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Original Article

Individualized accelerated isotoxic concurrent chemo-radiotherapy for stage III non-small cell lung cancer: 5-Year results of a prospective study

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ABSTRACT

Background: Stage III non-small cell lung cancer (NSCLC) still has a poor prognosis. Prior studies with individualized, accelerated, isotoxic dose escalation (INDAR) with 3D-CRT showed promising results, especially in patients not treated with concurrent chemo-radiotherapy. We investigated if INDAR delivered with IMRT would improve the overall survival (OS) of stage III NSCLC patients treated with concurrent chemotherapy and radiotherapy.

Patients and methods: Patients eligible for concurrent chemo-radiotherapy were entered in this prospective study. Radiotherapy was given to a dose of 45 Gy/30 fractions BID (1.5 Gy/fraction), followed by QD fractions of 2 Gy until a total dose determined by the normal tissue constraints. The primary endpoint was OS, secondary endpoints were loco-regional relapses and toxicity.

Results: From May 4, 2009 until April 26, 2012, 185 patients were included. The mean tumor dose was 66.0 ± 12.8 Gy (36–73 Gy), delivered in a mean of 39.7 fractions in an overall treatment time of 38.2 days. The mean lung dose (MLD) was 17.3 Gy. The median OS was 19.8 months (95% CI 17.3–22.3) with a 5-year OS of 24.3%. Loco-regional failures as first site of recurrence occurred in 59/185 patients (31.8%). Isolated nodal failures (INF) were observed in 3/185 patients (1.6%). Dyspnea grade 3 was seen in 3.2% of patients and transient dysphagia grade 3 in 22%.

Conclusions: INDAR with IMRT concurrently with chemotherapy did not lead to a sign of an improved OS in unselected stage III NSCLC patients.

Non-small cell lung cancer (NSCLC) stage III is diagnosed in approximately 30% of lung cancer patients [1]. For the majority of these patients, concurrent chemo-radiotherapy is the treatment of choice [1]. Because the prognosis remains poor and the first site of recurrence is local in about one third of patients, several research groups have investigated radiation dose intensification as a way to improve local tumor control and eventually the overall survival (OS). In concurrent chemo-radiotherapy, dose escalation by adding once-daily 2 Gy fractions did not improve the OS [2]. The results of randomized trials investigation dose re-distribution within the tumor are awaited [3–5].

As another way to intensify and escalate the radiotherapy dose without increasing toxicity, we and others have reported on accelerated, individualized isotoxic dose escalation [6–12]. In non-concurrent radiotherapy schedules, acceleration of the radiotherapy led to improved survival [13] and individualized isotoxic dose prescription will push the dose to the upper limit for each patient [11]. In non-concurrent chemotherapy and radiotherapy or radiotherapy alone, this strategy appeared to be promising, while the early results in concurrent chemo-radiotherapy seemed to be similar to standard fractionation radiotherapy [6,13]. However, these studies were done with 3-dimensional conformal radiotherapy (3D-CRT) techniques, whereas with intensity modulated radiotherapy (IMRT) it is expected that the dose may be increased further [14]. Moreover, long-term results are lacking.

We therefore report here on the OS and toxicity results with a minimum follow-up of 5 years of a prospective study of accelerated, individualized isotoxic radiotherapy dose escalation with concurrent chemotherapy in stage III NSCLC.

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Patients and methods

Patients

From May 4, 2009 until April 26, 2012, patients eligible for concurrent chemo-radiation were entered in this prospective study conducted at Maastro clinic, where the radiotherapy was delivered. Systemic therapy was administered in the referring hospitals. Included were patients with stage III (7th TNM edition), histological or cytological confirmed NSCLC, no prior thoracic radiation and a work-up according to national guidelines, including a staging whole body FDG-PET-CT scan and a MRI or contrast-enhanced CT scan of the brain. A WHO Performance Status (WHO PS) of 0 to 2 was required. All patients had to have a moderate to good lung function ($FEV_1 \geq 30\%$ and DLCO $\geq 30\%$ of predicted value). The presence of supraclavicular lymph nodes, pleural fluid that was negative for malignancy on cytological examination and cardiac comorbidities including arrhythmia or a decreased ejection fraction were no exclusion criteria. Patients with other invasive cancers within the last five years were also allowed provided they were in clinical complete remission at the time of enrollment.

