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ORIGINAL REPORT

Mature Results of an Individualized Radiation Dose Prescription Study Based on Normal Tissue Constraints in Stages I to III Non–Small-Cell Lung Cancer

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ABSTRACT

Purpose
We previously showed that individualized radiation dose escalation based on normal tissue constraints would allow safe administration of high radiation doses with low complication rate. Here, we report the mature results of a prospective, single-arm study that used this individualized tolerable dose approach.

Patients and Methods
In total, 166 patients with stage III or medically inoperable stage I to II non–small-cell lung cancer, WHO performance status 0 to 2, a forced expiratory volume at 1 second and diffusing capacity of lungs for carbon monoxide ≥ 30% were included. Patients were irradiated using an individualized prescribed total tumor dose (TTD) based on normal tissue dose constraints (mean lung dose, 19 Gy; maximal spinal cord dose, 54 Gy) up to a maximal TTD of 79.2 Gy in 1.8 Gy fractions twice daily. Only sequential chemoradiation was administered. The primary end point was overall survival (OS), and the secondary end point was toxicity according to Common Terminology Criteria of Adverse Events (CTCAE) v3.0.

Results
The median prescribed TTD was 64.8 Gy (standard deviation, ± 11.4 Gy) delivered in 25 ± 5.8 days. With a median follow-up of 31.6 months, the median OS was 21.0 months with a 1-year OS of 68.7% and a 2-year OS of 45.0%. Multivariable analysis showed that only a large gross tumor volume significantly decreased OS ($P < .001$). Both acute (grade 3, 21.1%; grade 4, 2.4%) and late toxicity (grade 3, 4.2%; grade 4, 1.8%) were acceptable.

Conclusion
Individualized prescribed radical radiotherapy based on normal tissue constraints with sequential chemoradiation shows survival rates that come close to results of concurrent chemoradiation schedules, with acceptable acute and late toxicity. A prospective randomized study is warranted to further investigate its efficacy.

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INTRODUCTION

The prognosis for non–small-cell lung cancer (NSCLC) remains poor, even in patients suitable for treatment with curative intent.[1] Local failure remains an important problem,[2] resulting in 2-year local tumor control rates as low as 20%.[3,4] The ability of radiotherapy to achieve local control is mainly hampered by the radiation sensitivity of normal structures, including lungs and spinal cord. Several approaches have been applied to improve local control, including increasing the radiation dose and/or concomitant chemotherapy.[5-10] Various strategies have been used to escalate radiation dose, such as improving target volume definition and using innovative imaging and treatment delivery techniques, such as four-dimensional computed tomography (4D-CT), positron emission tomography (PET) scans,[4,11-13] and intensity-modulated radiation therapy (IMRT).[11,14-17] Dose escalation can be performed by assigning different radiation dose levels to different risk groups.[7,9] However, we previously demonstrated in a modeling study and a subsequent feasibility trial that high local tumor control rates with low adverse effects could be achieved by individualized radiation dose prescription based on normal tissue dose constraints.[16,17] Since overall treatment time is of vital importance in

radiotherapy for NSCLC,[4,8,18] radiation should preferentially be delivered in < 4 weeks. The theoretical gain of such a scheme was estimated to be approximately 25% for tumor control probability compared with the standard schedule of 60 Gy in 2 Gy fractions in 6 weeks.[16] Here, we report the mature results of a large prospective study applying this individualized maximal tolerable dose approach.

