Original Article

Toxicity Report of a Phase 1/2 Dose-Escalation Study in Patients With Inoperable, Locally Advanced Nonsmall Cell Lung Cancer With Helical Tomotherapy and Concurrent Chemotherapy

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BACKGROUND: The objective of the current study was to evaluate the feasibility and toxicity of radiation dose escalation with concurrent chemotherapy using helical tomotherapy (HT) in patients with inoperable, locally advanced, stage III nonsmall cell lung cancer (LANSCLC) (grading determined according to the American Joint Committee on Cancer 6th edition grading system). **METHODS:** This phase 1/2 study was designed to determine the maximum tolerated dose (MTD) of radiotherapy in patients with LANSCLC administered concurrently with docetaxel and cisplatin. Radiotherapy was delivered using HT. A dose per fraction escalation was applied starting at 2 grays (Gy), with an increase of 6% per dose cohort (DC). The Radiation Therapy Oncology Group acute radiation morbidity score was used to monitor pulmonary, esophageal, and cardiac toxicity. **RESULTS:** Dose escalation was performed in 34 patients over 5 DCs to a dose per fraction of 2.48 Gy. No differences were observed in acute toxicity between the different DCs. However, a significant increase in late lung toxicity in DC IV, which received a fraction size of 2.36 Gy, necessitated a halt in further dose escalation with the MTD defined as 2.24 Gy per fraction. The overall incidence of acute grade $\geq$3 esophageal and pulmonary toxicity was 24% and 3%, respectively (grading determined according to the Radiation Therapy Oncology Group-European Organisation for Research and Treatment of Cancer toxicity scoring system). The overall incidence of late lung toxicity was 21%, but the incidence was an acceptable 13% in DCs I, II, and III. The local response rate was 61% on computed tomography images. **CONCLUSIONS:** The use of HT to 67.2 Gy with concurrent cisplatin/docetaxel was feasible and resulted in acceptable toxicity. A full phase 2 study has been initiated to establish the true local response rate at the MTD of 2.24 Gy per fraction. ***Cancer* 2010;116:241–50.** © *2010 American Cancer Society.*

KEYWORDS: lung cancer, chemoradiation, dose escalation, intensity-modulated radiotherapy, image-guided radiotherapy.

Curative treatment for inoperable, locally advanced, stage III nonsmall cell lung cancer (LANSCLC) remains a challenge. The survival rate at 5 years is dismal, and the low local control rate is a challenge for modern radiotherapy. It has been demonstrated that improving local control has an impact on survival.[1] Many factors have contributed to improving the local control rate, including an increase in the nominal dose,[2] an increase in the biologically equivalent dose (BED),[3] the use of technical innovation in radiation delivery,[4] and the addition of concurrent chemotherapy.[5]

In this prospective study, we incorporated several of these approaches. The increased BED was conceived as an increase in the nominal dose while maintaining a fixed overall treatment time (OTT), a so-called dose-per-fraction escalation.[6] Often in dose escalation trials, the OTT is prolonged with increasing dose steps, but it has become evident that

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there is an adverse effect on outcome with the prolongation of treatment.[7] Finally, because of its known radiosensitizing effect[8] and the need for a platinum-containing doublet as effective systemic treatment, we adopted the cisplatin/docetaxel combination.[9,10]

To adequately achieve dose escalation in patients who, on average, had large, bulky disease, we wanted to validate and justify the use of a rotational intensity-modulated radiotherapy technique (IMRT), called helical tomotherapy (HT). Compared with IMRT, the HT optimization procedure and dose delivery is much more refined and can lead to dose distributions that are even more conformal while limiting the dose to the surrounding normal tissues (conformal avoidance).[11] The downside of this technique could be the low-dose spread in healthy lung tissue, a subject that had not yet been examined in a clinical setting at the start of the study.

Because of the increase in BED and the possible influence of low-dose spread, the primary endpoint of the current study was monitoring of toxicity. Secondary endpoints were to evaluate efficacy parameters in terms of overall response rate and survival, to monitor quality of life (QOL), and to examine changes in tumor volume during therapy.

