and perihilar structures. The identified dose-response for damage to the proximal bronchial tree warrants caution in future dose-intensification protocols, especially when using hypofractionation.

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INTRODUCTION

For patients with locally advanced non–small-cell lung cancer (NSCLC), radiation therapy (RT) continues to be the backbone of treatment. Randomized trials through the Radiation Therapy Oncology Group (RTOG), in the era before modern imaging and treatment planning methods, demonstrated improved local control with increasing doses of RT and established a benchmark dose of 60 Gy using conventional fractionation.[1] A dose of 69.6 Gy in twice daily treatments was shown to be superior to lower doses in a phase I/II study,[2] but was not significantly better in a randomized comparison with 60 Gy.[3] In most of the randomized concurrent chemotherapy trials, patients were treated to doses of 60 to 66 Gy but nevertheless still experienced local failure rates of approximately 30%.[4] Given these suboptimal results, strategies of treatment intensification to improve outcomes continue to be explored.

Retrospective and nonrandomized prospective data have suggested that further dose escalation in NSCLC may be associated with better outcomes.[5-8] However, for patients with locally advanced disease, the benefit of dose escalation beyond 60 Gy using conventional fractionation has not been supported by level I evidence. A recent randomized study by the RTOG in patients with locally advanced NSCLC showed worse survival rates for patients receiving 74 Gy versus 60 Gy with concurrent chemotherapy.[9]

As an alternative to pure dose escalation, accelerated treatment schedules may allow for improved outcomes by shortening overall treatment time, as demonstrated in the Continuous Hyperfractionated Accelerated Radiotherapy trial.[10] However, such

highly fractionated dose-intensification schedules present extraordinary logistical challenges. Alternatively, hypofractionation can be used to shorten radiation treatment time more conveniently.[11]

To investigate the safety and feasibility of treatment intensification through hypofractionation in a broad patient population, we initiated a phase I clinical trial of dose-per-fraction escalation for patients with NSCLC. Given concern for increased toxicity with hypofractionated RT and concurrent chemotherapy, patients were allowed sequential but not concurrent chemotherapy. Intensity-modulated radiotherapy (IMRT) was used to minimize high doses received by normal structures. Radiobiological modeling suggested limiting treatment time to no more than 5 weeks (25 fractions),[12] with dose-per-fraction (and total dose) escalation guided by normal tissue complication probability (NTCP) modeling for pneumonitis risk. Preliminary results have been presented[13] and were negative for grade 3 or greater pneumonitis or grade 4 or greater esophagitis, the protocol-defined primary and secondary dose-limiting toxicities (DLTs), respectively. Now, with more mature results we report on other DLTs, particularly late effects, with supportive dose-response data.

PATIENTS AND METHODS

Eligibility Criteria

This prospective single-institution phase I study was approved by the local institutional review board and was monitored by an independent data safety committee. Patients were required to be age 18 years or older, with an Eastern Cooperative Oncology Group performance status of 0 to 2 and a histologically or cytologically proven primary lung cancer for which full-dose radiation therapy was recommended (eg, a conventional dose of at least 60 Gy in 6 weeks). Because this was a phase I trial, all stages were eligible, including patients with recurrent tumors. Exclusion criteria included concurrent chemotherapy, previous thoracic RT, previous chemotherapy with bleomycin or gemcitabine, and regular use of supplemental oxygen. The remaining eligibility criteria have been published previously.[13] All patients were required to provide informed consent at the time of enrollment according to institutional and federal guidelines.

Treatment

Protocol treatment consisted of IMRT over a course of 25 once-per-day fractions given 5 days per week as described previously.[13] Greater than 95% of fractions were delivered via helical tomotherapy. The gross tumor volume consisted of gross disease as seen on computed tomography (CT) and/or fluorodeoxyglucose positron emission tomography imaging. No elective nodal irradiation was performed. A four-dimensional computed tomography scan was used to account for tumor motion and define an internal target volume. A clinical target volume margin of 6 mm accounted for microscopic disease, with an additional 2-mm margin for set-up uncertainty to create the planning target volume (PTV). Dose was prescribed such that 95% of the PTV volume received the prescription dose.

