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Mature results of a phase II trial on individualised accelerated radiotherapy based on normal tissue constraints in concurrent chemo-radiation for stage III non-small cell lung cancer ☆

Angela van Baardwijk [a,*], Bart Reymen [a], Stofferinus Wanders [a], Jacques Borger [a], Michel Öllers [a], Anne-Marie C. Dingemans [b], Gerben Bootsma [c], Wiel Geraedts [d], Cordula Pitz [e], Ragnar Lunde [f,h], Frank Peters [g], Philippe Lambin [a], Dirk De Ruysscher [a]

[a] *Department of Radiation Oncology (MAASTRO Clinic), GROW – School for Oncology and Developmental Biology, Maastricht University Medical Centre, Maastricht, The Netherlands*
[b] *Department of Pulmonology, GROW – School for Oncology and Developmental Biology, Maastricht University Medical Centre, Maastricht, The Netherlands*
[c] *Department of Pulmonology, Atrium Medical Centre, Heerlen, The Netherlands*
[d] *Department of Pulmonology, Orbis Medical Centre, Sittard, The Netherlands*
[e] *Department of Pulmonology, Laurentius Hospital, Roermond, The Netherlands*
[f] *Department of Pulmonology, Sint Jans Gasthuis, Weert, The Netherlands*
[g] *Department of Medical Oncology, Orbis Medical Centre, Sittard, The Netherlands*

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KEYWORDS
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Abstract ***Background:*** Sequential chemotherapy and individualised accelerated radiotherapy (INDAR) has been shown to be effective in non-small cell lung cancer (NSCLC), allowing delivering of high biological doses. We therefore performed a phase II trial (clinicaltrials.gov; NCT00572325) investigating the same strategy in concurrent chemo-radiation in stage III NSCLC.

Methods: 137 stage III patients fit for concurrent chemo-radiation (PS 0-2; FEV_1 and DLCO $\geqslant 30\%$) were included from April 2006 till December 2009. An individualised prescribed dose based on normal tissue dose constraints was applied: mean lung dose (MLD) 19 Gy, spinal cord 54 Gy, brachial plexus 66 Gy, central structures 74 Gy. A total dose between 51 and 69 Gy was delivered in 1.5 Gy BID up to 45 Gy, followed by 2 Gy QD. Radiotherapy was started at the 2nd or 3rd course of chemotherapy. Primary end-point was overall survival

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* *Corresponding author:* Tel.: +31 88 44 55 666; fax: +31 88 44 55 667.
E-mail address: angela.vanbaardwijk@maastro.nl (A.van Baardwijk).

[h] Currently working in Laurentius Hospital, Roermond, The Netherlands.

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(OS) and secondary end-point toxicity common terminology criteria for adverse events v3.0 (CTCAEv3.0).

Findings: The median tumour volume was 76.4 ± 94.1 cc; 49.6% of patients had N2 and 32.1% N3 disease. The median dose was 65.0 ± 6.0 Gy delivered in 35 ± 5.7 days. Six patients (4.4%) did not complete radiotherapy. With a median follow-up of 30.9 months, the median OS was 25.0 months (2-year OS 52.4%). Severe acute toxicity (⩾G3, 35.8%) consisted mainly of G3 dysphagia during radiotherapy (25.5%). Severe late toxicity (⩾G3) was observed in 10 patients (7.3%).

Interpretation: INDAR in concurrent chemo-radiation based on normal tissue constraints is feasible, even in patients with large tumour volumes and multi-level N2–3 disease, with acceptable severe late toxicity and promising 2-year survival.