MATERIALS AND METHODS

Patient Eligibility

Candidates for inclusion in the current study were patients who had a cytologic or histologic diagnosis of a stage III, inoperable LANSCLC with a life expectancy of at least 12 weeks, a Karnofsky performance status (KPS) $\geq$80, and a maximum weight loss of 10% within the last 3 months (grading determined according to the American Joint Committee on Cancer 6th edition grading system). Initial workup consisted of bronchoscopy, pulmonary function tests (PFTs), computed tomography (CT) of the thorax, positron emission tomography (PET) using the radio-labeled glucose analogue F18-fluorodeoxyglucose (FDG-PET), magnetic resonance imaging (MRI) of the brain, and additional imaging studies as indicated. Patients were eligible to enter the study when they were deemed fit for a combined-modality approach after multidisciplinary review. Patients had to sign an informed consent before entering the study protocol. The treatment protocol was reviewed and approved by the competent authorities and the institutional ethics committee and was registered (National Clinical Trial no. NCT00379717 and European Union Drug Regulating Authorities Clinical Trial no. EUDRACT2006-003708-21).

Treatment Protocol

This study was designed to determine the maximum tolerated dose (MTD) of radiotherapy in a concurrent setting with fixed-dose chemotherapy plus docetaxel and cisplatin at a dose of 20 mg/m^2 each administered weekly and starting on Day 1 of radiotherapy for 6 cycles. Radiotherapy was delivered in 30 daily fractions. The OTT was set between 40 days and 44 days. This upfront chemoradiation was followed by 2 cycles of consolidation chemotherapy with docetaxel 75 mg/m^2 and cisplatin at 75 mg/m^2 administered up to 4 weeks after the completion of radiation with a 3-week interval.

The radiotherapy fraction size was escalated when the cumulative acute grade 3 dose-limiting toxicity (DLT) incidence was $<$50% for at least 3 patients who had a minimum follow-up of 3 months after the start of radiotherapy. To allow for a full 3-month assessment of at least 3 patients per cohort, inclusion in that same dose-escalation cohort was continued as long as required with a minimum of 5 patients. Grade 5 toxicity would result in an immediate halt of the study and acceptance of the previous cohort's dose as the MTD.

Dose specifications are summarized in Table 1. A protocol amendment was issued in February 2008 that omitted the consolidation chemotherapy after an interim toxicity analysis and based on literature data indicating that there was no benefit from consolidation chemotherapy.[12]

Radiotherapy Technique

Patients were referred for a planning CT and FDG-PET in the treatment position on a dedicated PET-CT scanner (GeminiTF64; Philips Healthcare, Best, the Netherlands). Delineation was performed of the macroscopic (gross) tumor volume (GTV); the clinical target volume and planning target volume (CTV/PTV) for involved lymph nodes and the primary tumor separately; and the lungs, esophagus, spinal cord, thyroid gland, kidneys, heart, liver, and stomach. The CTV for the lymph nodes consisted of the entire FDG-PET-involved lymph node region[13,14] with an isotropic 3-mm expansion for the PTV. The primary CTV was a 5-mm margin around the GTV in the lungs or airway without bone, vessel, or other mediastinal organs unless there was proven invasion by the tumor. The PTV for the primary tumor was the isotropic expansion of 5 mm or 8 mm around the CTV in case of upper/middle or lower lobe locations, respectively. Protocol dose constraints are listed in Table 1.

Table 1. Dose Parameters per Dose Cohort (Total Dose, Dose per Fraction, and Biologically Equivalent Dose) and the Dose/Volume Constraints for Plan Acceptance

	Dose Cohort, Gy				
Dose Parameter, Gy	**I**	**II**	**III**	**IV**	**V**
TD	60	63.6	67.2	70.8	74.4
FD	2.00	2.12	2.24	2.36	2.48
BED	64.8	69.9	75.1	80.3	85.7

Organ	**Dose Constraint, Gy**		**Volume Constraint, %[a]**		
	Minimum/maximum	**nMLD[b]**	**V_{20}**	**V_{40}**	**V_{66}**
PTV	95%/107% of TD		—	—	—
Lung	—	<17 (20)[c]	<30 (35)[c]	—	—
Esophagus	—	—	—	<50	<30
Heart	—/66	—	—	<50	—
Spinal cord	—/53	—	—	—	—

TD indicates total dose; Gy, grays; FD, dose per fraction; BED, biologically equivalent dose; nMLD, normalized mean lung dose; PTV, planning target volume.
[a]Volume is expressed as the lung volume in cc (V) that received *x* Gy (V_x) of radiation.
[b]The nMLD is a recalculated value that takes into account the FD.
[c]Minor violation.

