Outcomes of Stereotactic Ablative Radiotherapy for Centrally Located Early-Stage Lung Cancer

Cornelis J. A. Haasbeek, MD, PhD, Frank J. Lagerwaard, MD, PhD, Ben J. Slotman, MD, PhD, and Suresh Senan, MRCP, FRCR, PhD

Introduction: The use of stereotactic ablative radiotherapy (SABR) in centrally located early-stage lung tumors has been associated with increased toxicity. We studied outcomes after delivery of risk-adapted SABR of central tumors.

Methods: SABR was delivered in eight fractions of 7.5 Gy to 63 such patients between 2003 and 2009. Of these, 37 patients had a tumor at a central hilar location, whereas 26 patients had tumors abutting the pericardium or mediastinal structures. Survival outcomes were compared with patients with peripheral tumors treated during the same time period using fewer fractions of SABR.

Results: Median follow-up was 35 months. Late grade III toxicity was limited to chest wall pain ($n = 2$) and increased dyspnoea ($n = 2$). No grade IV/V toxicity was observed, but grade V toxicity could not be excluded with certainty in nine patients who died of cardiopulmonary causes. Distant metastases were the predominant cause of death; cardiovascular deaths were not associated with a paracardial tumor location. No significant differences in outcomes were observed between these 63 patients and 445 other SABR patients treated for peripheral early-stage lung tumors. Three-year local control rates were 92.6% and 90.2% ($p = 0.9$). Three-year overall survival rates were 64.3% and 51.1% with median survival rates of 47 and 36 months, in favor of the group of patients with central tumors ($p = 0.09$).

Conclusions: Use of risk-adapted SABR delivered in eight fractions of 7.5 Gy did not result in excess toxicity for centrally located early-stage lung tumors, and clinical outcomes were comparable with those seen for peripheral lesions.

Key Words: Stereotactic radiotherapy, SABR, SBRT, Early stage lung cancer, Toxicity.

(*J Thorac Oncol.* 2011;6: 2036–2043)

Department of Radiation Oncology, VU University Medical Center, Amsterdam, The Netherlands.

Disclosure: Department of Radiation Oncology, VU University Medical Center has a Master Research Agreement with Varian Medical Systems. S.S., B.J.S., and F.J.L. have received speakers honoraria from Varian Medical Systems. C.J.A.H.: no financial disclosures.

Address for correspondence: Cornelis J. A. Haasbeek, MD, PhD, Department of Radiation Oncology, VU University Medical Center (VUMC), de Boelelaan 1117, Amsterdam 1081 HV, The Netherlands. E-mail: cja.haasbeek@vumc.nl

ISSN: 1556-0864/11/0612-2036

Non-small cell lung cancer (NSCLC) is the leading cause of cancer related mortality worldwide, with more than 1 million deaths every year.[1] Surgery is widely considered to be the treatment of choice in fit patients who present with early-stage disease.[2] In patients with significant comorbidity who are at increased risk of surgical morbidity and mortality, stereotactic body radiation therapy (SBRT), nowadays known as stereotactic ablative radiotherapy (SABR), is increasingly considered as a standard treatment alternative.[3–6] SABR is a form of high-precision radiotherapy, characterized by the use of extremely high biological doses of radiation delivered in a few fractions, usually between 3 and 8 in a 2- to 3-week period.[7]

Most available data on SABR outcomes has been derived from treating small, peripherally located early-stage lung tumors, where local control rates in excess of 85% were reported with very low toxicity.[8,9] Studies evaluating SABR for peripheral lesions have reported an incidence of total toxicities, both acute and late, of less than 10%.[4] Nevertheless, some reports of outcomes after treatment for centrally located lung tumors with SABR suggest cause for concern. One cited a 2-year freedom from severe toxicity of only 54% when SABR fraction doses ranging from 20 to 23 Gy were used.[10] Another group reported a 33% incidence of grades III to IV toxicity in nine patients with central tumors.[11]

The effect of radiation schedules can be recalculated and expressed as biologically effective dose (BED_{10} for tumor and BED_3 for normal tissues).[12] The total dose expressed as BED can be used to compare different dose schedules. Conventionally fractionated schedules typically use doses with a BED_{10} for tumor tissue of approximately 70 to 80 Gy. Modern SABR schedules use dose schedules equivalent to a BED_{10} of at least 100 to 105 Gy to achieve very high local control rates.[9,13] Achieving this BED_{10} without excessive toxicity for central tumors requires the use of lower doses per fraction, as fractionation relatively decreases the dose (BED_3) for normal tissues. Since 2003, we consistently applied such a "risk adapted" SABR approach using smaller fraction sizes for tumor locations that overlapped normal organs at risk for toxicity.[8] For target volumes overlapping the central hilus, heart, or mediastinal structures, we applied eight fractions of 7.5 Gy. The present report analyzes the clinical outcomes of this treatment schedule.