The prescribed dose was assigned using a Bayesian dose-escalation scheme incorporating predicted risk for pneumonitis and respecting additional normal tissue constraints (Appendix [online-only]).[12,13] After an initial pilot phase of five patients, subsequent patients were grouped into one of five dose-escalation bins according to $rNTD_{mean}$, defined as mean fraction-normalized lung dose divided by the normalized prescription dose. At a given dose level, patients with higher $rNTD_{mean}$ (and therefore higher bin number) were predicted to be at higher risk for radiation pneumonitis. Dose was escalated in parallel within each bin during the trial as described in the Appendix.

The dose levels shared by all bins were as follows: 57 Gy at 2.28 Gy/fraction (bins 4 and 5 starting dose), 63.25 Gy at 2.53 Gy/fraction (bin 3 starting dose), 69.25 Gy at 2.77 Gy/fraction, 75 Gy at 3.0 Gy/fraction (bin 2 starting dose), 80.5 Gy at 3.22 Gy/fraction (bin 1 starting dose), and 85.5 Gy at 3.42 Gy/fraction. Using the linear-quadratic conversion, the estimated equivalent doses for late effects at 2 Gy per fraction for these dose levels were estimated as 60, 70, 80, 90, 100, and 110 Gy, respectively (assuming an α/β ratio of 3 Gy).[12] RT was delivered using daily CT-based image guidance.

According to protocol, the maximum-tolerated dose (MTD) of each bin was defined as the maximum dose level at which a $\leq$ 20% risk of DLT was identified for that bin. As per the iterative Bayesian design, the study would continue to accrue to all bins with further up/down dose adjustments until the target accrual of 75 evaluable patients was met. Evaluable patients were defined as those who completed more than 80% of the prescribed RT course and returned for at least one toxicity assessment. Patients accrued to a given bin were eligible for dose escalation beyond a given dose level if at least three patients within the bin (or in bins with larger $rNTD_{mean}$ values) had been previously treated at that dose and received follow-up for 3 months without evidence of DLT.

Follow-Up and Data Collection

Patients were seen once per week during the course of their radiotherapy treatments and received a chest CT and follow-up examination 1 month after radiotherapy was completed. Repeat imaging and clinical follow-up was then performed every 3 to 4 months for the first 3 years and every 6 months thereafter. For patients who died in the absence of progressive disease, medical records were reviewed and/or the next of kin were contacted to ascertain the cause of death.

Definitions and Statistical Analysis

The primary end point of this study was grade 3 pneumonitis as defined by the National Cancer Institute Common Toxicity Criteria for Adverse Events version 3.0, with the additional requirement of radiographic findings consistent with radiation pneumonitis. All other toxicities were coded according to National Cancer Institute Common Toxicity Criteria for Adverse Events criteria. Late toxicities were defined as those occurring more than 90 days from the start of treatment. In the presence of uncertainty regarding the attribution of a toxicity (eg, disease progression versus treatment), the toxicity was included in the analysis if the consensus of the institutional safety monitoring committee was that the toxicity was at least possibly related to protocol treatment. DLT was defined as grade 3 or greater radiation pneumonitis, grade 4 or greater acute esophagitis, or any other grade 3 or greater toxicity. Local failure was defined according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria.[14]

Local control was analyzed with death as a competing risk and cumulative incidences were compared using Gray's test.[15] Risk factors for radiation pneumonitis were assessed by logistic regression using a generalized linear model. The observed rate of pneumonitis was compared with that predicted by NTCP modeling using a χ^2 test for goodness of fit. Overall survival and grade 4 to 5 toxicity estimates were calculated using the Kaplan-Meier method with time-to-event defined from the start date of radiation therapy and patients censored at the time of last follow-up (or death from disease or intercurrent illness in the case of the toxicity analysis). Univariate analyses for censored toxicity data were conducted using the log-rank test for categoric variables and a Cox proportional hazards model for continuous variables.

For analysis of radiation dosimetry, the variable DXcc was defined as the largest dose (in Gy) such that X cm3 of a structure received greater than or equal to that dose. VX was defined as the volume percentage of a structure that received greater than or equal to dose X (in Gy). Dmax was defined as the maximum voxel dose within an organ. NTCP curves as a function of dose were calculated using point estimates at 2 years generated from the Cox proportional hazards model while varying the dose parameter. The NTCP curves were checked by plotting point estimates of toxicity incidences for dose quartiles centered at the quartile means. All statistical analyses were performed using R version 2.13.1 with the cmprsk package (The R Foundation for Statistical Computing, www.r-project.org).