Treatment delivery was performed on the TomoTherapy HiArt II system (TomoTherapy Inc., Madison, Wis), which is a linear accelerator that combines 6-megavolt (MV) IMRT with megavoltage CT imaging (MVCT) before treatment.[15,16] The gantry rotates continuously while the patient is translated through the bore, resulting in a helical treatment. Instead of choosing a fixed-beam setup, tomotherapy patients are treated with 51 equispaced beam directions per gantry rotation, which allows a much greater degree of freedom in the modulation because of the significant increase in the number of beamlets.[17,18]

The tumor region was scanned on a daily basis, and positioning was done using the integrated registration with the planning CT.[19-21] Although a difference in resolution exists between kilovolt and MVCT images, the quality of MV imaging is sufficient for patient positioning.[22] Positioning was done both on bony and soft tissue anatomy and incorporated respiratory motion, because the MVCT procedure can be considered a "slow" CT. Daily MVCT allows the clinician to take into account any changes in internal anatomy that affect positioning based on tumor response during treatment.

Toxicity Monitoring

Acute DLTs were defined as esophageal, pulmonary and, cardiac toxicities and were scored according to a modified Radiation Therapy Oncology Group (RTOG)-European Organization for Research and Treatment of Cancer (EORTC) acute toxicity scoring table. All other toxicities were graded according to version 3.0 of the National Cancer Institute Common Toxicity Criteria for Adverse Events. Toxicity was monitored at least once weekly by the treating medical and radiation oncologist in patients who received ambulatory treatment and daily when patients were hospitalized because of excessive toxicity. During follow-up, patients were seen every 3 months during the first 2 years and every 4 months to 6 months thereafter. For late toxicity, the RTOG late morbidity scoring for esophagus, heart, and lungs was used together with the Subjective, Objective, Management, and Analytic/Late Effects in Normal Tissues (SOMA-LENT) scoring system for the lungs and esophagus.[23] PFTs were repeated at every visit. The impact of the treatment schedule on QOL was assessed, using standardized questionnaires (the Functional Assessment of Cancer Therapy-Lung and the EORTC QLQ C30) at the beginning and at the end of treatment.

Response Assessment

Tumor size and metabolism were assessed before treatment and 3 months after the start of chemoradiation (and at least 2 weeks after the last consolidation chemotherapy) using PET-CT. Response Evaluation Criteria in Solid Tumors were used to evaluate treatment response based on CT studies. For FDG-PET, the standardized uptake

value (SUV) (SUV = [decay-corrected activity per mL tissue]/[injected activity]*[body mass]) was calculated. The SUV was acquired by manually positioning a 3-dimensional, ellipsoidal region of interest that covered the target. To minimize partial volume effect, the pixel with the maximum SUV value (SUV_{max}) within the volume of interest was identified. SUV values were normalized further to the circulating serum glucose level ($SUV_{max.glu} = SUV_{max} \times$ serum glucose [mg percentage]/100). In addition, a metabolic volume was calculated by adding all pixels with an SUV $\geq$2.5 within the region of interest. Patients were considered complete metabolic responders when the metabolic volume became zero.[24] In further follow-up, a scheduled CT scan of the thorax was obtained at least every 3 months, and an FDG-PET study was obtained yearly.

Statistical Analysis

Analyses of variance and Student *t* tests were performed using Statview software (version 5.0.1; SAS Institute Inc., Cary, NC). *P* values were considered significant at $<.05$, in which case, the 95% confidence interval (95% CI) also was calculated. Kaplan-Meier analysis was used for actuarial analysis with CIs using the "Greenwood method," and overall survival was calculated from initial diagnosis. Simple regression analysis was used to identify the correlation between dose-volumetric characteristics and the degree of late lung DLT.