PATIENTS AND METHODS

Study Population

From December 2004 until June 2007, all consecutive eligible patients at MAASTRO Clinic were entered onto this prospective study. Included were those with stage III (except pleural effusion) or medically inoperable stage I to II disease, histologic or cytologic confirmed NSCLC, no prior thoracic radiation, and a workup according to national guidelines.[19] A WHO performance status of 0 to 2 and a weight loss of < 10% in 6 months were required. All patients had to have a moderate-to-good lung function (a forced expiratory volume in 1 second [FEV_1] ≥ 30% of predicted value and a diffusing capacity of lungs for carbon monoxide [DL_{CO}] not corrected for alveolar volume ≥ 30%). During the study period, induction chemotherapy was standard of care for patients with N2/N3 and T4 tumors and consisted of three courses of gemcitabine (1,250 mg/m^2 on days 1 and 8) in combination with cisplatin (75 mg/m^2) or carboplatin (area under the concentration-time curve [AUC] 5) on day 1. Cycles were repeated every 21 days, and standard dose-reduction rules were applied. An interval between chemotherapy and radiotherapy of at minimum 14 days was mandatory. In this study, no concurrent chemoradiation was given. During the study period, only a limited number of patients who enrolled in another study protocol received concurrent chemoradiotherapy. The study has been approved by the institutional review board and registered in the National Cancer Institute trial database (NCT00573040). Informed consent with regard to treatment was obtained from all patients.

Radiotherapy Treatment Planning

A PET-CT scan was performed before start of radiation (Biograph, Siemens, Knoxville, TN), and delineation was based on fused PET-CT images as described earlier.[17] The total gross tumor volume (GTV) consisted of the primary tumor (GTV-1), which is the (postchemotherapy) CT-based volume, and the initially PET-positive lymph nodal areas (GTV-2).[20] Nodes that proved to be malignant on mediastinoscopy or transesophageal/transbronchial fine-needle aspiration, even if they were PET-negative, were also included in GTV-2. No elective hilar or mediastinal irradiation was carried out. For the clinical target volume (CTV-1 and CTV-2), a margin of 5 mm around GTV was used. The planning target volume was created by adding a 10-mm margin to CTV-1 and a 5-mm margin to CTV-2. For calculation of the mean lung dose (MLD), the volume of both lungs minus the GTV was considered.[20] The spinal cord was drawn at the inner margin of the bony spinal canal.

A 3D conformal treatment plan was calculated (XiO, CMS, St Louis, MO) according to the International Commission on Radiation Units and Measurements guidelines[21] using a fast Fourier transform convolution algorithm for inhomogeneity corrections. Patients were irradiated on a linear accelerator (Elekta SL 15, Elekta Oncology Systems, Crawley, United Kingdom or Siemens Oncor, Siemens Medical Solutions, Concord, CA). Treatment verification was performed using electronic portal imaging device measurements.[22]

Treatment

For all enrolled patients, the following radiation doses were individually escalated until a dose-limiting normal tissue constraint was reached: a maximal MLD between 10.0 and 19.0 Gy (standard deviation, ± 1.0 Gy), a maximal dose for the cord of 54.0 ± 0.5 Gy, maximal dose to great vessels or main bronchi of 70.2 Gy, and maximal dose for the plexus brachialis of 66 Gy.[23-27] The maximal allowed MLD was dependent on lung function tests: FEV_1 and DL_{CO} ≥ 50% and an MLD of 19 Gy (group 1), FEV_1 and DL_{CO} ≥ 40% and less than 50% of an MLD of 15 Gy (group 2), and FEV_1 and DL_{CO} ≥ 30% and less than 40% of an MLD of 10 Gy (group 3). No specific esophageal dose constraint was used because acute esophagitis was not considered to be dose-limiting with radiation alone.[17,28] The maximal allowed total tumor dose (TTD) was 79.2 Gy[26] in twice daily fractions of 1.8 Gy with an interfraction interval of at least 8 hours. To minimize the effect of accelerated repopulation, a short overall treatment time should be chosen.[4,29] To achieve this, a twice daily scheme was preferred, since this might spare normal tissues and could allow high-dose irradiation of tumors next to critical organs compared with hypofractionation.[16] The biologic equivalent dose for tumors in 2 Gy fractions was calculated using the linear quadratic model[29-31] and corrected for overall treatment time ($EQD_{2,T}$) as previously described.[16]