Table 1. Patient and Treatment Characteristics

Characteristic	No. of Patients	%
Total patients	79	100
Age, years		
< 50	6	9
50-69	47	59
≥ 70	26	32
Sex		
Female	33	42
Male	46	58
Stage		
I/II	7	9
IIIA	21	27
IIIB	35	44
IV	10	13
Recurrent	6	8
Histology		
Adenocarcinoma	24	30
Squamous cell carcinoma	26	33
NSCLC, NOS	22	28
Other NSCLC	7	9
Bin assignment, $rNTD_{mean}$		
Pilot (NA)	5	6
1 (0.00-0.119)	6	7
2 (0.12-0.179)	8	10
3 (0.18-0.239)	27	34
4 (0.24-0.309)	29	37
5 (0.31-0.410)	4	5
Performance status		
0	48	61
1	30	38
Not recorded	1	1
Prescribed radiation dose, Gy		
57	47	59
63.25	11	14
69.25	3	4
75	12	16
80.5	4	5
85.5	2	3
Chemotherapy		
Neoadjuvant	17	21
Adjuvant	33	41
Both	3	4
None	25	32
Other*	1	1

Abbreviations: NA, not applicable; NSCLC, non–small-cell lung cancer; NOS, not otherwise specified; $rNTD_{mean}$, mean normalized tissue (lung) dose divided by normalized prescription dose.
*Patient received erlotinib before, during, and after radiation.

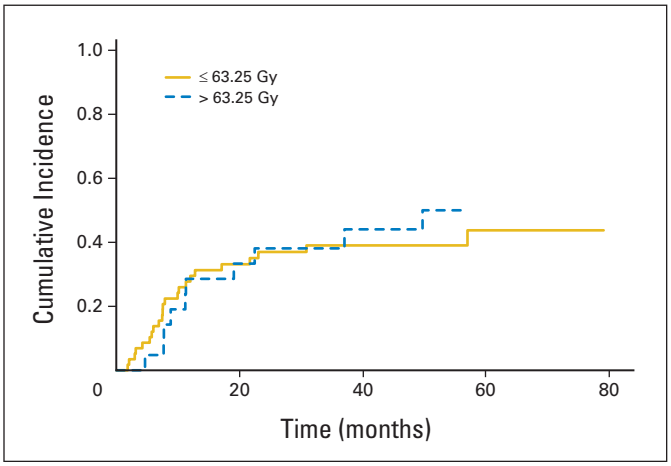

Fig 1. Cumulative incidence of local failure according to total dose delivered ($P = .81$), with death as a competing risk.

RESULTS

Patients

A total of 79 patients were enrolled onto the trial from 2004 to 2010 and a summary of patient and treatment characteristics is listed in Table 1. After five patients were treated on the pilot study at a dose of 57 Gy without DLT, dose escalation proceeded as per protocol. Dose escalation was limited in 44 patients (56%), who had to be assigned to lower dose levels because of their inability to meet normal tissue constraints, usually in the esophagus. There was a trend for better performance status to be correlated with higher prescribed dose ($P = .054$). Larger PTV size was associated with higher bin number ($P = .001$) and lower prescribed dose ($P = .003$). The median delivered dose was 57 Gy (range, 22.8 to 85.5 Gy) in 25 fractions. Patients not eligible for per-protocol analysis included two who did not receive at least 80% of the prescribed course of radiotherapy and two patients treated to a prescribed 57 Gy but who were lost to follow-up after completing treatment. None of the excluded patients had grade 3 or greater toxicity attributable to treatment.

Survival and Local Control

With a median follow-up period of 17.0 months (range, 2.3 to 79 months) from the time of treatment, the median overall survival rate was 16.0 months with a 3-year overall survival of 29%. For patients with a performance status of 0 who received sequential chemotherapy, median survival was 23.6 months. When this article was written, 15 patients were alive with a median follow-up of 49 months. As shown in Figure 1, there was no significant difference in local control in patients treated to 69.25 Gy and higher compared with those treated at the 57 and 63.25 Gy dose levels ($P = .81$).

Toxicity

Of the 75 patients evaluable for per-protocol toxicity analysis, there were no instances of grade 3 or higher acute or late esophageal toxicities; 48% of patients (n = 36) experienced grade 2 acute esophagitis and 28% (n = 21) had grade 2 late esophageal toxicity. One patient developed a grade 2 sensory brachial plexopathy 1 year after completing RT to a dose of 57 Gy to a malignant right axillary lymph node and a right upper-lobe tumor invading the chest wall.

