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## Prognostic factors of local control and disease free survival in centrally located non-small cell lung cancer treated with stereotactic body radiation therapy

Marloes Duijm<sup>a</sup>, Noëlle C. van der Voort van Zyp<sup>b</sup>, Patrick V. Granton<sup>a</sup>, Paul van de Vaart<sup>b</sup>, Mirjam E. Mast<sup>b</sup>, Esther Oomen-de Hoop<sup>a</sup>, Mischa S. Hoogeman<sup>a</sup> and Joost J. Nuyttens<sup>a</sup>

<sup>a</sup>Department of Radiation Oncology, Erasmus MC Cancer Institute, Rotterdam, The Netherlands; <sup>b</sup>Department of Radiation Oncology, Haaglanden MC, The Hague, The Netherlands

### ABSTRACT

**Background:** Stereotactic body radiation therapy (SBRT) results in high local control (LC) rates in patients with non-small cell lung cancer (NSCLC). For central lung tumors, risk-adapted fractionation schedules are used and underdosage to the Planned Target Volume (PTV) is often accepted to respect the dose constraints of the organs at risk in order to avoid high rates of toxicity. The purpose of this study was to analyze the effect of PTV underdosage and other possible prognostic factors on local- and disease control after SBRT in patients with central lung tumors.

**Material and Methods:** Patients with centrally located NSCLC treated with SBRT were included. The doses were converted into biologically equivalent dose using  $\alpha/\beta$ -value of 10 Gy (BED<sub>10</sub>). Underdosage to the PTV was defined as the (percentage of) PTV receiving less than 100 Gy BED<sub>10</sub>; (%PTV < 100 BED<sub>10</sub>). Potential prognostic factors for LC and Disease Free Survival (DFS) were evaluated using Cox regression analysis.

**Results:** Two hundred and twenty patients received  $\leq 12$  fractions of SBRT. LC-rates were 88% at 2 years and 81% at 3 years. Twenty-seven patients developed a local recurrence. Both the PTV < 100 BED<sub>10</sub> and %PTV < 100 BED<sub>10</sub> were not prognostic for LC. Tumor size and forced expiratory volume in 1 second (FEV<sub>1</sub>) were independently prognostic for LC. Disease progression was reported in 75 patients with DFS-rates of 66% at 2 years and 56% at 3 years. Disease recurrence was independent significantly associated with larger tumor diameter, lower lobe tumor location and decreased FEV<sub>1</sub>. Grade 4–5 toxicity was reported in 10 patients (8 with ultra-central tumors) and was fatal in at least 3 patients.

**Conclusion:** Decrease in tumor coverage was not correlated with the local recurrence probability. The LC and DFS were promising after SBRT of centrally located NSCLC with tumor size, FEV<sub>1</sub> and tumor location (for DFS only) as prognostic factors.

### ARTICLE HISTORY

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### Introduction

Stereotactic body radiation therapy (SBRT) is the golden standard in patients having early stage non-small cell lung cancer (NSCLC) not suitable for surgery [1,2]. Over more than 15 years ago, reports of high-grade toxicity after stereotactic radiotherapy resulted in the definition of a ‘central lung tumor’ together with the proposal of risk-adapted fractionation schedules [3,4] and accompanying dose constraints for organs at risk (OAR) [5]. Despite these risk-adapted schedules and dose constraints, high-grade toxicity has been reported in recent prospective studies [6–8]. This resulted in a higher awareness for toxicity in the treatment of central lung tumors, wherein prioritizing dose constraints of the OAR over tumor coverage is recommended.

Additionally, a clear fractionation consensus for centrally located lung tumors is missing. As such, risk-adapted schedules vary between institutes. These different risk-adapted schedules are not all resulting in the same biologically

equivalent dose (using an  $\alpha/\beta$ -ratio of 10 Gy; BED<sub>10</sub>). Multiple studies report high local control (LC) rates when prescribing a minimum of 100 Gy BED<sub>10</sub> [9–12]. However, a fractionation schedule with a minimum dose of 100 Gy BED<sub>10</sub> covering more than 95% of the Planned Target Volume (PTV), can still result in a wide variety of dose distributions to the PTV. This variety of dose in combination with the heterogeneity of stereotactic treatment plans, asks for additional PTV parameters to define the optimal treatment plan that gives adequate local tumor control [13]. Therefore, additional PTV parameters, such as D<sub>mean</sub> [13,14] and D<sub>95%</sub> [14], have been proposed by various studies in the stereotactic treatment of NSCLC. Additionally, the ICRU 91 suggests the use of the median dose to the PTV (D<sub>50%</sub>) as a representative absorbed-dose value for the PTV [15].

Taking the increased priority of the OAR dose constraints and the previous mentioned studies in mind, the question can be raised whether only a prescribed dose of more than 100 Gy BED<sub>10</sub> is enough for adequate tumor control.

Moreover, prioritizing the OAR constraints can result in a reduced PTV coverage and the effect of this underdosage on the LC probability is unknown. The purpose of this research is to determine the effect of reduced tumor coverage and other possible prognostic factors on local and disease control in patients with centrally located NSCLC treated with SBRT.

## Material and methods

We identified patients having  $T_{1-4}N_0M_0$  NSCLC treated between 2006 and 2016 with risk-adaptive stereotactic radiotherapy in 2 Dutch centers: Erasmus Medical Center (EMC) and Haaglanden Medical Center (HMC). Tumors were considered central when the tumor was located within 2 cm of the esophagus and/or the bronchial structures (trachea, main bronchus, bronchus intermedius or upper-, middle- or lower-lobe bronchi). Patients were excluded if they had: a second lung nodule, previous radiation with overlapping fields, chemotherapy during SBRT and if they did not have any follow-up. Diagnostic work-up consisted of a PET scan. An MRI scan of the brain was not performed in these patients without nodal disease.