End Points

The primary end point was overall survival (OS), and the secondary end point was toxicity. Patients were seen before the start of radiotherapy (baseline), weekly during radiotherapy, and regularly afterwards. Survival status was evaluated in February 2009 using the "Gemeentelijke Basis Administratie" system, a decentralized population registration system containing information

Table 1. Patient, Tumor, and Treatment Characteristics

Characteristic	No. of Patients	%
Age, years		
Median	69.0	
Range	44-88	
Sex		
Male	115	69
Female	51	31
WHO PS		
0	39	23
1	82	49
2	28	17
3	2	1
Histology		
Squamous cell carcinoma	21	13
Adenocarcinoma	56	34
Large cell	74	42
Unknown	2	1
Clinical stage		
I	48	29
II	16	10
IIIA	35	21
IIIB	64	38
IV	3	2
Induction chemotherapy		
Yes	92	55
No	74	45
GTV (tumor load), mL		
Median	50.3	
Range	1.1-2,286.9	
Prescribed TTD, Gy		
Median	64.8	
Range	50.4-79.2	
$EQD_{2,T}$ (corrected for proliferation), Gy		
Median	66.0	
Range	51.9-73.1	
MLD, Gy		
Median	14.8	
Range	2.4-21.7	
OTT, days		
Median	25	
Range	1-50	

Abbreviations: PS, performance status; GTV, total gross tumor volume; TTD, total tumor dose; $EQD_{2,T}$, equivalent dose in 2 Gy fractions corrected for proliferation; MLD, mean lung dose; OTT, overall treatment time.

Table 2. Treatment Characteristics According to Different Lung Function Groups and Stage

Characteristic	No.	Total GTV (mL)			TTD (Gy)			% Receiving 79.2 Gy	MLD (Gy)		
		Median	SD	Range	Median	SD	Range		Median	SD	Range
Group 1 (FEV_1-DL_{CO} 30%-40%)	25	10.8	35.8	1.1-138.4	79.2	10.6	50.4-79.2	52.1	8.9	2.3	4.1-12.7
Group 2 (FEV_1-DL_{CO} 40%-50%)	26	49.1	123.6	1.5-510.2	64.8	9.9	50.4-79.2	15.4	12.3	4.1	2.4-16.3
Group 3 (FEV_1-DL_{CO} > 50%)	115	64.7	224.3	1.1-2,286.9	64.8	9.5	50.4-79.2	17.4	16.2	4.1	4.3-21.7
Stage											
I	48	10.9	59.0	1.1-343.3	79.2	10.2	50.4-79.2	52.1	9.1	3.8	2.4-17.3
II	16	52.2	62.9	5.7-181.3	70.2	9.5	54.0-79.2	25.0	14.4	9.2	5.0-19.6
IIIA	35	64.7	76.8	1.5-333.2	61.2	7.9	50.4-79.2	2.9	15.3	4.1	5.0-19.6
IIIB	64	73.2	296.4	6.5-2,286.9	61.2	9.2	50.4-79.2	10.9	16.9	3.7	5.6-21.7
Total group	166	50.3	194.8	1.1-2,286.9	64.8	9.9	50.4-79.2	22.3	14.8	4.6	2.4-21.7

Abbreviations: GTV, total gross tumor volume; TTD, total tumor dose; MLD, mean lung dose; SD, standard deviation; FEV_1, forced expiratory volume in 1 second; DL_{CO}, diffusing capacity of lungs for carbon monoxide.

about all inhabitants of the Netherlands. No specific protocol was used with regard to imaging during follow-up; imaging was performed according to local guidelines or if it was clinically indicated. Acute and late toxicity were scored according to Common Terminology Criteria of Adverse Events (CTCAE) v3.0.