Study design and procedures

Chemotherapy was given in the referring hospital. It consisted of 1 cycle of cisplatin or carboplatin–gemcitabine (cisplatin 75 mg/m^2, carboplatin AUC 5, gemcitabine 1250 mg/m^2), followed by concurrent cisplatin–vinorelbine (cisplatin 40–50 mg/m^2, vinorelbine 15–20 mg/m^2) or concurrent cisplatin–etoposide every 3 weeks (cisplatin 75–80 mg/m^2 day 1 or carboplatin AUC 5 depending on the cardiovascular history or limited renal function, etoposide 100 mg/m^2 day 1–3) with radiotherapy. The regimen depended on the referring hospital. Dose-reduction was applied according to guidelines and in case of renal failure cisplatin was substituted by carboplatin. Radiation treatment planning was performed during the first cycle of chemotherapy and radiotherapy was intended to start at the first day of the second cycle of chemotherapy, according to Dutch guidelines. The study was approved by the institutional review board and registered on clinicaltrials.gov (NCT01166204). Informed consent was obtained from all patients prior to radiotherapy.

Radiotherapy treatment planning

A PET-CT scan and a 4D-CT scan were performed before start of radiotherapy (Biograph TruePoint 40, Siemens Healthineers, Germany) and delineation was based on fused PET-CT images. The total gross tumor volume (GTV) consisted of the primary tumor (GTV-1; CT based volume based on the midventilation scan). Only the initial PET-positive lymph nodal areas, based on the diagnostic PET-CT before any treatment, and nodes proven to be malignant on mediastinoscopy or EBUS were included in GTV-2. No elective mediastinal irradiation was carried out. For the Clinical Target Volume (CTV-1 and CTV-2) a margin of 5 mm around the GTV was used. The Planning Target Volume (PTV) was created by adding a 10 mm margin to CTV-1 and a 5 mm margin to CTV-2. For the calculation of the mean lung dose (MLD), the volume of both lungs minus GTV was considered. The external surface of the esophagus was delineated from the cricoid to the gastro-esophageal junction. The spinal cord was drawn at the inner margin of the bony spinal canal.

An IMRT plan was calculated (XiO 4.3.4, CMS, Inc., USA) according to the ICRU Report 83 using a Fast Fourier Transform convolution-superposition algorithm taking into account inhomogeneity corrections. Patients were irradiated with Siemens Oncor linear accelerators. All patients were treated with 6MV or 10MV photon beams. Treatment verification was performed using EPID measurements.

Treatment description

For all patients enrolled, the prescribed dose was individually escalated until the following dose-limiting normal tissue constraints were reached: MLD of 19.0 ± 1.0 Gy, spinal cord Dmax of 54.0 ± 0.5 Gy, plexus brachialis Dmax of 66 Gy, V35 of the esophagus $\leq$65% or Dmax of 74 Gy, mean heart dose of 46 Gy and mediastinal structures (including the large blood vessels and the bronchi up to the third generation) at a Dmax of 69 Gy. Since most tumors were centrally located and/or had involved mediastinal nodes the maximal allowed dose was 69 Gy to respect a dose inhomogeneity with a maximum of 107% to great vessels or main bronchi of 74 Gy. The dose was delivered in an accelerated scheme: 1.5 Gy fractions twice daily up to 45 Gy with an interfraction interval of at least 8 h, followed by once daily fractions of 2 Gy based on the ESPATÜ phase III trial scheme [15]. The biological equivalent dose for tumor in 2 Gy fractions was calculated using the linear quadratic model (25–27) and corrected for overall treatment time ($EQD_{2,T}$).