Treatment planning and delivery of both centers have been previously described [16,17]. Briefly, the treatment in the HMC was initially delivered with a stereotactic linear accelerator (Novalis, Brainlab AG, Munich Germany), that was replaced by a linear accelerator with cone-beam CT-guidance (Elekta AB, Stockholm, Sweden) in 2013. Patients were treated with 60 Gy in 8 fractions 3 times a week or, 60 Gy in 12 fractions 4 times a week if the PTV overlapped with or was too close to the OAR. The PTV consisted of an Internal Target Volume (ITV) that was expanded with 5 mm (6 mm in craniocaudal direction) for the Novalis linear accelerator and 6 mm in all directions for the Elekta linear accelerator. Until 2014, the ITV was created by expanding the Gross Tumor Volume (GTV) based on 6 scans taken randomly during the breathing cycle. Thereafter, the ITV was created by contouring the tumor in 10 respiratory phases of the 4D CT scan. The treatment dose was prescribed to the 100% isodose line and the maximum dose was not allowed to exceed 140%. At least 95% of the PTV had to receive 100% of the prescribed dose and 99% of the PTV had to receive 90% of the prescribed dose. In EMC, patients were treated with the Cyberknife Robotic Radiosurgery System (Accuray Inc, Sunnyvale, AC) with 5 fractions of 9–12 Gy or, when the tumor was close to the esophagus, 6–7 fractions of 7–8 Gy, except in 2 patients who received 3 fractions of 20 Gy. The PTV consisted of the GTV plus 5 mm. The dose to the PTV was prescribed to the 70–90% isodose line covering at least 95% of the PTV. At both institutions, underdosage was allowed in order to meet the dose constraints of the OAR (Table S1 in Supplementary materials) or an acceptable dose to the OAR at the discretion of the treating physician.

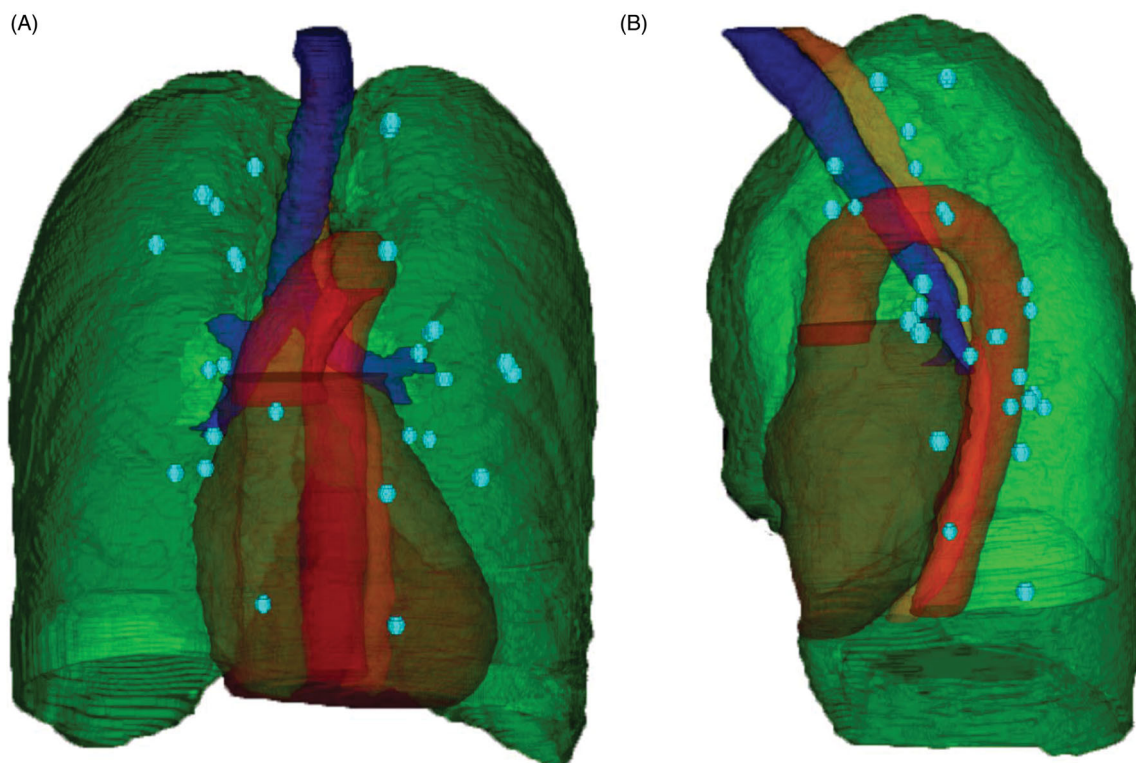
Follow-up was generally performed 3 weeks, 3, 6, 12, 18 and 24 months following SBRT and annually thereafter. Patient records from hospitals and general practitioners were screened for disease control, survival status and toxicity. A local recurrence was defined as a recurrence within or

adjacent to the PTV. Disease progression was defined as a tumor recurrence in any part of the body. In the absence of a biopsy, (local) tumor recurrence was defined as a 20% increase in tumor size on the CT scan compared with the previous CT scan according to the Response Evaluation Criteria In Solid Tumors (RECIST, version 1.0). In addition, a corresponding avid lesion on the PET scan was required. In order to visualize the location of all the local recurrences, we contoured the center of the treated tumor as a small 3D circle (diameter 7 mm) on one CT scan. Local control was calculated from the start of SBRT until the moment of diagnosis of the local recurrence. For patients without an event, the last date of a follow-up visit in the hospital was used. Overall survival and disease free survival (DFS) were calculated using the first date of SBRT and the date of death or disease progression, respectively. For patients without an event, the last date of follow-up visit or the last date of contact was used. As the last date of follow-up contact was used, death was not a competing risk for disease recurrence. Underdosage of the tumor is described as absolute and relative volume of the PTV receiving less than 100 Gy BED<sub>10</sub>. All cases with grade 3 or higher toxicity according to the definition of the Common Terminology Criteria for Adverse Events (version 4.03) were scored. Toxicity was considered acute if it