Statistical Methods

Considering an increase in 2-year OS of 10% compared with that of a standard radiation schedule to be successful, the number of patients to be included was calculated to be 157 (power = 0.8; alpha = .05; p0 = 25%; p1 = 35%). SPSS for Windows software (SPSS, Chicago, IL) was used for statistical analysis. OS was calculated from the start of radiotherapy. The Kaplan-Meier method was used for univariate survival analysis (log-rank test). The Cox proportional hazards model was used for multivariate analysis testing the following variables: total GTV, weight loss, $EQD_{2,T}$, TTD, stage, WHO performance status, age, induction chemotherapy, sex, and lung function tests. Variables were considered statistically significant if the likelihood ratio test resulted in $P < .05$. Crude incidences of pulmonary complaints (cough and dyspnea) and esophageal dysphagia (maximum score) were calculated for the acute phase (90 days from start of radiotherapy) and for the late phase (> 90 days from start of radiotherapy).

RESULTS

Patient and Treatment Characteristics

Between December 2004 and June 2007, 166 patients (115 males and 51 females) with a median age of 69.0 ± 10.4 years (range, 42 to 88 years) were enrolled. Patient and tumor characteristics are presented in Table 1. Sixty percent of patients (n = 99) had stage III disease, 9.6% (n = 16) had stage II, and 28.9% (n = 48) had stage I. However, in the poor lung function group (group 1; n = 25; maximum MLD 10 Gy), 80% had stage I disease (n = 20), while this percentage was 34.6% in group 2 (9 of 26; maximum MLD 15 Gy) and 16.5% in group 3 (19 of 115; maximum MLD 19 Gy). Ninety-two (55%) patients received induction chemotherapy. The median total GTV was 50.3 ± 194.8 mL (range, 1.1 to 2,286.9 mL; Table 2). The median prescribed TTD for the total group of patients was 64.8 ± 11.4 Gy. TTD according to lung function groups and stage is depicted in Table 2. The median $EQD_{2,T}$ was 66.0 ± 7.1 Gy (range, 51.9 to 73.1 Gy). The median delivered TTD of 64.8 ± 11.4 Gy (range, 5.4 to 79.2 Gy) was delivered in twice daily fractions in all patients in a median overall treatment time of 25 ± 5.8 days (range, 2 to 50 days). The median MLD was 14.8 ± 4.6 Gy (range, 2.4 to 21.7 Gy; Table 2), and in 55 (33.1%) patients, the MLD was dose-limiting. Three patients did not complete their radiation schedule: one patient died after three fractions because of bronchopneumonia and cardiac arrhythmia, one patient stopped after 12 fractions because the schedule was too exhausting, and one patient switched to a once-daily schedule. In four (2.4%) patients, a major protocol violation was encountered: three patients had stage IV