Endpoints

The primary endpoint was OS, secondary endpoints were locoregional relapses and toxicity. Patients were seen before start of radiotherapy, weekly during treatment, 1 month after radiotherapy and according to the standard protocol in the region, every 3–6 months for the first 2 years and yearly afterward. Toxicity was scored according to Common Terminology Criteria for Adverse Events v4.0 (CTCAE). Clinical tests (imaging) were used to determine local progression or distant failure. Local progression was defined as at least a 20% increase in the sum of diameters of target lesions. If progression was suspected a (PET-)CT was performed and if necessary, a biopsy was considered. These patients were discussed at the MDT. Survival status was evaluated on July 27, 2018, using the GBA system, a decentralized population registration system containing information about all inhabitants of The Netherlands.

As is standard procedure at Maastro Clinic, the toxicity of patients was evaluated on a bi-yearly basis with all radiation oncologists and physicists, in order to make sure that not more than expected toxicity occurred.

Statistical analysis

Based on the results of our previous study [6], we hypothesized that IMRT would enable us to escalate the radiotherapy dose to 3D-CRT that would lead to an increase in the median OS with 2.5 months, i.e. from 25 months to 27.5 months. A sample size of 185 patients was estimated to show with a power of 80% our hypothesis. OS was defined as time from the first day of treatment NSCLC until death using the Kaplan–Meier method (log-rank test for comparison of survival). Median survival rates are expressed with their 95% confidence intervals (CI). Crude incidences of pulmonary complaints (cough and dyspnea) and esophageal dysphagia were also calculated. SPSS23 was used for calculations.

Results

Patient characteristics

From May 4, 2009 to April 26, 2012, 185 patients were included. Their characteristics, including previous malignancies, are depicted in Table 1. Most patients were male and their mean age was almost

Table 1
Patient and tumor characteristics. Results are expressed as proportions or as the mean ± standard deviation and the range, unless otherwise indicated.

Gender		
Male: 113 (61.1%)		
Female: 72 (38.9%)		
Age (years)		
63.9 ± 8.9 (44–86)		
Body Mass Index (kg/m^2)		
24.6 ± 4.6 (16.3–35.0)		
Smoking		
Never 2.9%		
Current 36.8%		
Former 60.3%		
Pack Years 34.3 ± 18.6 (0–90)		
Weight loss last 6 months		
>10%: 10.8%		
<10%: 89.2%		
FeV1 (% predicted value)		
Mean: 79.5 ± 21.4% (30.1–122.0)		
Median: 81.0%		
≤50%: 17 patients (9.2%)		
DLCO (% predicted value)		
Mean: 69.2 ± 20.1% (31.5–120.0)		
Median: 68.0%		
≤40%: 9 patients (4.7%)		
WHO performance status		
0	67 (36.2%)	
1	105 (56.8%)	
2	11 (5.9%)	
3	1 (0.2%)	
4	1 (0.2%)	
Other invasive cancer within the last 5 years		
32 patients (17.3%)		
Non-small cell lung cancer:11 patients		
Small cell lung cancer: 1 patient		
Head and neck cancer: 6 patients: floor of mouth (1), tongue (2), parotic gland (1), supraglottic (1), vallecular (1)		
Breast cancer: 3 patients		
Soft tissue sarcoma grade 1: 2 patients		
Renal cell cancer: 1 patient		
Prostate cancer: 1 patient		
Rectal cancer: 1 patient		
Bladder cancer: 1 patient		
Melanoma skin cancer: 1 patient		
Astrocytoma grade 3: 1 patient		
Squamous cell carcinoma of the esophagus: 1 patient		
Diffuse large cell B-cell lymphoma: 1 patient		
Histology		
Squamous	55 (29.7%)	
Adenocarcinoma	49 (26.9%)	
Large cell	26 (14.1%)	
NSCLC-NOS	55 (29.7%)	
Location of the primary tumor (number of patients/ percentage)		
Right lower lobe	15	(8,5%)
Middle lobe	9	(4.6%)
Right upper lobe	70	(37.8%)
Left lower lobe	17	(9%)
Left upper lobe	69	(37.3%)
Unknown (“Tx”)	5	(2.8%)

Table 1 (*continued*)