**Table 1.** Patient- and tumor-characteristics ( $n = 220$ ).

	n (%) / median (IQR, range)	
Age (years)	76	(68–82, 51–94)
Gender		
Female	89	(40%)
Male	131	(60%)
COPD		
No COPD	39	(18%)
GOLD I–II	113	(51%)
GOLD III–IV	61	(28%)
Unknown	7	(3%)
Charlson Comorbidity Index		
0–2	128	(58%)
3–5	83	(38%)
6–9	9	(4%)
WHO Performance Scale		
0	74	(34%)
1	117	(53%)
2	14	(6%)
3–4	6	(3%)
Unknown	9	(4%)
Tumor histology		
No pathology available	91	(42%)
Squamous cell carcinoma	68	(31%)
Adenocarcinoma	40	(18%)
Large cell carcinoma	18	(8%)
Different	3	(1%)
Disease stage TNM 8th		
IA/IB	83	(38%)
IIA/IIB	115	(52%)
IIIA	22	(10%)
Prescribed amount of fractions		
3 Fractions of 20 Gy	2	(1%)
5 Fractions of 9/10/11/12 Gy	82	(37%)
6 Fractions of 7/8 Gy	17	(8%)
7 Fractions of 7 Gy	18	(8%)
8 Fractions of 7.5 Gy	69	(31%)
12 Fractions of 5 Gy	32	(15%)
Tumor diameter (mm)	44	(33–58, 9–105)

COPD: Chronic Obstructive Pulmonary Disease; Gy: Gray; IQR: interquartile range; PTV: Planned Target Volume.



**Figure 1.** Pattern of recurrence: (A) anterior view and (B) lateral view. Small light blue circles represent the center of mass of each tumor reporting local recurrence. Color legend at risk: orange: esophagus, dark blue: bronchial tree (trachea, main bronchus, bronchus intermedius or upper-, middle- or lower- lobe bronchi), light red: aorta, dark red: heart.

occurred within 3 months from the start of the SBRT and late if it occurred thereafter.

Because of variations in the treatment schedules, all doses were converted into a  $BED_{10}$  using the following formula:  $BED = D \times \left(1 + \frac{d}{\alpha/\beta}\right)$  with  $D$  = total dose,  $d$  = dose per fraction and  $\alpha/\beta$ -value is 10 Gy. Dosimetric PTV parameters were derived from the dose volume histogram (DVH) of each patient: maximum and minimum point dose ( $D_{max}$ ,  $D_{min}$ ), mean dose ( $D_{mean}$ ), dose to 2%/50%/98 percent of the PTV ( $D_{2\%}/D_{50\%}/D_{98\%}$ ) and volume of the PTV receiving less than 100 Gy  $BED_{10}$  ( $PTV < 100 BED_{10}$ ).

Cox regression was used to determine LC and DFS and to test possible prognostic factors for (local) disease control. The following factors were entered into the univariate analyses: age, gender, previous (lung)malignancies, WHO status (0 versus  $\geq 1$ ), Charlson Comorbidity Score (CCS; 0–2 versus  $\geq 3$ ), Chronic Obstructive Pulmonary Disease (COPD; GOLD 0–1 versus 2–4), Forced Expiratory Volume in 1 second ( $FEV_1$ ), endobronchial tumor location, availability of pathology, localization of the tumor in the upper/middle lobe or mediastinum versus the lower lobe, disease stage (TNM 8th; IA–IIA versus IIB–IIIA), tumor size, PTV volume, prescribed dose ( $<100$  Gy  $BED_{10}$  versus  $\geq 100$  Gy  $BED_{10}$ ),  $D_{max}$   $BED_{10}$ ,  $D_{min}$   $BED_{10}$ ,  $D_{mean}$   $BED_{10}$ ,  $D_{2\%}$   $BED_{10}$ ,  $D_{50\%}$   $BED_{10}$  (as a continuous variable and dichotomized to  $<100$  Gy  $BED_{10}$  versus  $\geq 100$  Gy  $BED_{10}$ ),  $D_{98\%}$   $BED_{10}$ ,  $PTV < 100 BED_{10}$  and percentage of the PTV receiving less than 100 Gy  $BED_{10}$  ( $\%PTV < 100 BED_{10}$ ). The univariate analyses was followed by a multivariate analyses (MVA) with backward selection for all factors having a  $p$ -

value  $< .20$ . When multiple correlating variables were significant in univariate analyses, only the factor with the highest clinical relevance was entered in the MVA. The proportional hazards assumption, assuming that the hazard between the groups is constant over time, was checked for each variable that was entered into the Cox regression. Kaplan-Meier estimates were calculated for all clinical outcomes and curves were compared using log-rank tests. Tumor size was not only analyzed as a continuous variable, but also dichotomized with a cutoff of 5 cm, such that we could examine the relevance of this cutoff criteria used by the RTOG 0813 study for inclusion (in which tumors had to be  $\leq 5$  cm) [8]. In all analyses a  $p$ -value  $\leq .05$  was considered statistically significant. Analyses were performed using IBM SPSS statistics version 25.0.0.1 software package (SPSS Inc., Chicago, IL). This retrospective study received approval from the medical ethical committees of both centers.