RESULTS

Treatment Feasibility

Between October 2006 and August 2008, 34 patients were included in the current study. Their baseline characteristics are summarized in Table 2. All patients received the prescribed radiotherapy dose with a mean treatment time of 42 days; the only exception was 1 patient who died because of early progressive disease. The dose intensity of concurrent cisplatin and docetaxel was 94% for each. Dose reductions and/or the omission of concurrent chemotherapy were mainly because of esophageal toxicity (n = 4) or hematologic toxicity (n = 3). In the consolidation phase (n = 23), dose intensity in Dose Cohort (DC) I was 94% but dropped to 64% in DC II and to 59% in DC III. Consolidation chemotherapy could not be administered to 6 patients (2 patients died, and 4 patients had progressive disease) and was given only for 1 cycle in 2 patients because of recall esophageal toxicity. In 15 patients who received 2 cycles of consolidation chemotherapy, the dose intensity was 98% with minor reductions because of persistent esophageal toxicity or infection. The mean OTT for patients who received any consolidation chemotherapy was 86 days.

Table 2. Baseline Patient and Tumor Characteristics

Characteristic	No. of Patients	%
Age, y		
Mean	66	
Range	45-75	
Sex		
Men	25	74
Women	9	26
Cohort		
I (60.0 Gy)	5	15
II (63.6 Gy)	7	21
III (67.2 Gy)	11	32
IV (70.8 Gy)	10	29
V (74.4 Gy)	1	3
Type of carcinoma		
Adenocarcinoma	9	26
Spinocellular carcinoma	18	53
Large cell carcinoma	4	12
Unspecified	3	9
Staging[a]		
Tumor classification		
T1	3	9
T2	12	35
T3	0	0
T4	19	56
Lymph node status		
N0	6	18
N1	1	3
N2	18	53
N3	9	26
Disease stage		
IIIA	10	29
IIIB	24	71
No. of involved lymph nodes		
0	6	18
1	8	23
2	7	21
3	2	6
4	6	18
≥5	5	14

Gy indicates grays.
[a]Grading determined according to the American Joint Committee on Cancer 6th edition grading system.

Acute Toxicity

Episodes of acute pulmonary and esophageal toxicity are summarized in Table 3. The cumulative incidence of grade $\geq$3 DLT was 27% and consisted mainly of esophageal toxicity (24%) and 1 patient who experienced acute lung toxicity (cough). The cumulative incidence of grade $\geq$3 esophageal toxicity was 36% (95% CI, 16-56%) and

Table 3. Incidence (%) of Acute Toxicity During Chemoradiation and Consolidation Chemotherapy in Dose Cohorts I, II, and III (n = 23) and Dose Cohorts IV and V (n = 11)

Grade of Toxicity[a]	Incidence, % C1	C2	C3	C4	C5	C6	P1	P2
Lung								
DC I-III								
0	74	65	61	48	52	39	48	74
1	22	30	30	35	22	30	26	13
2	4	4	9	17	26	30	26	13
3	0	0	0	0	0	0	0	0
DC IV-V								
0	55	55	55	73	64	73	—	—
1	45	36	36	18	27	9	—	—
2	0	9	9	9	9	9	—	—
3	0	0	0	0	0	9	—	—
Esophagus								
DC I-III								
0	96	91	70	39	30	26	39	61
1	4	4	26	39	43	35	26	22
2	0	4	4	17	17	13	22	13
3	0	0	0	4	9	26	13	4
DC IV-V								
0	100	73	27	9	18	27	—	—
1	0	27	64	82	45	36	—	—
2	0	0	9	9	36	36	—	—
3	0	0	0	0	0	0	—	—

C1-C6 indicate chemoradiation Courses 1-6; P1-P2, consolidation chemotherapy Courses 1 and 2; DC, dose cohort.
[a]Grading determined according to the Radiation Therapy Oncology Group-European Organisation for Research and Treatment of Cancer toxicity scoring system.

Table 4. Incidence (%) of Late Toxicity Scored at 3 Months, at 6 Months, and at 1 Year of Follow-Up After the Start of Treatment

Grade	Incidence, % FU1	FU2	FU3
RTOG			
Lung			
0	22	24	15
1	47	24	40
2	25	32	30
3	3	12	10
4	0	4	5
5	3	4	0
Esophagus			
0	78	76	80
1	19	16	15
2	3	8	0
3	0	0	5
SOMA-LENT scale			
Lung			
0	3	4	0
1	34	28	40
2	50	40	35
3	6	20	20
4	6	8	5
Esophagus			
0	41	48	35
1	31	16	35
2	22	32	20
3	3	4	5
4	3	0	5

FU1 indicates follow-up 3 months after starting treatment; FU2, follow-up 6 months after starting treatment; FU3, follow-up 1 year after starting treatment; RTOG, Radiation Therapy Oncology Group; SOMA-LENT, Subjective, Objective, Management, and Analytic/Late Effects in Normal Tissues.