1. Introduction

Non-small cell lung cancer (NSCLC) is one of the most frequently diagnosed cancers and the leading cause of cancer death.[1] Stage III disease represents about one third of all NSCLC with concurrent chemo-radiation as treatment of choice[2] and only for a selected group chemotherapy and surgery. As local tumour control remains low, strategies for improvement have been investigated including increasing radiation dose, accelerated hyperfractionated radiation and targeted agents.[3–8] Increasing the dose is challenging due to the tolerance of normal tissues, e.g. lung and spinal cord. In most dose-escalation trials, a certain threshold for organs at risk has been implemented together with a fixed dose (e.g. 74 Gy). As a consequence, the dose will be dependent on tumour volume; only patients with relatively small volume disease being capable to receive a high dose. In order to deliver the highest possible radiation dose to every individual patient we developed a strategy in which the radiation fields were kept as small as possible with selective nodal irradiation based on Fluordeoxyglucose - Positron Emission Tomography - Computer Tomography (FDG-PET-CT) scans[9] and accelerated radiotherapy in order to increase the biological effectiveness.[10,11] As such, patients receive the highest possible biological radiation dose with the best therapeutic ratio. We previously demonstrated that individualised accelerated radiotherapy (INDAR) with radiotherapy alone or sequential chemo-radiation is feasible with acceptable toxicity and promising results.[12]

Another strategy to improve local control and overall survival (OS) is concurrent chemo-radiation.[2,5] A meta-analysis based study showed a significant benefit in OS for concurrent chemo-radiation compared to sequential chemo-radiation, but at the expense of more transient oesophageal toxicity.[2] Most patients received a dose of 60 Gy in 30 fractions in 6 weeks in this meta-analysis, at present considered to be the standard scheme in concurrent chemo-radiation. However, dose escalation in concurrent chemo-radiation seems feasible,[3,13] and indirect evidence suggests that radiation dose escalation may also improve survival in the context of concurrent chemo-radiation.[14]

We hypothesised that combining concurrent chemo-radiation with INDAR based on normal tissue constraints could further improve survival in stage III NSCLC. Here, we report the mature results of a large prospective phase II study applying this INDAR approach in concurrent chemo-radiation.

2. Methods

2.1. Patients

From 1st April 2006 until 31st December 2009 patients eligible for concurrent chemo-radiation were entered in this prospective study conducted at MAASTRO clinic. Included were patients with stage III, except pleural effusion (Union for International Cancer Control, TNM 6th edition),[15] histological/cytological confirmed NSCLC, no prior thoracic radiation and a work-up according to national guidelines,[16] including a staging FDG-PET-CT scan and a Magnetic Resonance Imaging (MRI) or a contrast-enhanced CT scan of the brain. A World Health Organisation Performance Status (WHO-PS) of 0–2 was required and a weight loss of less than 10% in 6 months. All patients had to have a moderate to good lung function FEV_1 (Forced Expiratory Volume in the first second) ⩾ 30% and DLCO (Carbon Monoxide Diffuse Capacity) ⩾ 30% of predicted value.

2.2. Study design and procedures

Chemotherapy consisted of 1–2 cycles of carboplatin–gemcitabine (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, 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. The study was approved by the institutional review board and registered on clinicaltrials.gov (NCT00572325). Informed consent was obtained from all patients prior to radiotherapy.

2.2.1. Radiotherapy treatment planning

A PET-CT scan and a 4D-CT scan was performed before start of radiation (Biograph, Siemens) and delineation was based on fused PET-CT images.[9,11] The total gross tumour volume (GTV) consisted of the primary tumour (GTV-1; CT based volume based on the midventilation scan) and GTV-2.[9] Only the initial PET-positive lymph nodal areas, based on the diagnostic PET-CT before any treatment, and nodes proven to be malignant were included in GTV-2. No elective mediastinal irradiation was carried out, according to European Organisation for Research and Treatment of Cancer (EORTC) guidelines.[9] For the Clinical Target Volume (CTV-1 and CTV-2) a margin of 5 mm around 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.[9] The spinal cord was drawn at the inner margin of the bony spinal canal.

A 3D conformal treatment plan was calculated (XiO, CMS, Inc.) according to the International Commission on Radiation Units and Measurements (ICRU) Report 50[17] using a Fast Fourier Transform convolution-superposition algorithm taking into account inhomogeneity corrections. Patients were irradiated with a linear accelerator (Siemens Oncor, Siemens Medical Solutions, Concord, CA). All patients were treated with 6 MV or 10 MV photon beams.[9,18] Treatment verification was performed using EPID measurements.