There were no incidents of grade 3 or greater radiation pneumonitis according to protocol definitions; 12 of the patients (16%) experienced grade 2 pneumonitis. This was not significantly different from the 17% risk predicted by the NTCP model ($P = .73$). The PTV volume, residual lung volume receiving at least 5 Gy (V5), V10, and mean residual lung dose were all significant predictors of grade 2 pneumonitis on univariate analysis, but total dose was not (Appendix).

There were six incidents of grade 4 to 5 toxicity identified that were felt to be possibly or likely related to RT (Table 2 and Fig 2A). One

Table 2. Patients With Grade 4-5 Toxicity

Age (years)	Sex	Stage	Bin	Dose (Gy)*	Grade	Interval (months)†	Toxicity
69	M	IIIB	3	63.25	5	1.2	HSV/CMV pneumonitis; history of pre-RT low-dose methotrexate
66	F	IIA	1	85.5	5	55	Fatal hemoptysis
58	M	IIIB	3	75	5	7.9	Fatal hemoptysis
63	M	IIIB	1	75	5	1.6	Lung abscess
62	M	IIIA	3	75	5	8.1	Fatal hemoptysis and abscess
61	F	IV	3	75	4	10.3	Lung abscess, bronchocavitary fistula, tracheoesophageal fistula

Abbreviations: CMV, cytomegalovirus; HSV, herpes simplex virus; RT, radiation therapy.
*All treatments prescribed over a course of 25 fractions.
†From completion of radiation therapy.

patient treated to a dose of 63.25 Gy died as a result of progressive hypoxemia with bilateral lung infiltrates in the absence of disease progression 1 month after RT. A diagnosis of herpes simplex virus and cytomegalovirus pneumonitis was made by bronchoalveolar lavage. A second patient died of a lung abscess 1.6 months after completing RT to a dose of 75 Gy. Three other patients treated to doses of 75 to 85.5 Gy died as a result of massive hemoptysis 8 or more months after treatment. One of these patients had an endobronchial stent placed before RT. A postmortem examination revealed an arteriole that had bled into a necrotic perihilar lung cavity corresponding to the PTV and adjacent to the previously placed stent. The other two patients were without radiographic evidence of disease recurrence at the time of death. One patient experienced a grade 4 bronchocavitary fistula 10 months after receiving a dose of 75 Gy. A stent was placed, which was followed by development of a distal tracheoesophageal fistula.

On univariate analysis, higher delivered dose was significantly associated with the development of any grade 4 to 5 toxicity (hazard ratio, 1.13; 95% CI, 1.04 to 1.23; $P = .0036$). The 2-year incidence of these toxicities was 31% (± 13%) in patients treated to 75 Gy or higher compared with 1.8% (± 1.7%) of patients treated to lower doses ($P < .001$). Analysis of additional variables is listed in Table 3.

As grade 4 to 5 toxicities seemed to be dependent on total dose and not bin number, the decision was made to report an MTD for all patients rather than for each bin. An MTD was identified at 63.25 Gy and was largely determined by late toxicities in patients receiving ≥ 75 Gy. Only three patients were treated to 69.25 Gy, so the safety of this dose level cannot be determined with the MTD definition of ≤ 20% DLT.

Given similarities in the late grade 4 and 5 toxicities seen in our study, an exploratory analysis was performed with the hypothesis that these toxicities could be linked to normal tissue dosimetry. Complete dosimetric data could not be obtained in 11 patients, none of whom experienced significant toxicity. Parameters related to lung, heart, and esophageal doses were not significant, whereas doses given to small volumes of the proximal bronchial tree were significant (Table 4). Of these, D3cc seemed to be the most significant ($P = .004$), while Dmax, D1 cm^3, and D2 cm^3 were significant to lesser degrees. For the parameters found to be significant on univariate analysis, the 2-year probability of late grade 4 to 5 toxicity was estimated as a function of equivalent dose delivered at 2 Gy per fraction (EQD2) using an α/β ratio of 3 Gy (Fig 2B). The EQD2 doses predicting a 5% complication rate at 2-years for these parameters ranged from 75 Gy (D3cc) to 83 Gy (Dmax).