## Results

For this analysis 220 patients were eligible. Patient- and treatment characteristics are shown in Table 1. The diagnosis was confirmed by pathology in 58% of patients. All but one patient had a diagnostic PET-CT scan. In this patient pathology was available. The majority of the patients was diagnosed with stage I (38%) or stage II lung cancer (52%). The most commonly used fractionation schedules were 5 fractions (37%), 8 fractions (31%) and 12 fractions (15%).



**Table 2.** Results of the Cox regression analyses focusing on patient- and dosimetric factors prognostic for local recurrence for patients with T<sub>1-4</sub>N<sub>0</sub>M<sub>0</sub> NSCLC treated with SBRT.

Characteristic	Local control median (IQR)/n (%)	Local progression median (IQR)/n (%)	Univariate analysis	
			Hazard Ratio (95%CI)	p-value
Age	76 (68–81)	71 (62–77)	0.97 (0.93–1.01)	.091
FEV <sub>1</sub> <sup>a</sup>	64 (50–80)	60 (48–72)	0.98 (0.96–1.01)	.119
Gender				
Male	117 (89%)	14 (11%)	1	
Female	76 (85%)	13 (15%)	1.18 (0.55–2.51)	.672
Localization of tumor				
UMM	140 (90%)	16 (10%)	1	
Lower	53 (83%)	11 (17%)	2.26 (1.05–4.88)	.038
WHO status <sup>b</sup>				
0	64 (86%)	10 (14%)	1	
1–4	120 (88%)	17 (12%)	1.12 (0.51–2.45)	.775
COPD <sup>c</sup>				
0–1	63 (91%)	6 (9%)	1	
2–4	125 (87%)	19 (13%)	1.30 (0.52–3.25)	.580
Pathology available				
No	83 (91%)	8 (9%)	1	
Yes	110 (85%)	19 (15%)	1.97 (0.86–4.51)	.107
CCS				
0–2	113 (88%)	15 (12%)	1	
≥3	80 (87%)	12 (13%)	1.14 (0.53–2.44)	.741
Previous malignancies <sup>d</sup>				
No	115 (86%)	18 (14%)	1	
Yes	78 (90%)	9 (10%)	0.84 (0.38–1.87)	.666
Previous lungca <sup>d</sup>				
No	175 (89%)	22 (11%)	1	
Yes	18 (78%)	5 (22%)	1.51 (0.57–4.02)	.404
Endobronchial tumor				
No	154 (87%)	23 (13%)	1	
Yes	39 (91%)	4 (9%)	1.05 (0.36–3.08)	.923
Disease stage				
IA–IIA	122 (93%)	9 (7%)	1	
IIB–IIIA	71 (80%)	18 (20%)	4.43 (1.97–9.94)	<.001
Tumordiameter (mm)	42 (32–54)	54 (38–62)	1.04 (1.02–1.06)	.001
PTV volume (cc)	75 (42–135)	118 (50–157)	1.00 (1.00–1.01)	.054
PTV < 100 BED <sub>10</sub> (cc)	1.2 (0.2–27.4)	4.2 (0.4–75.4)	1.00 (1.00–1.00)	.593
%PTV < 100 BED <sub>10</sub>	2% (0–38%)	2% (1–55%)	2.26 (0.79–6.43)	.127
Prescribed dose BED <sub>10</sub>				
<100	56 (84%)	11 (16%)	1	
≥100	137 (90%)	16 (10%)	0.45 (0.20–0.98)	.045
PTV D <sub>max</sub> BED <sub>10</sub>	144 (127–175)	139 (122–157)	0.99 (0.98–1.01)	.193
PTV D <sub>2%</sub> BED <sub>10</sub>	139 (121–163)	134 (115–152)	0.99 (0.98–1.01)	.203
PTV D <sub>mean</sub> BED <sub>10</sub>	122 (102–136)	115 (97–132)	0.99 (0.97–1.01)	.278
PTV D <sub>50%</sub> BED <sub>10</sub>	123 (103–137)	117 (98–132)	0.99 (0.97–1.01)	.279
PTV D <sub>98%</sub> BED <sub>10</sub>	100 (84–105)	92 (77–104)	0.99 (0.97–1.01)	.383
PTV D <sub>min</sub> BED <sub>10</sub>	75 (64–90)	72 (56–85)	0.99 (0.97–1.01)	.186
PTV D <sub>50%</sub> BED <sub>10</sub>				
<100	39 (85%)	7 (15%)	1	
≥100	154 (89%)	20 (11%)	0.49 (0.21–1.12)	.092

<sup>a</sup>24 cases missing; <sup>b</sup>9 cases missing; <sup>c</sup>7 cases missing; <sup>d</sup>proportional hazard assumption is violated.

BED<sub>10</sub>: Biologically Effective Dose using  $\alpha/\beta$ -ratio of 10 Gy; CCS: Charlson Comorbidity Score; COPD: Chronic Obstructive Pulmonary Disease; D<sub>max</sub>: maximum point dose; D<sub>mean</sub>: mean dose; D<sub>min</sub>: minimum point dose; D<sub>2%</sub>: dose to 2% percent of the PTV; FEV<sub>1</sub>: Forced Expiratory Volume in 1 second; NSCLC: non-small cell lung cancer; PTV: Planned Target Volume; PTV < 100 Gy BED<sub>10</sub>: volume of the PTV which is receiving less than 100 Gy BED<sub>10</sub>; SBRT: Stereotactic Body Radiation Therapy; UMM: upper/middle lobe or mediastinum; %PTV < 100 Gy BED<sub>10</sub>: percentage of the volume of the PTV which is receiving less than 100 Gy BED<sub>10</sub>.