0% for DCs I, II, and III versus DCs IV and V, respectively ($P = .01$). Peak incidence of grade $\geq$3 esophageal toxicity in DCs I, II, and III was 26% at Week 6 of concurrent chemoradiation. Serious, non-DLT adverse events (grade $\geq$3) that were observed included a 25% incidence of infection and a 14% hematologic complication rate (mainly lymphopenia and 1 patient with grade 4 pancytopenia). Grade 1 through 3 fatigue was observed in 46% of patients. The grade 1 and 2 gastrointestinal toxicity rate was 41% (nausea and constipation). In 14 patients, we recorded 1 or more episodes of hospitalization for an average of 16 days (range, 2-37 days) with a peak incidence at Week 6 of chemoradiation. The most frequent reasons for hospitalization were esophageal toxicity (41%) and infection (27%). The QOL assessment revealed a decrease in several functioning parameters with an increase in most symptom scores after treatment. The global health status diminished from a mean score of 59 at the start of treatment to 51 at the end of treatment ($P < .001$). By the end of concurrent chemoradiation, we observed an average weight loss of 4.1% (range, from −17% to +6%) and a drop in the median KPS from 100 to 80, whereas 24% of patients experienced a drop in KPS $\geq$30.

Late Toxicity

The incidence of late esophageal and pulmonary toxicity is summarized in Table 4. One patient developed esophageal stenosis, which necessitated a stent. Other episodes of late gastrointestinal toxicity consisted mainly of persistent weight loss, which occurred in 80% of episodes with a simultaneous diagnosis of progressive disease and subsequent second-line therapy. Cumulative late lung toxicity grade $\geq$3 was 21% and 29% according to the RTOG and SOMA-LENT scores, respectively. Grade $\geq$3 SOMA-LENT lung toxicity was scored as such because of dyspnea (4 patients), cough (1 patient), radiologic changes (6 patients), and decreased lung function (3 patients).

These subjective and objective symptoms resulted in the management of grade ≥3 cough, dyspnea, and chest pain in 4 patients, 6 patients, and 1 patient, respectively.

The mean changes in PFTs were +1% (standard deviation [SD], 22%) and −14% (SD, 23%) for 1-second forced expiratory volume (FEV_1) and carbon monoxide diffusion capacity (DLCO), respectively. In 41% of patients, a grade 2 decline in PFT was registered during follow-up. The incidence of grade ≥3 RTOG late lung toxicity in DCs I, II, and III was 14% (95% CI, 0%-28%) versus 44% (95% CI, 7%-82%) in DC IV ($P = .06$). Two patients in DC IV died of radiopneumonitis at 4 months and 5 months after the start of radiotherapy, respectively; in those patients, the relative lung volumes (V) that received 20 grays (Gy) (V_{20}) were 24% and 23%, and the a normalized mean lung dose (nMLD) was 13.6 Gy and 8.3 Gy, respectively. The low-dose distribution (<20 Gy) for these 2 patients is illustrated in Figure 1

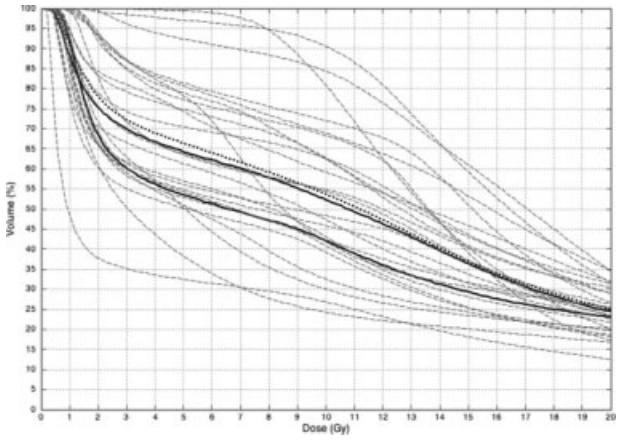

Figure 1. Low dose distribution (<20 grays [Gy]) in the lungs is illustrated by solid lines for patients who had grade 5 late lung toxicity and by dashed lines for all other patients. The dotted line indicates the average distribution.

compared with the entire study population. No medication that had a known possible interaction with radiation was identified. The respective PFTs for both patients before treatment were 88% and 87% for FEV_1 and 77% and 84% for DLCO.