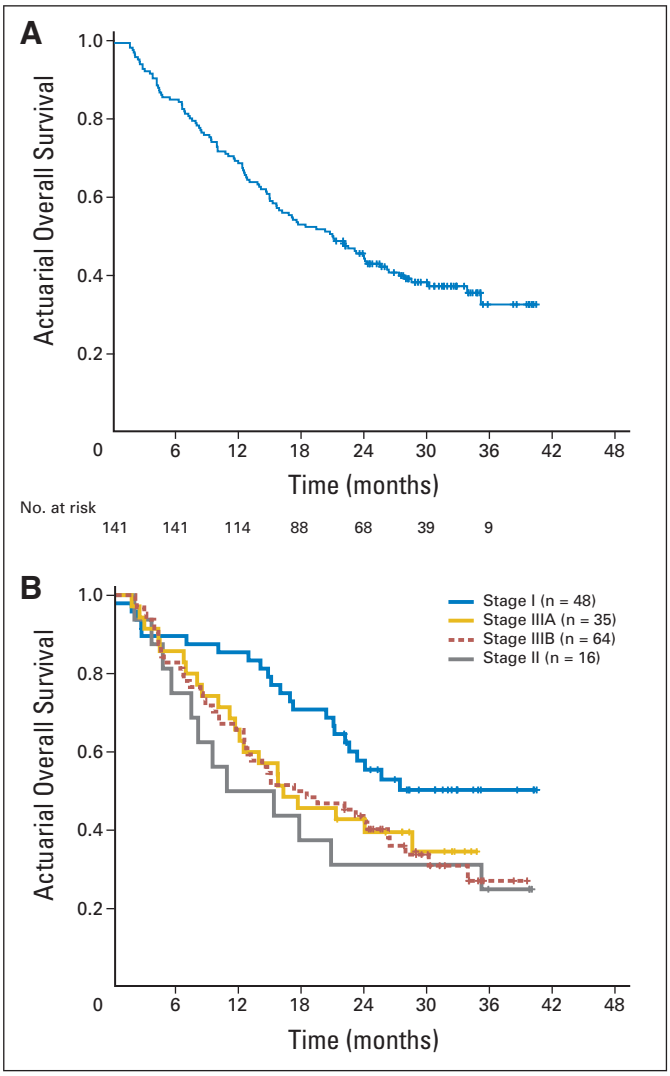

Fig 1. Actuarial overall survival in months for (A) the total group of patients and (B) for different disease stages.

disease (simultaneous solitary brain metastasis treated with resection or stereotactic radiosurgery followed by sequential chemoradiotherapy for the lung tumor) and in one patient, an MLD of 21.7 Gy was accepted to achieve a TTD of 50.4 Gy.

Survival

The median follow-up time for the total group of patients was 31.6 months (95% CI, 29.9 to 33.4 months). Minimal follow-up was 22 months. At the time of analysis 103 (62%) patients had died. The median OS was 21.0 months (95% CI, 15.8 to 26.2 months) with a 1-year OS of 68.7% and a 2-year OS of 45.0% (Fig 1). For the different disease stages, the median OS was as follows: stage I, not reached; stage II, 10.8 months (95% CI, 0 to 22.3 months); stage IIIA, 16.2 months (95% CI, 7.6 to 24.8 months); and stage IIIB, 17.2 months (95% CI, 8.4 to 26.0 months). Seventy-five patients (45%) had a recurrence (33% locoregional failure, 51% metastases, and 16% a combination of both as first event).

Univariate and Multivariate Analysis

On univariate analysis, OS was better with a higher $EQD_{2,T}$ ($P = .012$) and a higher TTD ($P = .022$), while patients with a large GTV showed a worse OS ($P < .001$). A trend for a better OS was observed for early stages ($P = .052$). All other factors investigated were not correlated with OS (Table 3). On multivariate analysis only, GTV was an independent risk factor for OS ($P < .001$). Figure 2 shows the survival curves according to GTV and TTD.

Toxicity

Acute toxicity during and directly after radiotherapy was mainly mild (Figs 3A-3C). Most patients (n = 76) developed no (45.8%) or mild dysphagia (27.1%, grade 1; 21.7%, grade 2), while eight patients (4.8%) had acute grade 3 dysphagia. In all these patients, dysphagia was transient (late grade 3, 0%). Before start of radiotherapy, seven patients (4.2%) had grade 3 and one patient (0.6%) had grade 4 dyspnea (dyspnea at rest; the radiation oncologist and pulmonologist decided that the patient was able to undergo radical treatment, which he completed). During radiotherapy, 60.3% had mild dyspnea (42.2%, grade 1; 18.1%, grade 2) while grade 3 (7.8%) and grade 4 (2.4%) dyspnea was found in 10% of patients. Grade 3 and 4 dyspnea were mainly observed in patients known to have dyspnea before start of treatment. Acute cough was observed in 131 patients (78.9%): 51.2%, grade 1; 15.7%, grade 2; and 12.0%, grade 3. No severe skin reaction was observed.