DISCUSSION

This study demonstrated that without concurrent chemotherapy, hypofractionated RT up to 63.25 Gy in 25 fractions (and possibly up to 69.25 Gy) is well-tolerated when strict normal tissue constraints are respected. No grade ≥ 3 radiation pneumonitis was observed. However, other grade 4 to 5 toxicities, including late effects, were manifest and found to correlate with total prescribed dose. We attributed late grade 4 to 5 toxicities to cause damage to central and perihilar

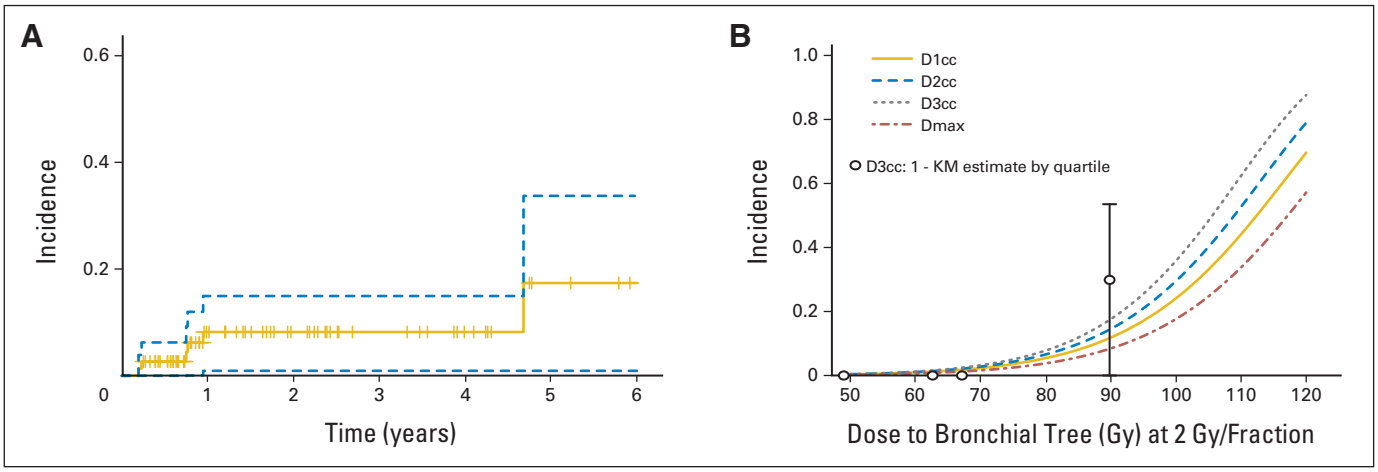

Fig 2. (A) Incidence (1 − Kaplan-Meier [KM] estimate) of any grade 4 or 5 toxicity in patients censored at the time of death or last clinical follow-up. Dashed lines represent the 95% CI. (B) Two-year probabilities of late grade 4 or 5 toxicity according to dose-per-fraction normalized dose (EQD2) to the proximal bronchial tree and estimated using a Cox proportional hazards model. Open circles represent the 1 − KM estimate (± 95% CI) for quartiles of EQD2 D3cc (centered at the quartile mean). DXcc, maximum dose D such that X cm^3 of the structure received a dose ≥ D; Dmax, maximum dose to any voxel within structure.

Table 3. Univariate Analysis of Any Grade 4-5 Toxicity

Variable	No. of Events	%	*P*
Dose received, Gy			< .001
≤ 69.25	1 of 57	2	
75-85.5	5 of 18	28	
Age, years			.41
≤ 60	1 of 24	4	
> 60	5 of 51	10	
Performance status			.054
0	6 of 46*	13	
1	0 of 28*	0	
Radiation treatment time, days†			.16
Bin assignment, $rNTD_{mean}$			.06
Pilot (NA)	0 of 4	0	
1 (0.00-0.119)	2 of 6	33	
2 (0.12-0.179)	0 of 8	0	
3 (0.18-0.239)	4 of 27	15	
4 (0.24-0.309)	0 of 26	0	
5 (0.31-0.410)	0 of 4	0	
PTV, cm^3†			.9
Chemotherapy			.23
Any	3 of 54	6	
None	3 of 21	14	

Abbreviations: NA, not applicable; PTV, planning target volume; $rNTD_{mean}$, mean normalized tissue (lung) dose divided by normalized prescription dose.
*Total No. of patients adds up to only 74 because of missing data.
†Analyzed as a continuous variable.