2.2.2. Treatment description

For all patients enrolled, the prescribed dose was individually escalated until a dose-limiting normal tissue constraint was reached: a maximal MLD of 19.0 ± 1.0 Gy, a maximal spinal cord dose of 54.0 ± 0.5 Gy, and a maximal plexus brachialis dose of 66 Gy was applied.[19–22] Since most tumours 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.[22,23] No specific oesophageal dose constraint was used, except a Dmax of 74 Gy.[24] 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-hours, followed by once daily fractions of 2 Gy based on the ESPATÜ phase III trial scheme.[13] The biological equivalent dose for tumour in 2 Gy fractions was calculated using the linear quadratic model[25–27] and corrected for overall treatment time ($EQD_{2,T}$).[10]

2.4. End-points

Primary end-point was OS, secondary end-point progression free survival (PFS) and toxicity. Patients were seen before start of radiotherapy, weekly during treatment, 1 month after radiotherapy and every 3–6 months for the first 2 years and yearly afterwards. Additional toxicity information was collected by validated questionnaires from 2009 on. Acute ($<$90 days from start of radiotherapy) and late ($\geqslant$90 days from start of radiotherapy) toxicity was scored according to Common Terminology Criteria for Adverse Events v3.0 (CTCAE). Clinical tests (imaging) were used to determine local progression or distant failure. If progression was suspected a (PET-) CT was performed and if necessary a biopsy was considered. Survival status was evaluated in February 2011 using the GBA system, a decentralised population registration system containing information about all inhabitants of The Netherlands.

3. Statistical analysis

Assuming an increase in 2-year OS of 10% compared to a classical concurrent chemo-radiation schedule to be successful, a number of 145 patients was calculated to provide sufficient statistical power (power = 0.8, alpha = 0.05, p0 = 35%, p1 = 45%). Due to the clinical implementation of Intensity-Modulated Radiation Therapy (IMRT) the inclusion of patients was closed at 137 patients, since IMRT results in other dose distributions than 3DCRT. The SPSS software (SPSS for Windows, Chicago, IL) was used for statistical analysis. OS was defined as time from diagnosis till death using the Kaplan–Meier method (log-rank test for comparison of survival). PFS was defined as the time from diagnosis until first clinical event (local or distant progression or death from any cause). Median survival rates are expressed with their 95% confidence intervals (CI). The Cox proportional hazards model was used for multivariate analysis testing the following variables: primary tumour, nodal and total gross tumour volume (GTV-1, GTV-2, total GTV), EQD2,T, Total tumour (TTD), stage, WHO-PS, gender, age, histology and type of chemotherapy. Crude incidences of pulmonary complaints (cough and dyspnoea), oesophageal dysphagia were calculated.

4. Findings

4.1. Patient and treatment characteristics

Between 1st April 2006 and 31st December 2009 137 patients, 88 males and 49 females with a median age of

Table 1
Patient, tumor and treatment characteristics.

Characteristic	No. of patients	(%)
Age (median in years and range)	63.2	(40–80)
Sex		
Male	88	(64.2)
Female	49	(35.8)
WHO-PS		
0	68	(49.6)
1	58	(42.3)
2	10	(7.3)
3	1	(0.7)
Histology		
Squamous cell carcinoma	40	(29.2)
Adenocarcinoma	22	(16.1)
Large cell/undifferentiated	73	(53.2)
Unknown	2	(1.5)
Clinical stage		
IIB	1	(0.7)
IIIA	50	(36.5)
IIIB	86	(62.8)
Type of concurrent chemotherapy		
Cisplatin–etoposide	94	(68.6)
Cisplatin–vinorelbine	39	(28.5)
Carboplatin based	4	(2.9)
Gross tumour volume		
Median (range) total tumour load in cc	76.4	(3.7–518.9)
Prescribed TTD		
Median (range) in Gy	65.0	(51–69)
$EQD_{2,T}$ corrected for proliferation		
Median (range) in Gy	53.9	(43.1–63.1)
MLD		
Median (range) in Gy	16.3	(4.4–21.0)
OTT		
Median (range) in days	35	(18–48)