Italic values indicate significant  $p \leq .05$ .

Local control rates were 92% at 1 year, 88% at 2 years and 81% at 3 years. Twenty-seven patients (12%) were diagnosed with a local recurrence. No clear pattern of local relapse could be visualized when delineating all recurrences on one CT scan (Figure 1). Relative and absolute PTV underdosage were both not prognostic for a local recurrence (PTV <100 BED<sub>10</sub>  $p = .593$  and %PTV <100 BED<sub>10</sub>  $p = .127$ ). The median PTV receiving less than 100 Gy BED<sub>10</sub> was 4.2 cc in patients with a recurrence compared to 1.2 cc in patients without a recurrence. The median percentage of the PTV receiving less than 100 Gy

BED<sub>10</sub> was the same in patients with and without a local recurrence (both 2%, Table 2).

Factors prognostic for the development of a local recurrence using univariate analysis were a larger tumor diameter (continuous variable), higher disease stage, a tumor localized in the lower lobe and a prescribed dose of <100 Gy BED<sub>10</sub> (Table 2). The 1 year LC rate was significantly higher for tumors <5 cm compared to tumors ≥5 cm (96% versus 84%,  $p < .001$ , Figure 2a). When the prescribed dose was lower than 100 Gy BED<sub>10</sub>, patients were twice as likely to develop a local recurrence: Hazard Ratio (HR) 2.24, 95% Confidence

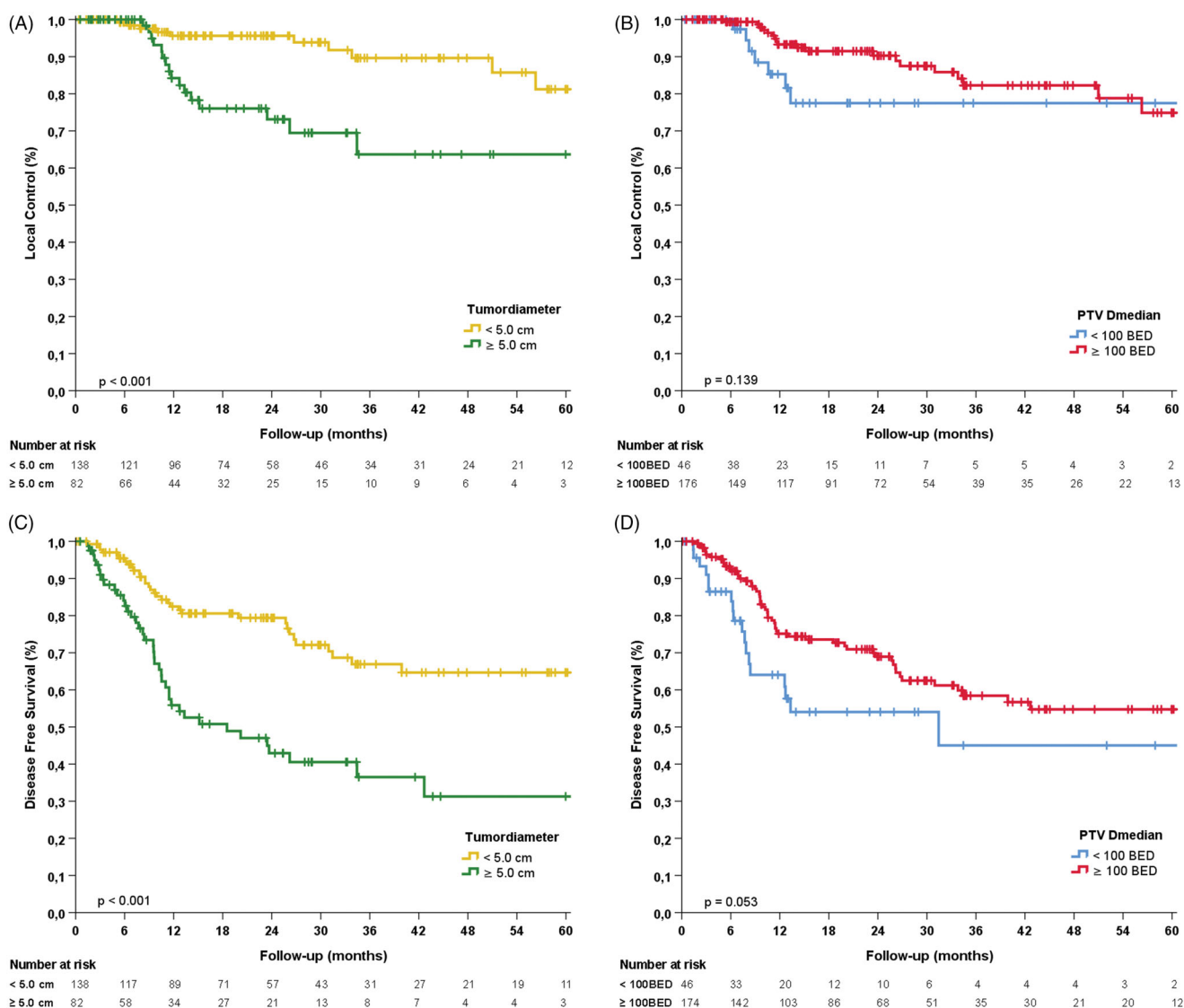


Figure 2. Kaplan-Meier curves for local control (A,B) and disease free survival (C,D).