Regarding late toxicity (> 90 days postradiotherapy), only two patients (1.2%) had grade 1 dysphagia (Figs 3A-3C). Most patients (57.8%) had no dyspnea, while mild dyspnea was seen in 30.1% (21.7%, grade 1; 8.4%, grade 2) and grade 3 (3.0%) and grade 4 (1.8%) dyspnea in 5%. Grade 3 cough was observed in only one (0.6%) patient, while 91 patients had mild cough (50%, grade 1; 4.8%, grade 2). No myelitis was observed.

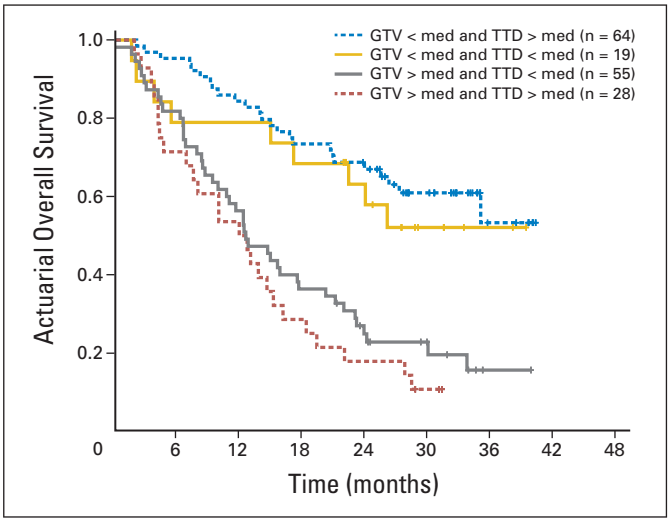

Fig 2. Actuarial overall survival in months according to gross tumor volume (GTV) and total tumor dose (TTD). med, median.

Table 3. UVA and MVA for Overall Survival

Variable	Overall Survival	
	UVA	MVA
GTV ≥ median *v* GTV < median	< 0.001	< 0.001
No weight loss *v* weight loss (< 10%)	0.002	0.211
$EQD_{2,T}$ ≥ median *v* $EQD_{2,T}$ < median	0.012	0.298
TTD ≥ median *v* TTD < median	0.022	0.224
Stage I-II *v* III-IV	0.052	0.859
WHO PS 0 *v* ≥ 1	0.204	NA
Age ≥ median *v* age < median	0.345	NA
Induction chemotherapy *v* no induction chemotherapy	0.383	NA
Sex	0.926	NA
FEV_1 and DL_{CO} ≥ 50% *v* FEV_1 and/or DL_{CO} < 50%	0.993	NA

Abbreviations: UVA, univariate analysis; MVA, multivariate analysis; GTV, total gross tumor volume; $EQD_{2,T}$, equivalent dose in 2 Gy fractions corrected for proliferation; TTD, total tumor dose; PS, performance status; NA, not analyzed; FEV_1, forced expiratory volume in 1 second; DL_{CO}, diffusing capacity of lungs for carbon monoxide.

DISCUSSION

Generally, patients with NSCLC receive a predefined radiation dose that is the same for all patients with a certain tumor stage. The typical radiotherapy strategy for stage III patients—60 to 66 Gy in 2 Gy fractions once daily for 6 weeks—was established in the 1980s.[32] This obviously does not take into account the wide diversity in patients with regard to tumor size, localization, and dose-limiting normal tissues. The importance of both dose-response[29,33] and overall treatment time[4] has been demonstrated for local tumor control. Therefore, this standard strategy will lead to underdosage in individuals who can tolerate higher radiation doses without undue toxicity, whereas for others, this fixed radiation dose cannot be prescribed. Since quantitative relationships between dose-volume parameters and toxicity have been established,[34-40] an individualized approach delivering the highest dose with the same toxicity level, emerged.[41] At the same time, radiation treatment acceleration would be a logical step, considering the high time-dependency for the outcome of radiotherapy.[4,18]

We previously investigated this hypothesis in a modeling study, estimating a gain in tumor control probability of approximately 25%