GTV = total gross tumour volume, TTD = total tumour dose, $EQD_{2,T}$ = equivalent dose in 2 Gy fractions corrected for proliferation, MLD = mean lung dose, OTT = overall treatment time and WHO-PS = World Health Organisation Performance Score.

63.2 ± 9.0 years (range: 40–80 years) were enrolled. Patient and tumour characteristics are presented in Table 1. Stage distribution was as following: IIB 0.7% ($n = 1$), IIIA 36.5% ($n = 50$), IIIB 62.8% ($n = 86$), including 8 patients (5.8%) with recurrent (stage III) disease. Stage IIIB ($n = 86$) consisted of 42 patients with T4N0-2 disease, 36 patients with T0-3N3 disease and 8 patients with T4N3 disease. Concurrent chemotherapy consisted in 94 patients (68.6%) of cisplatin–etoposide, in 39 patients (28.5%) of cisplatin–vinorelbine and in 4 patients carboplatin based (2.9%). The median interval between the 1st cycle of chemotherapy and start of radiotherapy was 22 ± 15.0 days (0–85 days). The median total GTV was 76.4 ± 94.1 cc (3.7–518.9 cc). Only 22 patients (16.1%) had N0 disease, while 3 (2.7%), 68 (49.6%) and 44 patients (32.1%) had N1, N2 or N3 disease respectively. The median dose for the total group of patients was 65.0 ± 6.0 Gy (51–69 Gy) delivered in a median OTT of 35 ± 5.7 days (18–48 days). This equals a median $EQD_{2,T}$ of 53.9 ± 3.9 Gy (range 43.1–63.1 Gy), which equals a dose of 72 Gy delivered in 36 once-daily fractions of 2 Gy. Five patients did not complete their radiation: 2 patients due to intercurrent disease (cerebrovascular accident, myocardial infarction) and 3 patients wished to stop since the schedule was too exhausting. The median MLD was 16.3 ± 3.5 Gy (range 4.4–21.0 Gy) and the dose to the spinal cord 49.2 ± 10.2 Gy (range 14.1–56.9 Gy). In 43 patients (31.4%) the MLD was dose-limiting. In 10 patients (7.3%) a protocol violation was encountered; 1 patient with stage IIB with a large tumour (315.1 cc) was included, and in 9 patients (6.6%) the dose constraints were not fulfilled: 2.2% an MLD > 20 Gy (resp. 20.2, 20.4 and 21.0 Gy) and 4.4% a maximal dose to the spinal cord > 54.5 Gy (resp. 54.8, 55.0, 55.3, 56.4, 56.4 and 56.9 Gy).

4.2. Survival

The median follow-up time was 30.9 months (95%CI 28.5–33.5 months). At the time of analysis 76 patients (55.5%) had died. The median OS was 25.0 months (95%CI 19.8–30.3 months) with a 1-year OS of 72.2% and a 2-year OS of 52.4% (Fig. 1a). For the different stages the median OS was as following: stage IIIA 24.2 months (95%CI 15.5–32.9 months) and stage IIIB 29.1 months (95%CI 18.1–40.1 months; $p = 0.51$; Fig. 1b). The median PFS was 14.0 months (95%CI 9.5–18.5 months) with a 1-year PFS of 54.7% and a 2-year PFS of 35.5% (Fig. 1c). Eighty patients (58.4%) showed recurrent disease: 5.1% ($n = 7$) an isolated local recurrence, 4.4% ($n = 6$) an isolated regional recurrence, 5.1% ($n = 7$) a combined local and regional recurrence and 27.0% ($n = 37$) distant metastases only. Out of these 37 patients, 21 (56.8%) had cerebral metastases as first site of progression. In another 16.8% ($n = 23$) local-regional progression was simultaneously (within 1 month) detected with distant metastases.