Interval (CI) 1.02–4.95,  $p = .045$ . A PTV  $D_{50\%}$  of  $< 100$  Gy  $BED_{10}$  was not prognostic for local recurrence (LC at 1 year 85% for  $D_{50\%}$  of  $< 100$  Gy  $BED_{10}$  versus 93% for  $D_{50\%}$  of  $\geq 100$  Gy  $BED_{10}$ ,  $p = .139$ , Figure 2b).

The MVA included age, localization of the tumor (upper/middle lobe or mediastinum versus lower lobe),  $FEV_1$ , availability of pathology (no versus yes), tumor diameter, %PTV  $< 100$   $BED_{10}$ , PTV  $D_{min}$   $BED_{10}$ , prescribed dose in  $BED_{10}$  ( $< 100$  Gy versus  $\geq 100$  Gy) and PTV  $D_{50\%}$   $BED_{10}$  ( $< 100$  Gy versus  $\geq 100$  Gy). Factors independently prognostic for local tumor recurrence in MVA were larger tumor size and lower  $FEV_1$ : HR tumor diameter 1.04, 95% CI 1.02–1.06,  $p = .001$  and HR  $FEV_1$  0.97, 95% CI 0.95–1.00,  $p = .031$ .

Disease progression was reported in 75 patients (34%). The DFS was 73% at 1 year, 66% at 2 years and 56% at 3 years. Disease free survival was significantly better for patients with tumors smaller than 5 cm ( $p < .001$ , Figure 2c). There was a trend for increased DFS in patients who received PTV  $D_{50\%}$  of  $\geq 100$  Gy  $BED_{10}$  ( $p = .053$ , Figure 2d). Factors prognostic for progressive disease using univariate analyses

were lower  $FEV_1$ , larger tumor size (continuous), larger PTV volume, tumors located in the lower lobe and disease stage IIB–IIIA (Table 3). Factors prognostic for progressive disease using multivariate analyses were larger tumor diameter (HR 1.03, 95% CI 1.02–1.04,  $p < .001$ ), lower  $FEV_1$  (HR 0.98, 95% CI 0.97–0.99,  $p = .004$ ) and localization of the tumor in the lower lobe (HR 1.87, 95% CI 1.12–3.11,  $p = .017$ ).

Thirty-eight percent of the patients had a tumor overlapping or adjacent to the proximal bronchial tree (PBT) and/or the esophagus; 67 patients to the PBT, 8 to the esophagus and 9 patients to both. The incidence of the local recurrences of these ultracentral tumors was only slightly higher compared to the central tumors: 14% versus 11%. The LC at 1 year was 91% for ultracentral tumors and 92% for central tumors ( $p = .095$ ). Although these comparable LC rates, almost all cases (8 of 10) of grade 4–5 toxicity occurred in the group of ultracentral tumors. These eight patients all had an ultracentral tumor due to proximity to the PTB. Details of the grade 4–5 toxicity cases are outlined below. In the group of 10 patients reporting grade 4–5 toxicity greater

**Table 3.** Results of the Cox regression analyses focusing on patient- and dosimetric factors prognostic for disease free survival for patients with T<sub>1-4</sub>N<sub>0</sub>M<sub>0</sub> NSCLC treated with SBRT.

Characteristic	Disease control median (IQR)/n (%)	Disease progression median (IQR)/n (%)	Univariate analysis	
			Hazard Ratio (95%CI)	p-value
Age	77 (70–81)	72 (64–79)	0.98 (0.95–1.00)	.066
FEV <sub>1</sub> <sup>a</sup>	65 (50–84)	60 (49–72)	0.99 (0.97–1.00)	.047
Gender				
Male	83 (63%)	48 (37%)	1	
Female	62 (70%)	27 (30%)	0.77 (0.48–1.24)	.281
Localization of tumor				
UMM	112 (72%)	44 (28%)	1	
Lower	33 (52%)	31 (48%)	2.36 (1.49–3.74)	<.001
WHO <sup>b</sup>				
0	50 (68%)	24 (32%)	1	
1–4	91 (66%)	46 (34%)	1.26 (0.77–2.07)	.354
COPD <sup>c</sup>				
0–1	52 (75%)	17 (25%)	1	
2–4	88 (61%)	56 (39%)	1.41 (0.82–2.42)	.220
PA available				
No	61 (67%)	30 (33%)	1	
Yes	84 (65%)	45 (35%)	1.22 (0.77–1.94)	.393
CCS				
0–2	84 (66%)	44 (34%)	1	
≥3	61 (66%)	31 (34%)	0.96 (0.61–1.53)	.877
Previous malignancies				
No	85 (64%)	48 (36%)	1	
Yes	60 (69%)	27 (31%)	0.86 (0.54–1.38)	.527
Previous lungca <sup>d</sup>				
No	131 (66%)	66 (34%)	1	
Yes	14 (61%)	9 (39%)	0.92 (0.46–1.86)	.821
Endobronchial tumor				
No	114 (64%)	63 (36%)	1	
Yes	31 (72%)	12 (28%)	1.04 (0.56–1.94)	.895
Disease stage				
IA–IIA	101 (77%)	30 (23%)	1	
IIB–IIIA	44 (49%)	45 (51%)	3.23 (2.03–5.13)	<.001
Tumordiameter (mm)	38 (30–51)	51 (39–61)	1.03 (1.02–1.04)	<.001
PTV volume (cc)	64 (39–129)	102 (67–154)	1.00 (1.00–1.00)	.003
Prescribed dose BED <sub>10</sub>				
<100	41 (61%)	26 (39%)	1	
≥100	104 (68%)	49 (32%)	0.70 (0.43–1.13)	.144
PTV D <sub>max</sub> BED <sub>10</sub>	144 (130–173)	140 (122–176)	1.00 (0.99–1.00)	.314
PTV D <sub>2%</sub> BED <sub>10</sub>	140 (122–164)	136 (115–163)	1.00 (0.99–1.00)	.258
PTV D <sub>mean</sub> BED <sub>10</sub>	122 (102–136)	120 (100–135)	0.99 (0.98–1.01)	.253
PTV D <sub>50%</sub> BED <sub>10</sub>	123 (103–136)	120 (101–136)	0.99 (0.98–1.01)	.252
PTV D <sub>98%</sub> BED <sub>10</sub> <sup>d</sup>	101 (85–106)	92 (82–105)	0.99 (0.98–1.01)	.244
PTV D <sub>min</sub> BED <sub>10</sub>	77 (64–89)	73 (62–89)	0.99 (0.98–1.01)	.307
PTV D <sub>50%</sub> BED <sub>10</sub>				
<100	28 (19%)	18 (24%)	1	
≥100	117 (81%)	57 (76%)	0.60 (0.35–1.01)	.056