Lymph node involvement (number of patients/ percentage)		
Station	*Right side*	*Left side*
1	19 (10,3%)	9 (4.8%)
2	57 (30.9%)	12 (6.6%)
3	15 (8.1%)	3 (1.5%)
4	90 (48.5%)	53 (28.7%)
5		38 (20.6%)
6		23 (12.5%)
7	88 (47.8%)	
8	8 (4.4%)	
10	60 (32.4%)	46 (25.0%)
Gross tumor volume (GTV) (sum of primary tumor and nodes) (ml)		
Mean: 120.4 ± 132.0 ml (16.8–708.5)		
Median: 72.6 ml		
Percentiles:		
25: 43.95 ml		
50: 72.57 ml		
75: 146.82 ml		

64 years. Ninety-seven percent was current or former smokers and 11% had weight loss over 10%. Nearly all patients had a WHO-PS 0–1, although 11 had PS 2 and 2 PS 3 or 4, which are clearly protocol violations. The mean volume of the tumor and the nodes together (GTV) was 120 ml (range 17–709).

Radiotherapy

The mean tumor dose was 66.0 ± 12.8 Gy, ranging from 36 Gy to 73 Gy, delivered in a mean of 39.7 fractions in an overall treatment time of 38.2 days (Table 2). The dose distribution is depicted in Table 2. The mean MLD was 17.3 Gy and the V20 27.4%. The mean esophageal dose was 29.0 Gy. The mediastinal structures were dose-limiting in 67% of the patients.

As expected because of the study design, there was a significant inverse correlation between the GTV and the tumor dose, with bigger GTVs receiving less dose ($p = 0.04$).

Overall survival

The median OS was 19.8 months (95% CI 17.3–22.3) with a 5-year OS of 24.3% (Fig. 1). The 3 months, 1, 2 and 3-year OS were 93.5%, 68.6%, 43.8% and 34.1%, respectively. The 6-year OS was 20.5%.

In a univariate analysis for OS, only the WHO-PS (better PS 0 vs. 1 was associated with a better OS; $p = 0.006$) was highly significantly related to the OS, whereas the GTV (bigger tumors have a worse OS, $p = 0.048$) (Fig. 2) and the total tumor dose (higher doses associated with a better OS; $p = 0.045$) were only borderline statistically significant. In a multivariate Cox regression analysis for OS, only the WHO-PS ($p = 0.002$) remained significantly related to the OS (GTV: $p = 0.25$; total radiation dose: $p = 0.70$).

Loco-regional failures

Loco-regional failures as first site of recurrence occurred in 59/185 patients (31.8 %). Isolated nodal failures (INF) were observed in 3/185 patients (1.6%) (Fig. 3A–C).

Table 2
Radiotherapy. Results are expressed as proportions or as the mean ± standard deviation and the range.

Total Tumor Dose (Gy)
Mean: 65.5 ± 5.6 (36.0–73.0)
Median: 69 Gy
Percentiles:
25: 63 Gy
50: 69 Gy
75: 69 Gy
Number of fractions
39.7 ± 3.4 (24–44)
Overall treatment time (days)
38.2 ± 26.8 (16–93)
Mean Lung Dose (MLD) Gy
17.3 ± 3.0 (4.9–21,2)
V20 (%)
27.4 ± 5.6 (20.7–37.0)
Mean Esophageal Dose (Gy)
29.0 ± 9.3 (6.3–54.1)

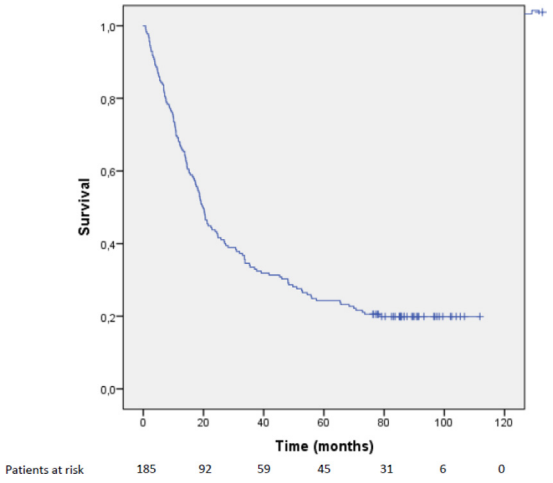

Fig. 1. Overall survival.