4.3. Uni- and multi-variate analysis survival

On univariate analysis, OS was better with a WHO-PS of 0 ($p = 0.009$), smaller nodal volume (GTV-2; $p = 0.015$) and a higher $EQD_{2,T}$ ($p = 0.037$). All other factors were not correlated with OS (Table 2). On multivariate analysis a favourable WHO-PS ($p = 0.006$), smaller nodal volume (GTV-2; $p = 0.022$) and a higher $EQD_{2,T}$ ($p = 0.044$) remained independent factors for a better OS.

4.4. Toxicity

Toxicity is depicted in Fig. 2. Severe acute toxicity ($\geqslant$G3, $n = 49$, 35.8%) consisted mainly of G3 dysphagia.

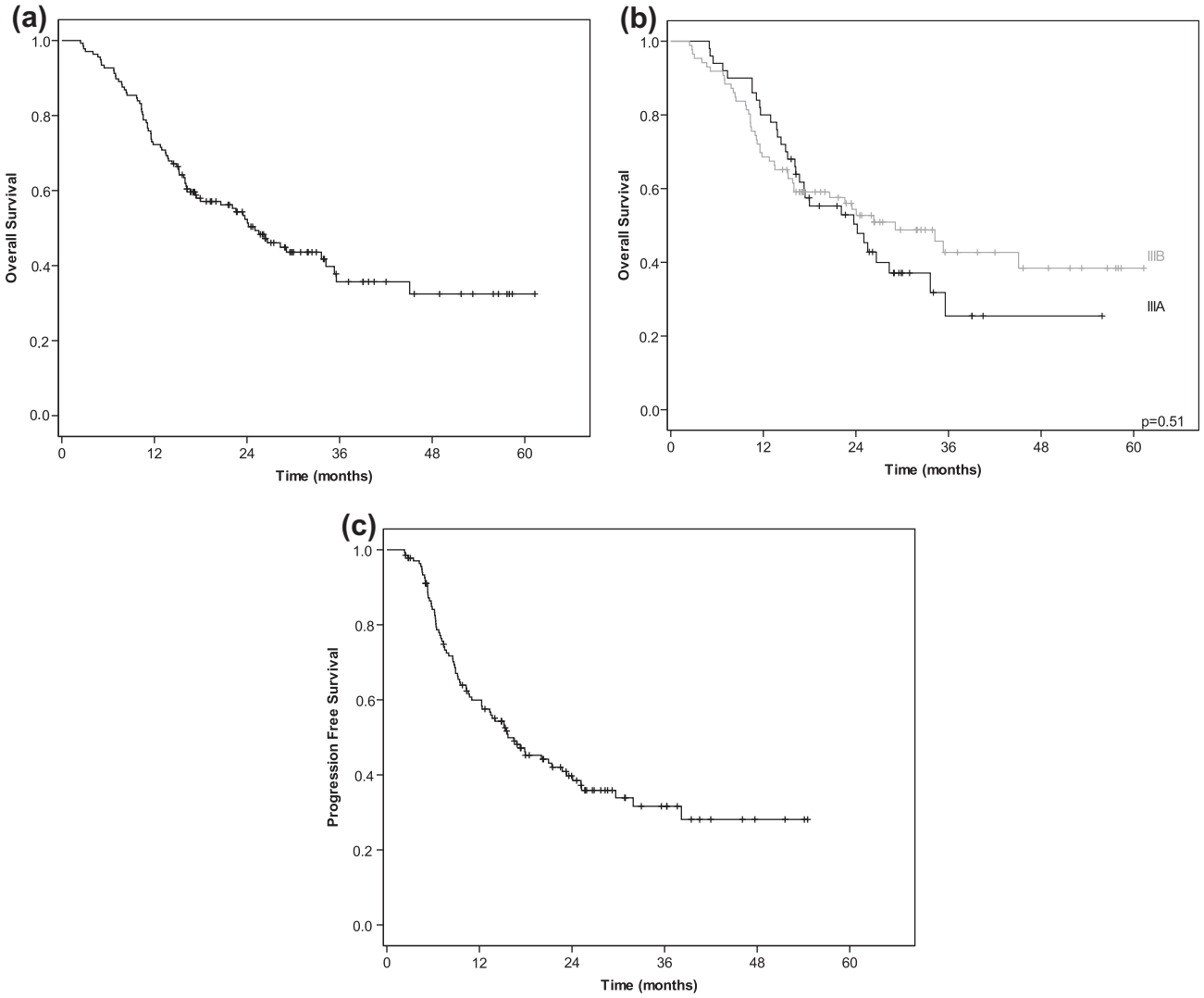

Fig. 1. Actuarial Overall Survival (OS) for total group of patients (a), for stages IIIA and IIIB (b), and the actuarial Progression Free Survival (PFS) (c) in months for the total group of patients.

Most patients developed no (8.8%) or mild dysphagia (G1:28.5%, G2:37.2%), while G3 dysphagia during radiotherapy was observed in 25.5% ($n = 35$). Severe pulmonary complaints were less frequent: G3 and G4 dyspnoea were observed in 2.9% and 0.7% respectively and G3 cough in 8.0% of patients. One month after radiotherapy G3 dysphagia was observed in only 9 patients (6.6%).

In total 6 patients (4.4%) died within 3 months after end of radiotherapy; two due to not otherwise defined pulmonary causes, 1 patient sepsis, 1 patient cardiomyopathy, 1 patient of an abdominal aorta aneurysm and 1 patient of an unknown cause at home.

For severe late toxicity ($\geqslant$G3; $\geqslant$90 days post-radiotherapy) 131 patients were available. In 10 patients (7.3%) $\geqslant$G3 toxicity was observed: in 6 patients (4.6%) this was a G3 dysphagia (in 5 patients due to a stricture or stenosis and in 