<sup>a</sup>24 cases missing; <sup>b</sup>9 cases missing; <sup>c</sup>7 cases missing; <sup>d</sup>proportional hazard assumption is violated.

BED<sub>10</sub>: Biologically Effective Dose; CCS: Charlson Comorbidity Score; COPD: Chronic Obstructive Pulmonary Disease; D<sub>max</sub>: maximum point dose; D<sub>mean</sub>: mean dose; D<sub>min</sub>: minimum point dose; D.p: dose to .. percent of the PTV; FEV<sub>1</sub>: Forced Expiratory Volume in 1 second; NSCLC: non-small cell lung cancer; PTV: Planned Target Volume; SBRT: Stereotactic Body Radiation Therapy; UMM: upper/middle lobe or mediastinum.

concession was done to the %PTV <100 BED<sub>10</sub>. The median %PTV <100 BED<sub>10</sub> was 26% in patients with grade 4–5 toxicity versus 2% in the rest of the patients. Three of the 10 patients received <100 Gy BED<sub>10</sub> in more than 90% of the volume of the PTV and in three patients less than 2.5% of the PTV received <100 Gy BED<sub>10</sub>.

One patient had grade 4 toxicity and nine patients had grade 5 toxicity. Grade 4 was scored because of a necrotic post obstruction pneumonia. The PET scan showed a fibrotic mass most likely caused by the radiation. Of the nine patients with grade 5 toxicity, three deaths were likely due to SBRT, while six deaths were possibly related to SBRT. The three patients with a death likely related to SBRT had hemoptoe 4.5, 9 and 22 months after treatment. The tumor

was adjacent to the intermediate bronchus or main bronchus, and there was no evidence of disease recurrence in these patients. Three other patients, having their death possibly related to SBRT, died due to fatal hemoptoe in the presence of disease recurrence. In this group, two patients did not have an ultracentral tumor. In the last three patients, respiratory failure was the cause of death which was also possibly related to the SBRT. One patient died due to a COPD exacerbation and two patients died of atelectasis in the lung in combination with disease progression. SBRT could not be excluded as a cause of death in these last three patients. Grade 3 or higher toxicity was scored in 12% (n=27) of the patients. The overall survival was 55% at 2 years, 42% at 3 years and 26% at 5 years.

**Discussion**

Stereotactic treatment of central lung tumors frequently comes with underdosage of the PTV due to nearby OARs, however as far as we know the consequences of this underdosage were still unknown. Within our cohort, neither the absolute nor the relative amount of PTV underdosage was prognostic for a local recurrence. We did find the following factors to be independent significantly prognostic: larger tumor size and a lower FEV<sub>1</sub> for local and disease recurrence and additionally a tumor location in the lower lobe for disease recurrence.

Our reported LC rates were comparable to other studies (Table 4) [6,9,10,14,18–25]. The univariate analysis showed a significant correlation between a prescribed dose of ≥100 Gy BED<sub>10</sub> and local tumor control. Previous studies confirmed the importance of a higher (prescribed) radiation dose on LC within the stereotactic treatment of centrally located NSCLC [10,14]. Tumor size has been frequently analyzed as a prognostic factor for local recurrence in patients with NSCLC treated with SBRT, but data is conflicting [26]. Concerning studies only including central lung tumors, tumor size has been analyzed within one small study without finding a correlation [6]. The authors stated that the study was underpowered due to the small number of events. For the same reason other central lung tumor studies were unable to define any prognostic factors [27,28]. However, within multiple combined (including both central and peripheral tumors) studies, larger tumor size was prognostic for local recurrence in SBRT treatment as in our analysis [9,14,20,21,25]. Only 2 studies analyzed FEV<sub>1</sub> as a prognostic factor, but without describing the same correlation we found [19,21]. However, a poor FEV<sub>1</sub> is commonly caused by smoking and it is known that people who smoked had worse outcomes [29]. Within our analysis, the incidence of local recurrences was almost similar between the ultracentral and central tumors and the LC rates were not significantly different. Other studies comparing LC for patients with an ultracentral versus a central lung tumor after SBRT confirmed these equal LC rates [30–32].