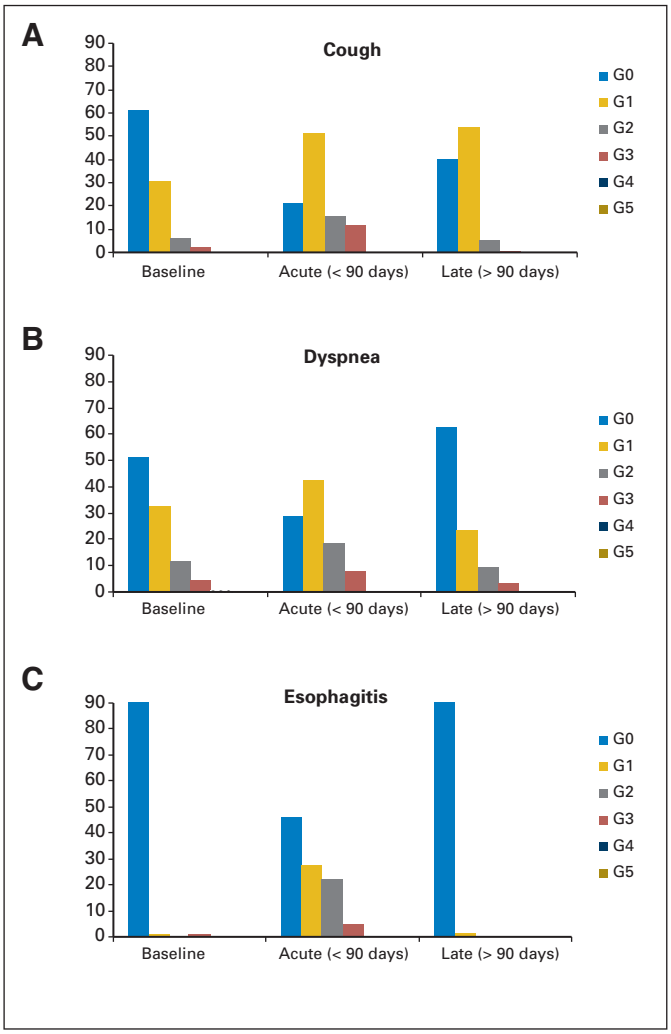

Fig 3. Percentage of patients with toxicity. Scoring according to Common Terminology Criteria of Adverse Events version 3.0 for baseline, acute toxicity within 90 days, and late toxicity after 90 days for (A) cough, (B) dyspnea, and (C) esophagitis. G, grade.

compared with the classical scheme of 60 Gy.[16] Subsequently, in a feasibility study (n = 28), we showed the safety of this approach.[17] This study evaluated the mature results of a prospective study that used an individualized dose prescription. The $EQD_{2,T}$ ($\geq$ 54 Gy) for all patients was higher than the $EQD_{2,T}$ equivalent for a classic scheme of 60 Gy in 2 Gy fractions once daily.

The median OS of 21 months for the total group was high, although rather low for stage II (median OS, 10.8 months; not significantly different compared with that for stage IIIA). This might be partially explained by the low number of patients (n = 16) and the high incidence of comorbidity in this group. In addition, according to guidelines, stage II patients did not receive induction chemotherapy as those with stage III would have.[42] However, the main factor for OS is tumor volume, and no difference in GTV was observed for stages II and IIIA (52.2 mL and 64.7 mL, respectively; *P* = not significant). Median OS for stage III patients was high at 17 months. These results are in line with the results of our feasibility study[17] and those of other dose-escalation studies. Adkison et al[43] reported similar findings in a phase I study that used a hypofractionated schedule with helical tomotherapy IMRT up to a maximal dose of 80.5 Gy. With a relatively short median follow-up of 8.1 months, they observed limited toxicity, a median survival of 18 months, and a 2-year OS of 46.8%. Recently, the results of a phase II trial combining induction chemotherapy with continuous hyperfractionated accelerated radiotherapy (CHART) in locally advanced NSCLC have been published,[44] in which 56 Gy was delivered in 36 fractions in 12 days; toxicity was mild, and the median OS was 15.7 months. Compared with other dose-escalation trials, we achieved good results in a group of patients with rather large tumors (median GTV, 50.3 mL *v* 47.3 mL in the Radiation Therapy Oncology Group trial), even when including individuals with an FEV_1 and/or DL_{CO} as low as 30% and patients older than age 80 years.[7,9,43,45]