1 patient an oesophageal ulcer). With regard to severe pulmonary toxicity a thoracic empyema or fistula was diagnosed in 2 patients (1.5%) 14 and 6 months after radiotherapy respectively. One patient had a pneumothorax 3 months after radiotherapy and developed an empyema subsequently. Three patients (2.3%) had grade 3 dyspnoea and 1 patient (0.8%) died of a radiation pneumonitis (grade 5) 3.5 months after radiotherapy. This patient was an 80-year old male (WHO-PS 1, FEV_1 76%, DLCO 77%), who received a dose of 65 Gy with a MLD of 19.5 Gy. No case of myelitis was observed.

5. Discussion

Although improvements in treatment of NSCLC have occurred, the prognosis of locally advanced NSCLC remains poor. The importance of both total radiation dose[26] and overall treatment time[7] have been demonstrated for local tumour control and survival.[2,7,14] Therefore many groups have tried to increase

Table 2
Univariate and multivariate analysis for overall survival (OS).

	Overall survival	
	Univariate	Multivariate
WHO-PS 0 versus WHO-PS $\geqslant$ 1	0.009	0.006
GTV-2 < median versus GTV-2 $\geqslant$ median	0.015	0.022
$EQD_{2,T}$ $\geqslant$ median versus $EQD_{2,T}$ < median	0.037	0.044
TTD $\geqslant$ median versus TTD < median	0.20	NA
Total GTV $\geqslant$ median versus total GTV < median	0.22	NA
Histology	0.44	NA
Stage IIIA versus IIIB	0.51	NA
Type of chemotherapy	0.71	NA
GTV-1 $\geqslant$ median versus GTV-1 < median	0.82	NA
Gender	0.83	NA
Age $\geqslant$ median versus age < median	0.85	NA

GTV = total gross tumour volume, TTD = total tumour, $EQD_{2,T}$ = equivalent dose in 2 Gy fractions corrected for proliferation, and WHO-PS = world health organisation performance score, NA = not analysed.