Table 4. Univariate Analysis of Late Grade 4-5 Toxicity (all patients)

Variable	*P*
Lung	
Mean	.63
V5	.48
V20	.66
V30	.37
PTV, cm^3	.41
Bronchial tree dose*	
Max	.020
Mean	.072
D1cc	.012
D2cc	.007
D3cc	.004
Heart dose	
Mean	.16
V5	.44
V50	.43
Esophageal dose	
Max	.66
Mean	.74
D1cc	.72
D2cc	.80
D3cc	.80

Abbreviations: DXcc, maximum dose D such that X cm^3 of the structure received a dose ≥ D, where D is measured in Gy; max, maximum; PTV, planning target volume; VX, percent volume receiving a dose of ≥ X Gy.
*Proximal bronchial tree defined as per Radiation Therapy Oncology Group 0813.

structures, specifically the proximal bronchial tree and surrounding vasculature. In support of this, we identified a relationship between severe late toxicity and the dose given to small volumes of the proximal bronchial tree, with maximum dose, D1cc, D2cc, and D3cc all significant on univariate analysis.

The potential for significant damage to central structures has been described in patients undergoing stereotactic body radiotherapy (SBRT) for early-stage NSCLC,[16] with subsequent protocols restricting eligibility based on location.[17] Although current protocols exist that allow SBRT for central tumors, our results indicate that late central toxicities can still limit dose-escalation strategies, even when a more fractionated approach is used. The rate of central toxicity seen in our cohort was somewhat surprising given the higher EQD2 doses in commonly used SBRT fractionation schemes for central lung lesions (eg, 50 Gy in five fractions as per the starting dose in RTOG 0813; EQD2 = 130 Gy for late effects). However, the size limitations in SBRT may naturally limit the volume of the bronchial tree receiving high doses. All patients who experienced grade 4 to 5 late toxicities in our cohort had gross tumor encasing or abutting a mainstem or proximal lobar bronchus. In addition, local invasion by the more advanced tumors in our study may have compromised the radiation tolerance of adjacent normal structures.

The risk for radiation pneumonitis in our study was well controlled following a procedure similar to that used by other groups investigating dose escalation.[18] However, our results are a reminder that the spectrum of toxicities from dose-intensified thoracic radiotherapy can be broad. In addition to pneumonitis and pulmonary fibrosis, patients treated to high biologic doses are at risk for bronchial stenosis, fatal hemoptysis,[19] and disruption of the fibrocartilagenous tracheobronchial tree.[20] These are toxicities that might not always be captured with high fidelity using conventional prospective reporting mechanisms or they may be misdiagnosed by outside physicians as disease progression despite no radiographic evidence of such. This theme has been alluded to in a recent editorial regarding the results of RTOG 0617, in which the higher number of deaths in the 74 Gy versus 60 Gy arm was felt to be attributable to RT-related normal tissue damage, even though there were no reported differences in toxicity rates between the two groups.[21]

These results also have implications for clinical trials in which dose is escalated to maintain a predicted rate of isotoxicity based on radiobiologic modeling of a single organ or tissue at risk. For example, the experimental arm in the currently open study RTOG 1106 uses hypofractionation to dose-escalate up to 85.5 Gy in 6 weeks with concurrent chemotherapy as long as mean lung doses of 20 Gy are achieved. In our study, the NTCP model for lung toxicity was accurate in predicting grade 2 radiation pneumonitis but did not control for late central toxicity, which was identified as the driving etiology behind dose-limiting adverse events. Accurate modeling of other toxicities is therefore needed to safely allow dose escalation using this paradigm.

For patients with NSCLC treated with IMRT, hypofractionated RT at doses of 57 to 63.25 Gy in 25 fractions was well-tolerated in the absence of concurrent chemotherapy and with strict normal tissue constraints. Grade 4 and 5 late toxicities were attributed to damage in central and perihilar structures, as supported by a significant correlation with dose delivered to the proximal bronchial tree. In addition to controlling for pneumonitis risk, radiation dose-escalation studies in

lung cancer should require strict limits to doses received by the proximal bronchial tree.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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Appendix

Bin assignment. Patients underwent four-dimensional computed tomography simulation and target volume segmentation as described in Patients and Methods. Normal structures were also segmented, including bilateral lungs (as a single structure), esophagus, and spinal cord. A 25-fraction preliminary radiation plan was optimized and used to calculate a 2-Gy per fraction equivalent mean lung dose normalized to the prescription dose ($rNTD_{mean}$). This conversion was performed with $\alpha/\beta = 3$ Gy for each volume element and has been described previously.[12]