Our results as well as those of other dose-escalation studies suggest that OS rates could be achieved with sequential chemotherapy and high-dose radiation schedules that come close to the results of concurrent chemoradiation schemes but with less acute toxicity.[46-52] Because the superior results of concurrent chemoradiotherapy over the sequential approach are probably due to improved local control,[6] we hypothesize that high-dose radiotherapy in sequential protocols might lead to similar local control rates. However, one of the drawbacks of this study is that local progression data should be interpreted with caution, since CT imaging was performed only if clinically indicated. Moreover, this was a single-arm, prospective study in a relatively heterogeneous group of patients and therefore should be followed by a prospective randomized study.

In our multivariate analysis, only size of GTV was an independent risk factor for death. Werner-Wasik et al[45] also showed in the Radiation Therapy Oncology Group 93-11 trial that an increasing GTV was strongly associated with a decreased median survival, whereas maximal radiation dose was not a significant factor. This might be explained by the fact that the spread in TTD was still limited and that higher doses are needed. It might also indicate that, especially for larger tumors, tumoricidal dose cannot be reached applying the studied protocol. Therefore other strategies, such as individualized dose prescription in concurrent chemoradiation and/or boosting certain parts of the tumor, need to be investigated.

As in other dose-escalation studies[7,38] and as predicted in our modeling study,[16] toxicity was generally mild. Severe esophagitis was observed in less than 5% of patients and was transient in all. Severe pulmonary symptoms were observed in approximately 10% of patients during treatment, mainly patients with pre-existing symptoms due to other lung diseases. Pulmonary symptoms did not increase during radiotherapy in the majority of patients. Even more assuring is that no late esophageal or spinal cord damage was observed. Only one patient had severe late pulmonary toxicity, but this particular patient already had grade 4 dyspnea before start of treatment. The currently available dose-volume relations for toxicity, although not perfect,[34-40] are apparently good enough to enable individualized radiation dose prescription.

Our strategy to prescribe the radiation dose based on individualized dose constraints is safe and feasible in daily practice and shows promising results. Further improvements are ongoing, including a recently closed prospective study in our department that investigated individualized dose prescription in concurrent chemoradiation and image-guidance as well as IMRT techniques.[11,43,53] The

addition of active breathing control might potentially give the opportunity to further dose escalation, while respecting normal tissue dose constraints.[54] In the future, further individualization of treatment might incorporate patient-specific factors, such as comorbidity,[39,40] as well as biologic tumor characteristics, such as hypoxia, growth factors, and cytokines,[55,56] along with imaging data to individualize margins and to refine the dose constraints beyond physical dose-volume parameters and simple patient characteristics as were used in this trial.

In conclusion, in line with our modeling and feasibility study, we showed that individualized prescribed radical radiotherapy in NSCLC based on normal tissue dose constraints has promising results. Furthermore, such a regimen can be applied safely, with acceptable acute and late toxicity. These results may be the basis for a prospective randomized trial that ultimately could demonstrate the superiority of this individualized approach.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Angela van Baardwijk, Stofferinus Wanders, Liesbeth Boersma, Jacques Borger, Michel Öllers, Philippe Lambin, Dirk De Ruysscher
Provision of study materials or patients: Angela van Baardwijk, Stofferinus Wanders, Liesbeth Boersma, Jacques Borger, Michel Öllers, Anne-Marie C. Dingemans, Gerben Bootsma, Wiel Geraedts, Cordula Pitz, Ragnar Lunde, Dirk De Ruysscher
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