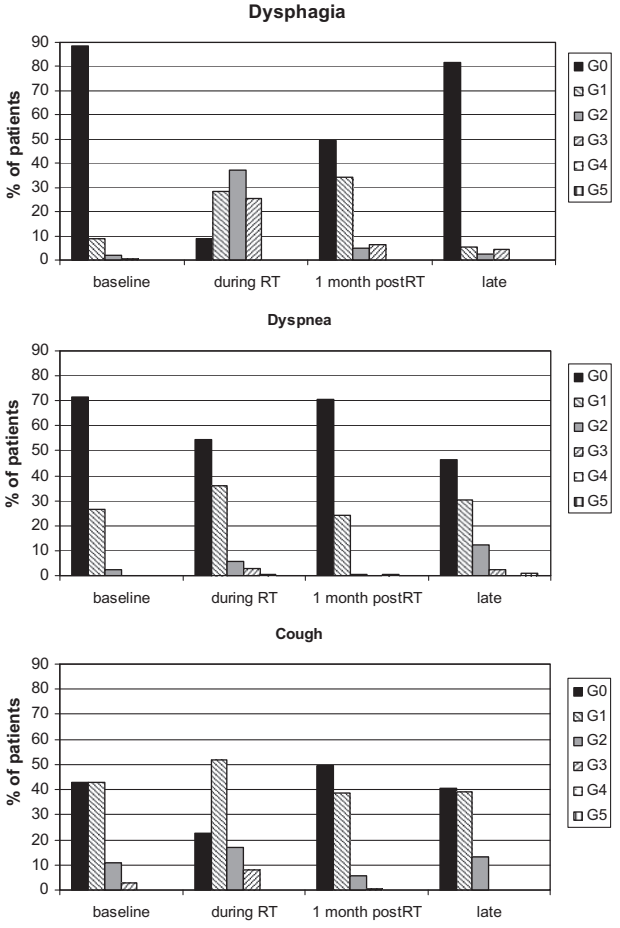

Fig. 2. Percentage of patients with toxicity: maximal scoring according to Common Terminology Criteria for Adverse Events v3.0 (CTCAE-criteria v3.0) for baseline, acute toxicity during radiotherapy, 1 month after radiotherapy and late toxicity (> 90 days) for cough (a), dyspnoea (b) and oesophagitis (c).

the dose and/or reduce the overall treatment time by applying accelerated radiotherapy.[6,12,28,29]

Another strategy to improve outcome in stage III NSCLC is concurrent chemo-radiation. A recent meta-analysis has shown the superiority of concomitant chemo-radiation over sequential chemo-radiation, 2-year survival of 35% and 30% respectively.[2] In the recent prospective phase II RTOG-0324 trial in which 93 patients were treated with concurrent carboplatin–paclitaxel–cetuximab and radiotherapy to a dose of 63 Gy in 35 once-daily fractions, the median survival was 22.7 months and the 2-year overall survival 49.3%.[8]

These results were stated to be better than any previously reported RTOG study and promising enough to be the basis of a randomised phase III trial. Without the addition of cetuximab, our results of a median overall survival of 25.0 months and a 2-year overall survival rate of 52.4% in a 137-patients prospective study are in line with the best results that were achieved in RTOG-0324.

Although the present trial is a phase II non-randomised mono-centre trial the selection criteria were not very stringent: no age criteria were applied (25% of patients > 70 years, 10.2% > 75 years), patients with N3 disease (32.1%), including supraclavicular node involvement and the median tumour volume was rather large (76 cc). In two phase I trials (RTOG 0117 and CCTG 0028) and in the randomised phase II CALGB 30105 trial the maximal tolerable dose was 74 Gy in 37 fractions in 7.4 weeks, which is biologically similar to our schedule. However, due to the dose constraints together with a fixed tumour dose, it is likely that the patients included in these studies had smaller tumours. Unfortunately no data on tumour volumes are available in the latter studies, although the percentage of IIIB disease was lower (11%, 23% and 50% respectively) compared to ours (63%). This might be caused by exclusion of N3 disease in supraclavicular nodes in some studies. Only 25% of patients included in our study would have been able to receive a physical dose of 74 Gy, due to MLD or spinal cord constraints.