The first patient died before PFTs were repeated, and the other patient had decreases of 18% and 46% in FEV_1 and DLCO, respectively. Figure 2 illustrates the dose distribution of the latter patient with the PET-CT at the time of active radiopneumonitis.

Response Evaluation

With a median follow-up at the time of analysis of 17 month in 17 surviving patients, we calculated a median survival of 17.9 months (95% CI, 12 months to not reached). Actuarial survival is illustrated in Figure 3. Response evaluation is summarized in Table 5. One patient died before any re-evaluation could be performed, and 2 additional patients died without control PET-CT images but with evidence of brain metastases on MRIs. Therefore, overall and local treatment responses were assessed in 33 patients and 31 patients, respectively. All patients who had progressive disease at 3 months failed in the brain (3 patients) or bone (3 patients).

DISCUSSION

To our knowledge, the current study is the first report on the use of HT and concurrent chemotherapy for LANSCLC. The treatment approach was feasible and had an acceptable dose intensity of radiation and chemotherapy in the concurrent phase. Radiotherapy could be given within the restricted delivery time in all patients. All radiation plans met the given dose constraints while maintaining sufficient PTV coverage even in this unbalanced patient population, in which the majority had stage IIIB disease. This suggested the usefulness of HT as a widely

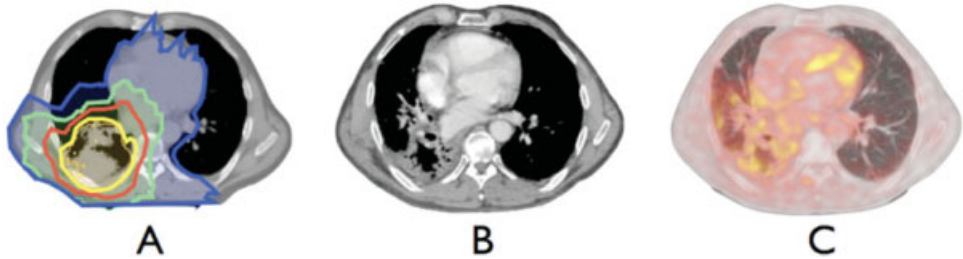

Figure 2. Dose distribution on (A) the planning computed tomography (CT) scan (blue line, 20 grays [Gy]; green line, 30 Gy; red line, 50 Gy; yellow line, 95% of the prescribed target dose) from a patient who died of a radiopneumonitis observed on (B) the CT scan 3 months after treatment with an increased metabolism (C) in the high-dose region on the corresponding F18-fluorodeoxyglucose-positron emission tomography image.

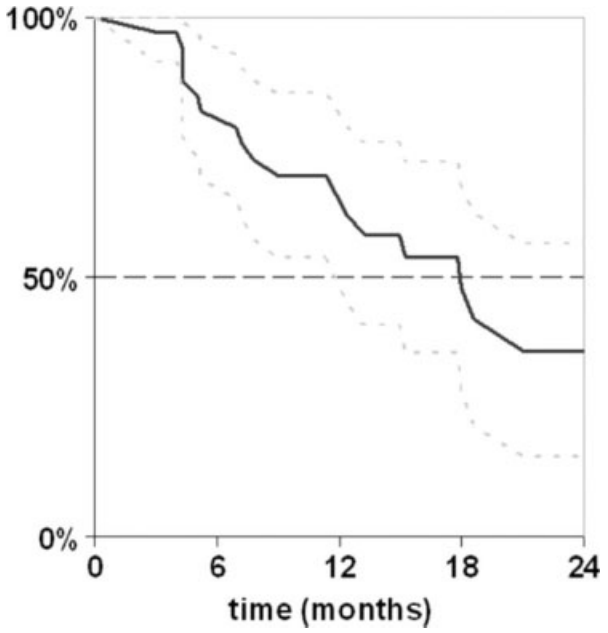

Figure 3. This graph illustrates a Kaplan-Meier of overall survival plot with the 95% confidence interval (in grays).