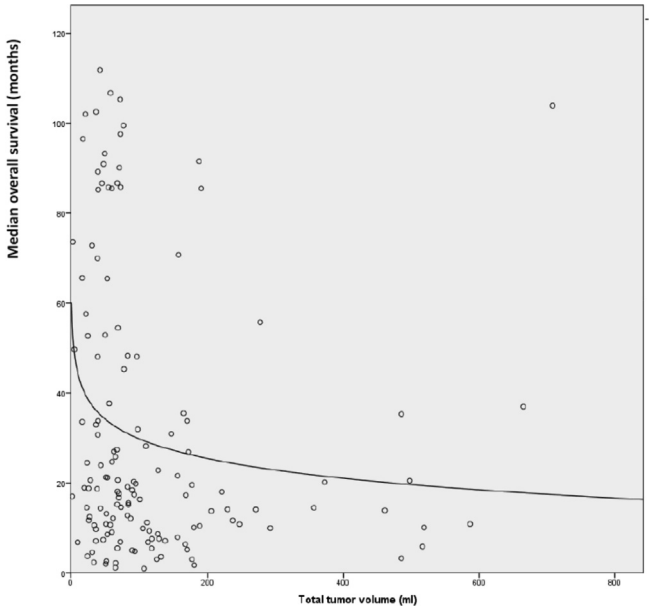

Fig. 2. Relation between overall survival and tumor volume. Median overall survival as a function of the total tumor volume. Circles depict patients, the full line is the logarithmic curve estimation (R^2 = 0.040). Larger tumors have a lower median overall survival than smaller and the smallest tumors have the best survival.