Prognostic factors for DFS after SBRT in NSCLC have rarely been published. Several studies have only reported local, regional- and distant control as separate analyses while others have reported only the DFS rates without possible prognostic factors. Three studies have confirmed our outcome that a larger tumor is correlated with disease recurrence, 2 analyzing DFS [6,25] and one analyzing distant control [21]. FEV<sub>1</sub> has been analyzed in one study focusing on DFS and one on distant control, but was not prognostic in either study [19,21]. Chang et al. investigated COPD for potential association with DFS, but did not find a relation [28]. In our cohort, patients with tumors located in the lower lobe were at higher risk for disease recurrence, this was confirmed by another study [33]. An explanation can be the more frequent upstaging due to unsuspected nodal involvement in lower lobe tumors that is seen after surgery. This can also be the case in tumors treated with SBRT [34]. With regards to tumor location, other analyses have an inferior

**Table 4.** Literature analyzing local control after stereotactic treatment of lung tumors.

	Number of patients	Number of local failures	Age	Gender	Histology	KPI	FEV <sub>1</sub>	Potential prognostic characteristics				Local control rates		
								Location	Tumor size	GTV volume	Tumor stage	Dose	1 year	2 year
<b>Central tumors</b>														
This manuscript	220	27	-	-	-	- <sup>d</sup>	++	+	+	+	+	+	+	+
Modh et al. <sup>a</sup> [18]	125	19	-	-	-	-	++	+	++	+	+	+	+	+
Roach et al. [6]	51	4	-	-	-	-	-	-	++	-	-	-	-	-
Rowe et al. [10]	47 <sup>b</sup>	2	-	-	-	-	-	-	-	-	-	-	-	-
Schanne et al. [19]	90	?	-	-	-	-	-	-	-	-	-	-	-	-
<b>Lung tumors (% central)</b>														
Bral et al. [20]	40 (43%)	3	-	-	-	-	-	+	+	+	+	+	+	+
Horner et al. [21]	126 (33%)	12	-	-	-	+	-	+	++	+	+	+	+	+
Olsen et al. [9]	130 (12%)	8	-	-	-	-	-	+	++	+	+	+	+	+
Park et al. [22]	251 (44%)	21	-	-	-	-	-	-	+	-	-	-	-	-
Samson et al. [23]	245 (52%)	13	-	-	-	-	++	-	-	-	-	-	-	-
Stephans et al. [24]	603 (26%)	?	-	-	-	-	++	-	-	-	-	-	-	-
Ye et al. <sup>c</sup> [25]	127 (40%)	22	+	+	-	-	+	+	+	+	+	+	+	+
Zhao et al. [14]	1092 (10%)	40	-	-	-	-	-	+	+	+	+	+	+	+

Age, tumor size, GTV volume and dose were analyzed as continuous variables, unless specified otherwise. <sup>a</sup>-tested in univariate analysis but not significant; <sup>+</sup> significant in univariate analysis; <sup>++</sup> significant in multivariate analysis. <sup>b</sup>patients with BED<sub>10</sub> < 80 (n = 17) were excluded from the local failure analysis; <sup>c</sup>amount of lesions irradiated; <sup>d</sup>local-regional failure as endpoint; <sup>e</sup>WHO status; <sup>f</sup>lower lobe versus other locations; <sup>g</sup>prescribed dose; <sup>h</sup>total dose in EQD<sub>2</sub> at PTV isodose center; <sup>i</sup>significant for various cutoffs: prescribed dose 100 Gy BED<sub>10</sub>, PTV<sub>mean</sub> 130 Gy BED<sub>10</sub>, PTV<sub>max</sub> 140 Gy BED<sub>10</sub>, PTV<sub>min</sub> 73 Gy BED<sub>10</sub>, PTV<sub>D95</sub> 87 Gy BED<sub>10</sub>, PTV<sub>D99</sub> 76 Gy BED<sub>10</sub>. <sup>j</sup>biologically equivalent dose using an α/β-ratio of 10 Gy. C/P: central versus peripheral location, EQD<sub>2</sub>: equivalent dose in 2 Gray fractions using α/β-ratio of 10 Gy, FEV<sub>1</sub>: Forced Expiratory Volume in 1 second, GTV: Gross Tumor Volume, KPI: Karnofsky Performance Index, PTV: Planned Target Volume.



local and distant control for central tumors compared with peripheral tumors [23,25]. There was no significant correlation between dose and disease control in our study, which is comparable to other studies analyzing dosimetry as prognostic factor for DFS or distant control [19,21,28,35].

Although some characteristics had missing values, we did enter all characteristics having a  $p$ -value of  $<.20$  into the MVA. This resulted in an analysis based on 196 patients with an adequate number of events (23 local failure events and 66 disease progression events) to run a reliable MVA. However, next to the prognostic patient characteristics, we did not find a relation between local recurrence and dose to the PTV or PTV underdosage. The number of events may be too small for an elaborate MVA and it may not be able to identify a potentially weaker association between dosimetric factors and disease control. In the MVA for both LC and DFS, we only included tumor size and not PTV volume and disease stage as these factors were highly correlated. Of the 3 factors tumor size was chosen as it is the most clinical relevant characteristic. A limitation of this study is its retrospective nature. Additionally, as mentioned in the tables, some characteristics did not fulfill the proportional hazard assumption in the Cox regression. Hence, the parameter being estimated by the Cox procedure may not be a meaningful measure of the between group difference and should be further examined in future research.

This analysis showed that stereotactic treatment of centrally located NSCLC resulted in promising local control and disease free survival rates which are partly determined by the size of the tumor, the FEV<sub>1</sub> and in case of DFS also by the lobe location of the tumor. Although underdosage of the PTV was not prognostic for a local recurrence, the balance between a high local tumor dose and respecting the dose constraints of the organs at risk will remain important in the stereotactic treatment of central lung tumors.

## Disclosure statement

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