Table 5. Treatment Response Evaluation 3 Months After the Start of Treatment

Treatment Response: CT Scan	No. of Patients (%)
Overall response, n = 33	
CR	0 (0)
PR	17 (52)
SD	10 (30)
PD	6 (18)
Target lesion/s, n = 31	
CR	0 (0)
PR	19 (61)
SD	12 (39)
PD	0 (0)

Treatment Response: FDG-PET (n = 31)	Mean ± SD Decrease, %
$SUV_{max.glu}$	54 ± 37
Metabolic volume, cc	78 ± 45
CMR, no. (%)	17 (55)
Non-CMR, no. (%)	14 (45)

CT indicates computed tomography; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; FDG-PET, F18 fluorodeoxyglucose-positron emission tomography; SD, standard deviation; $SUV_{max.ghu}$, maximum standardized uptake value further normalized to the circulating serum glucose level; CMR, complete metabolic response.

applicable technique for dose delivery in LANSCLC, even when doses were extended above the benchmark of 60 Gy.[1] In previous hypofractionated dose-escalation trials, escalation was performed using 3-dimensional conformal radiotherapy (CRT).[25-27] The use of CRT can be insufficient for large and/or centrally located lesions or for patients who have widespread lymph node involvement and can lead to increased toxicity rates and the inability to reach an appropriate dose.[28-30] Liu et al demonstrated that IMRT could reduce the irradiated volumes of normal lung tissue and other critical structures significantly while maintaining an adequate dose to the target volume.[31] When the complexity of target volumes increases, the difference between CRT and IMRT becomes even more significant in favor of IMRT. Therefore, the current results are in line with previous retrospective reports on static-beam IMRT in chemoradiation and dose-escalated conformal chemoradiation.[32,33] Compared with static IMRT, plan optimization possibilities with HT are more flexible and slightly better because of its rotational nature, resulting in the kind of dose delivery illustrated in Figure 2.[11] The dose to the nearby spinal cord could be limited to 50 Gy while expelling the 20-Gy isodose from the contralateral lung and maintaining the adequate coverage (>95% of prescribed dose) of the target. However, this study was not comparative, so we cannot exclude the possibility that other IMRT techniques may achieve comparable results as long as the same dose constraints can be met.

An issue in the delivery of consolidation chemotherapy was encountered. Although part of it was because of progressive disease, omissions, reductions, and postponements of consolidation chemotherapy reduced overall dose intensity and prolonged OTT. An intercurrent publication indicated no survival benefit but increased toxicity for consolidation chemotherapy.[12] In light of this finding, a protocol amendment was issued during the conduct of this study to allow further dose escalation without consolidation chemotherapy.

In their most recent meta-analysis, in which concurrent and sequential chemotherapy were compared, Auperin et al emphasized the 5.7-fold increase in the incidence of esophagitis to 18%[34] also reported in published, individual phase 3 studies with statistically significant increases in the rate of grade ≥3 esophagitis from 4% to 18%[35] and from 3% to 32%.[36] We concluded that the acute toxicity rate in the current dose-escalation trial of 24% and 3% for esophagus and lung, respectively was within the expected range and, thus, was acceptable. Encouraging for the use of HT was the observation of a

remarkable reduction in grade ≥3 esophagitis for the higher DCs, although no anatomic difference with respect to proximity between the esophagus and the PTV could be observed. We assumed that, because of the higher nominal dose in these higher DCs, the inverse planning system avoided the region of overlap between the esophagus and the PTV. Whether this reduced circumferential irradiation resulted in the lower toxicity rate is being investigated in a phase 2 study that incorporates more stringent dose constraints regarding the esophagus.