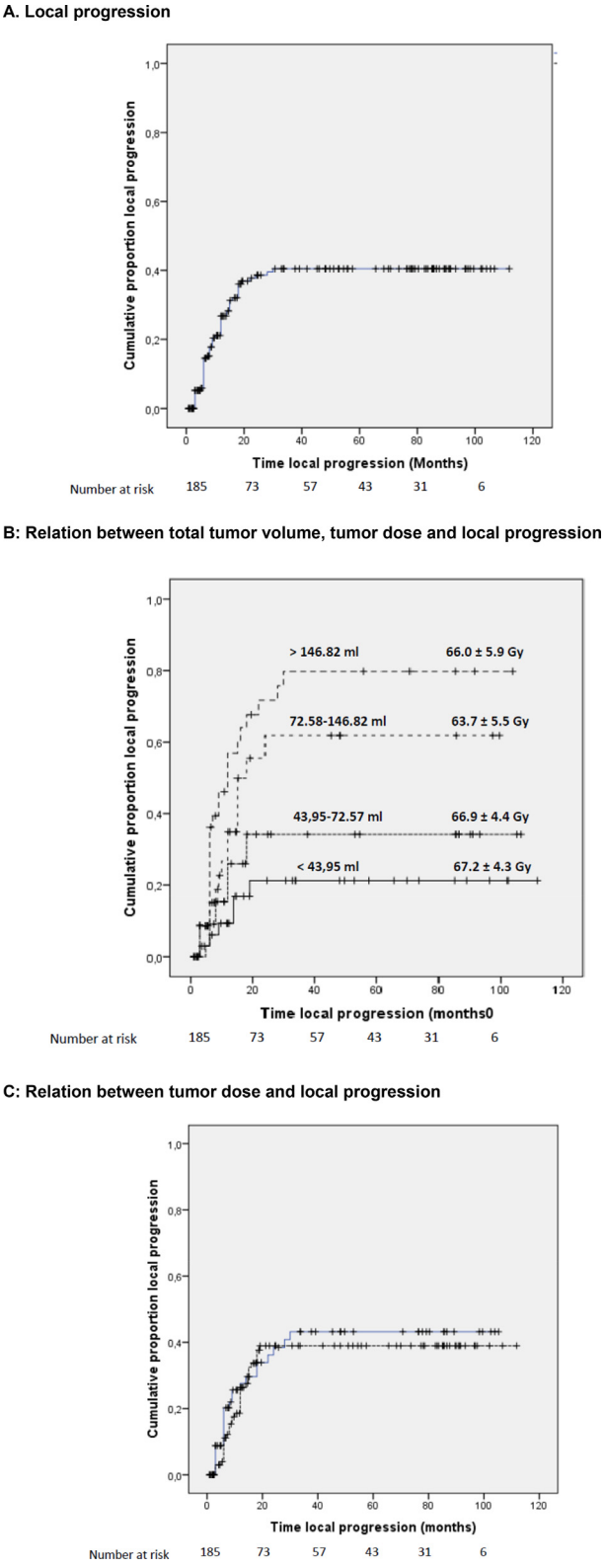

Fig. 3. (A) Local progression. Actuarial calculation of loco-regional tumor progression. (B) Relation between total tumor volume, tumor dose and local progression. Total tumor volume (primary tumor and involved lymph nodes) per percentile as a function of the cumulative incidence of local progression. The differences between the percentiles tumor volume are statistically significant ($p < 0.001$; log-rank test). The mean tumor dose and standard deviation per percentile tumor volume is depicted on the right side. (C) Relation between tumor dose and local progression. Local tumor progression as a function of the radiotherapy dose below (full line) or above (dotted line) the median (69 Gy). The difference is not statistically different ($p = 0.57$, log-rank test).

Toxicity

Toxicity is depicted in Table 3.

Dyspnea

Only 55% of the patients had no dyspnea before treatment. Approximately 56% of the patients had dyspnea grade 1 post treatment (37% before therapy), 2.7% grade 2 and 3.2% grade 3.

Dysphagia

No patient had dysphagia before treatment. About 44% of the patients developed grade 2 dysphagia and 22% grade 3. All dysphagia reversed to grade 0 within 3 months after therapy.

Discussion

There is an obvious need to improve the prognosis of patients with stage III NSCLC [1]. As the improved prognosis of patients treated with concurrent chemotherapy and radiotherapy over the sequential approach is thought to be due to improved local tumor control, many groups, including ours, have intensified the local treatment to try to improve the OS [6–12,16]. One possibility to increase the dose intensity is to prescribe the dose in an isotoxic way, which leads to the highest achievable dose with a constant level of side effects and at the same time to decrease the overall treatment time. Our previous studies were done with 3D-CRT and suggested that for sequential chemotherapy and radiotherapy and for radiotherapy alone, individualized, accelerated isotoxic radiotherapy is beneficial [13]. For 3D-CRT individualized, accelerated isotoxic radiotherapy concurrent with chemotherapy the long-term benefit of this strategy was uncertain [6].

As with IMRT we assumed that more patients should be able to receive a higher dose than with 3D-CRT [14], we studied this strategy prospectively in concurrent chemotherapy and radiotherapy and report here on the long-term data with a minimum follow-up of 5 years.

In the present study in stage III NSCLC patients, with isotoxic, accelerated radiotherapy given concurrently with standard chemotherapy, we could in the average patient only deliver about 66 Gy in 5 weeks (45 Gy/30 fractions BID of 1.5 Gy, followed by about 20 Gy/10 fractions QD of 2 Gy).

The toxicity was comparable to large series giving 60–66 Gy in 2 Gy QD fractions in 6–6.6 weeks, with only about 3% of dyspnea grade 3 and 22% transient grade 3 dysphagia. The strategy followed in this study is therefore safe.

The rate of local progression was also comparable to other series [2,17].