This series includes a rather large number of large cell carcinoma (53.2%), due to the historical tendency in some of the referring hospitals to specify a tumour as a large cell carcinoma if the histology was not typical adenocarcinoma or squamous cell carcinoma.

Since all patients included were treated from 2006, staging included a PET-CT scan and brain imaging. This might lead to some stage migration and therefore selection compared to some other studies. Nevertheless, our results are comparable with these of the aforementioned trials, even though a lower physical radiation dose was delivered, be it in a shorter overall treatment time, thus indirectly supporting the biological activity of the present schedule.

We observed a 2-year PFS of 39.7% and a 2-year OS of 52.4%, which is equal to or even better than observed

by other authors.[2,3,5,8] Results were even comparable to the results of 28 patients included in the ESPATÜ study with potentially resectable locally advanced NSCLC, who received accelerated chemo-radiation and no resection, showing a 2-year OS of 50%.[13] The meta-analysis showed a 2-year PFS for concurrent chemo-radiation of 22.7%. The first event was mainly distant metastasis (26.7%) and less frequently loco-regional recurrence (14.6%) or a combination of both (16.8%) in the present series, compared to 34% distant metastasis and 27% loco-regional recurrence in the meta-analysis, respectively.[2] Although the frequency of distant metastasis remains high, to the best of our knowledge, further treatment intensification by adding induction chemotherapy or consolidation chemotherapy or targeted agents to concurrent chemo-radiation has not demonstrated any survival benefit compared to concurrent chemo-radiation alone.[30,31]

Dose prescription was based on normal tissue constraints, like MLD. Although no single parameter can predict lung toxicity, the MLD together with the V20 are the most robust parameters predictive for lung toxicity.[9] The median radiation dose in this study was 65 Gy, and 27% of patients could receive the maximal allowed dose (69 Gy). By applying IMRT this number could probably be increased.[32,33] However, it is not totally clear whether applying IMRT techniques will lead to similar regional control rates, since the incidental dose to mediastinal lymph nodes is higher using 3D conformal techniques than IMRT. Future studies evaluating IMRT should answer this question, as well if the balance of dose-escalation by IMRT and reducing dose to elective nodes and organs at risk will lead to better control rates and similar or lower toxicity, like pneumonitis.

The rate of oesophageal toxicity was rather high although it consisted mainly of (transient) oesophageal toxicity (acute G3 dysphagia: 24%). This rate is somewhat higher than mentioned in literature (<20%) and might be caused by the fact that no specific oesophageal dose constraints were applied and the accelerated radiation scheme.[5] In 4% of patients severe late oesophageal toxicity was observed, which is in line with literature.[3,5] With regard to late pulmonary toxicity we focused on $\geqslant$ grade 3 (3%), since symptoms of pneumonitis, like dyspnoea and cough might be non-specific and intercurrent infections or exacerbation of COPD might confound scoring. We observed one lethal radiation pneumonitis (0.8%). This compares well with literature.[2,3,8]

In conclusion, INDAR in concurrent chemo-radiation based on normal tissue constraints is feasible. The maximal dose of 69 Gy is physically lower than prescribed in other dose-escalation schemes, but biologically equivalent due to the short overall treatment time, and is even feasible in patients with large tumour volumes and multi-level N2-3 disease. It has both acceptable transient acute toxicity as well as limited severe late toxicity and shows promising results with a 2 year OS of 52.4%. One of the challenges in the future is to further individualise treatment of stage III NSCLC, not only with regard to radiation dose, but also to tailor systemic therapy to the individual patient to find a balance between effect and toxicity.

Conflict of interest statement

None declared.

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