The study was halted in September 2008 because of 2 toxic deaths that were caused by late lung toxicity. In both patients, the pathology reports confirmed massive radiation-induced inflammation and fibrosis. The overall RTOG grade ≥3 late lung toxicity rate was 21%. This cumulative incidence of severe late lung toxicity seemed higher than the 9% to 15.6% that was reported in 3 other radiation dose-escalation trials. Only 1 patient with grade 5 toxicity was reported in those 3 studies combined.[26,27,37] However, those trials reported on patients with stage I, II, and III NSCLC; only 16% received induction chemotherapy, and no concurrent chemotherapy was allowed. However, the reported RTOG grade ≥3 late lung toxicity rate of 14% in DCs I, II, and III appeared to be acceptable.

An analysis of known dose-volume and dose-distribution parameters (V_{20} and nMLD), as identified in these dose-escalation studies and in other reports on the prediction of late lung toxicity, did not reveal why these 2 patients developed lethal radiopneumonitis.[38,39] At the start of this study, the nMLD still was considered valid as a planning constraint because it was proposed and used in a synchronous dose-escalation study using HT in patients who had inoperable stage I, II, and III NSCLC.[6,40] There may be a concern that the late lung toxicity in the current study was caused by an increase in the lung volume that received low-dose irradiation (dose littering), which is more common in complex irradiation techniques, such as HT.[41] However the low-dose region in the 2 patients who had grade 5 toxicity could not be singled out compared with all other study patients (Fig. 1). The relative lung volumes that received 5 Gy and 10 Gy (V_5/V_{10}) in the current series (Table 6) were comparable to the values reported in a clinical study using static-beam IMRT.[32] Preliminary correlation analyses of dose volumetric parameters and the occurrence of overall and RTOG grade ≥3 late lung toxicity were performed. Even in this small series, those analyses revealed the larger impact of high-dose regions and primarily the tumor volume compared with low-dose spread (Table 6). Although further analysis in a larger population certainly is warranted, our results corroborate those of Willner et al, who reported that the reduction in the high-dose region was more important than the often counterbalanced increase in the low-dose region.[42] Gopal et al demonstrated that local functional loss was nonexistent in lung subvolumes that received <10 Gy.[43] Compared with dose-escalated concurrent chemoradiation, the overall RTOG grade ≥3 late lung toxicity was equal to the 25% reported using CRT.[44] The reported 14% in DCs I, II, and III was in line with a retrospective analysis of IMRT for concurrent chemoradiation that even demonstrated an advantage over CRT.[32] Therefore, we decided that the MTD should be set at 2.24 Gy per fraction.

Table 6. Tumor Volume and Planning Details (Lung Subvolumes Receiving *x* Grays) and the Normalized Mean Lung Dose

		P[a]	
Variable	Median (Range)	LLT	Grade ≥3 LLT
Volume, cc[b]	250 (23-1099)	.03	.004
V_5	63 (29-99)	.79	.63
V_{10}	49 (16-91)	.49	.31
V_{20}	23 (11-35)	.16	.33
V_{30}	15 (6-27)	.07	.10
V_{40}	10 (4-22)	.06	.08
V_{50}	7 (2-19)	.03	.03
nMLD, Gy	13 (6-20)	.55	.43

LLT indicates late lung toxicity; nMLD, normalized mean lung dose; Gy, grays.
[a] *P* values reflect the strength of correlation with the occurrence of overall and grade ≥3 Radiation Therapy Oncology Group LLT.
[b] Volume is expressed as the lung volume in cc (V) that received *x* Gy (V_x) of radiation.

Although it was not a primary endpoint in the current study, response analysis revealed a complete metabolic response in 55% of patients. This appeared to be encouraging enough to continue the amended study as a full phase 2 study using a Bryant and Day design.[45] Unacceptable cumulative esophageal and pulmonary ≥ grade 3 toxicity (T) was set at 30%, and an unacceptable local metabolic response rate (R) was set at ≤50% (the probability for accepting poor response [αR] or rejecting good response [β] was set at 15%; the probability of acceptance of a toxic treatment [αT] was kept at 5%).

In this phase 1/2 study, we assessed the possibility of radiation dose escalation with HT and concurrent cisplatin/docetaxel. The MTD for concurrent chemoradiation was set at 67.2 Gy in 30 fractions. This treatment schedule

is feasible and has acceptable toxicity with a promising response rate. To confirm the treatment efficacy and toxicity at the MTD, this schedule currently us being investigated in a phase 2 study.

CONFLICT OF INTEREST DISCLOSURES

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