However, the OS (median 20 months and 5-year 25%) is certainly not superior compared with recent series who delivered the standard dose and fractionation schedule of 60–66 Gy in 30–33 QD fractions [2,15,17]. It may even be argued that in some of these studies the median and the 5-year OS results were better than in the current trial, but this may be due to our less stringent patient selection (10% of our patients had over 10% of weight loss over the last 6 months, the mean tumor volume was 120 ml, 13% had a WHO performance status of 2 or more, 17% had an invasive malignancy in the 5 years preceding enrollment and no restrictions for cardiac illness were included) and because in the present study the minimum follow-up was 5 years, which is longer than in most other trials. The bigger GTV in the present series compared to our previous study (120 ml vs. 76 ml, respectively) [6] may also explain the worse OS than expected. In order to estimate the impact of patients with negative prognostic factors in the present study, in an unplanned exploratory analysis, we omitted patients who would not be eligible for RTOG0617 [2], ESPATUE [15] or PROCLAIM [17]. Because we had no data on cardiac illness, we could not take this factor into account, in contrast to phase III studies that excluded patients with important cardiac co-morbidities, including uncontrolled cardiac arrhythmia [17] or a decreased ejection fraction [2]. Out of 185 patients, 59 (31.9%) were thus excluded. The median survival in this "good prognostic" group was 22.8 months (95% CI 15.7–30.0), with a 1-, 2-, 3-, 4- and 5-year OS of 71.8%, 49,1%, 39,1%, 35.5% and 29.1%, respectively. The median OS in PROCLAIM was 25 months with a 3-year OS of 37% [17]. In RTOG0617, the median OS was 28.7 months and 20.3 months in the 60 Gy and 74 Gy arm, respectively and a 1- and 2-year OS of 76.2%, 71.1% and 57.6% and 44.6% in the 60 Gy and 74 Gy arm, respectively [2]. The ESPATUE trial included only operable patients [15]. For the whole group, the 5-year OS was 33%.

Because our minimum follow-up exceeds 5 years in contrast to some recent phase III studies [2,17], our 5-year data will not further decrease because of actuarial calculations. We therefore believe that the OS of our patients with similar prognostic factors as in many other series is in the same range as expected, but there is no signal that our treatment schedule would be superior.

There is also no hint that this schedule would be harmful for patients, neither for OS, nor for local failure, nor for toxicity, which is in line with the results of the ESPATUE trial [15].

In the absence of a randomized comparison, it is not possible to draw firm conclusions, but we believe that our results do not support to use isotoxic, accelerated radiotherapy given concurrently with standard chemotherapy as a way to improve the prognosis.

The reasons for failure of isotoxic accelerated dose delivery with concurrent chemotherapy may be similar to that observed in phase III trials in head and neck cancer [18–21]. It seems that concurrent chemotherapy suppresses accelerated repopulation of tumor clonogens sufficiently, neutralizing the effect of treatment acceleration. In contrast to head and neck cancer, the schedule used in our study did not increase the toxicity. This may be due to a quite flat initial dose–response between the lung dose and dyspnea, the small time factor for radiation pneumonitis and to the observation that for acute dysphagia other parameters than radiation dose and volume are important, such as the level of neutropenia [22–24].

Radiation dose escalation by dose-redistribution within the tumor may theoretically lead to improved local tumor control without increasing side effects [3–5]. However, due to the mediastinal dose constraints, the dose escalation in the present series was moderate at best and possibly too low to lead to improved OS or local progression. The results of the completed or ongoing randomized studies testing higher dose escalation are eagerly awaited.

Nevertheless, the improvement in OS seen in the PACIFIC study by adding durvalumab after concurrent chemo-radiotherapy is pointing to the fact that immune therapy in combination with standard therapy is probably the most promising strategy for

Table 3
Toxicity.

Dyspnea			
	Grade	*Baseline*	*Maximal score*
	0	102 (55.1%)	71 (38.4%)
	1	68 (36.8%)	103 (55.7%)
	2	15 (8.1%)	5 (2.7%)
	3	0	6 (3.2%)
Dysphagia			
	Grade	*Maximal score*	
	0	23 (12.4%)	
	1	41 (22.2%)	
	2	81 (43.8%)	
	3	40 (21.6%)	

improvement of OS in stage III NSCLC [25]. Optimizing the combination of radiotherapy with immune therapy, as for instance is being tested in the NICOLAS trial (NCT02434081), is an example of this.

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Conflict of interest

Dr. De Ruysscher: none related to the current manuscript. Outside the current manuscript: advisory board of Astra Zeneca, Bristol-Myers-Squibb, Roche/Genentech, Merck/Pfizer, Celgene and has received investigator initiated grants from Bristol-Myers-Squibb, Astra Zeneca and Boehringer Ingelheim.

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The other authors do not have conflicts of interest.

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