Assignment to one of five dose-escalation groups (ie, bins) was performed according to $rNTD_{mean}$ as listed in Appendix Table A1. Patients with higher $rNTD_{mean}$ were predicted to be at higher risk for pneumonitis for a given prescription dose[12] (Kwa SL et al: Radiation pneumonitis as a function of mean lung dose: An analysis of pooled data of 540 patients. Int J Radiat Oncol Biol Phys 42:1-9, 1998). Once a patient was categorized into the appropriate bin, a dose level was chosen following the dose escalation rules outlined in the Dose Escalation section.

Dose escalation. An initial pilot phase of five patients treated to a dose of 57 Gy in 25 fractions was followed by a dose escalation study consisting of a set of five linked phase I trials, one for each of the bins. Dose to the planning target volume was escalated within each bin according to a Bayesian continual reassessment method (CRM) with the maximum-tolerated dose (MTD) defined as the maximum dose at which there was $\leq$ 20% dose-limiting toxicity (DLT). As a conservative measure, starting doses in each bin began at the dose level just below the level at which a 20% risk for grade 2 radiation pneumonitis was predicted (or at 57 Gy in the higher bins; Appendix Table A2). After every five patients had received follow-up for 3 months with radiographic and clinical evaluation, a posterior model for DLT was used as a prior model for the next cohort of patients who were to be treated at the re-estimated MTD. Using this approach, patients in a given bin were eligible for dose escalation beyond a given dose level if at least 3 patients within the bin (or in bins with larger $rNTD_{mean}$ values) had been treated at that dose and received follow-up for 3 months without evidence of DLT.

Once the continual reassessment method protocol identified the dose level for a new patient, the patient-specific radiation treatment plan was optimized at that dose level. If normal tissue constraints specified by the protocol were not met, the patient was dropped to a lower dose level. The spinal cord dose was restricted to fraction-normalized tissue dose (NTD) of 50 Gy and the esophageal dose was initially restricted to an NTD of 64 Gy, both with normalization to 2-Gy per fraction equivalents. However, the initial esophageal constraint proved to be too restrictive and therefore was changed to no more than 5 cm^3 of esophagus receiving an NTD in excess of 64 Gy. In addition, the effective volume (V_{eff}) of the esophagus was required to be less than 30%.

Table A1. Bin Definitions

Bin	$rNTD_{mean}$
1	0.00-0.119
2	0.12-0.179
3	0.18-0.239
4	0.24-0.309
5	0.31-0.41

Abbreviation: $rNTD_{mean}$, mean normalized tissue (lung) dose divided by normalized prescription dose.

Table A2. Dose Assignment Schema

		Estimated % NTCP Risk for Grade 2 Pneumonitis				
Dose (Gy)*	EQD2 (Gy)	Bin 1	Bin 2	Bin 3	Bin 4	Bin 5
57	60	0-11	11-12	12-15	15-22†	22-40†
63.25	70	0-11	11-13	13-16†	16-26	40-50
69.25	80	0-12	12-15	15-22	22-40	40-65
75	90	0-12	12-16†	16-26	26-50	50-80
80.5	100	0-13†	13-21	21-38	38-61	61-80+
85.5	110	10-21	15-23	26-50	High	High

Abbreviations: EQD2, equivalent dose for late effects ($\alpha/\beta = 3$ Gy) if delivered in 2–Gy fractions; NTCP, normal tissue complication probability.
*Prescription dose delivered over 25 fractions.
†Indicate starting dose level for each bin.

Table A3. Univariate Analysis of Grade 2 Radiation Pneumonitis

Variable	Coefficient	*P*
Chemotherapy, any	0.77	.35
Chemotherapy, adjuvant	1.49	.052
Age	0.013	.69
Bin	0.12	.66
Total dose delivered	−0.05	.30
PTV, cm^3	0.004	.028*
Lung dosimetry		
V5	4.4	.026
V10	4.9	.016
V20	3.7	.37
V30	11.4	.14
Mean	0.23	.027*

Abbreviations: PTV, planning target volume; VX, fraction of volume that received a dose of ≥ X Gy.
*Note that PTV volume and mean lung dose were significantly correlated ($P < .001$).