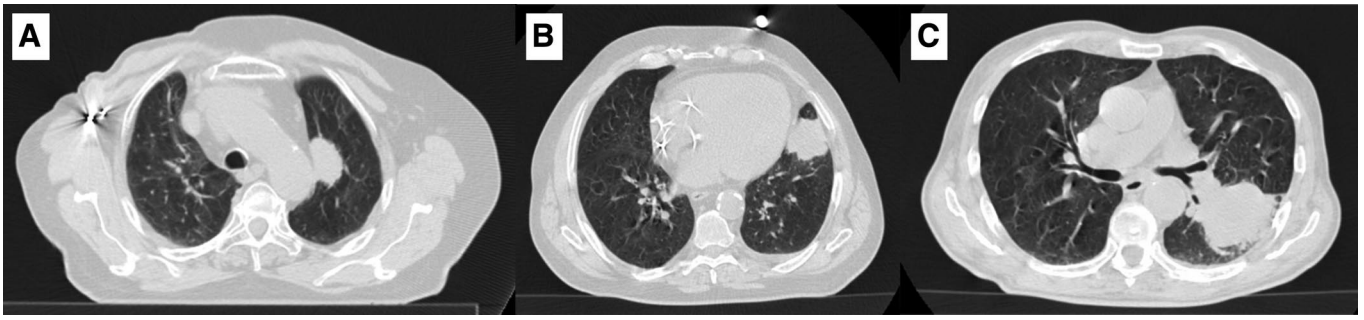

FIGURE 1. Patient examples with early-stage non-small cell lung cancer (NSCLC) in central tumor locations: (*A*) tumor adjacent to the aortic arch, (*B*) tumor adjacent to the left ventricle, and (*C*) tumor in a hilar location, extending to the chest wall. The patient in panel (*C*) is the patient who developed a rib fracture after treatment.

MATERIALS AND METHODS

Details of all SABR patients and treatments performed for early-stage NSCLC at the VU University Medical Center are entered into a prospective database. For this study, we evaluated patients with tumors in high-risk locations. Patients at "high risk" were defined by tumors (i) located in the proximal bronchial tree zone as defined by the Radiation Therapy Oncology Group[10,14] and/or (ii) located ≤1 cm from the heart or mediastinum (Figure 1). The proximal bronchial tree includes the carina, right and left main bronchi, right and left upper lobe bronchi, intermedius bronchus, right middle lobe bronchus, lingular bronchus, and right and left lower lobe bronchi; the proximal bronchial tree zone extends 2 cm in all directions. Patients in whom the planning target volume (PTV) overlapped with the esophagus were excluded from SABR. Tumors adjacent to the brachial plexus, for which this risk-adapted schedule was also applied, were excluded from the current analysis as plexopathy was not considered a potentially fatal complication.

A total of 63 patients fulfilled the inclusion criteria. Patients were treated between 2003 and 2009 and were all classified at that time as having stage I NSCLC using the Union for International Cancer Control tumor, node, metastasis classification version 6. In the recently introduced classification system version 7, 17 patients would currently be staged as stage II by tumor size exceeding 5 cm.[15] Patient characteristics are summarized in Table 1. Staging by ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) scan was performed in all patients to rule out regional and distant metastasis. Patients with suspected tumor-positive lymph nodes were not accepted for SABR treatment. Histological confirmation of the new primary lung tumor was obtained in 24 of 63 patients (38.1%). The diagnosis in other patients was made by a multidisciplinary tumor board based in all cases on a new or growing, FDG-PET-positive lesion with radiological characteristics of malignancy. Two previous prospective clinical trials in similar Dutch populations in our region,[16,17] as well as a single institution Dutch study,[18] revealed that the likelihood of a benign diagnosis with such a presentation was less than 5%. All patients were considered inoperable, and inoperability was assessed by a multidisciplinary tumor board, which often included a thoracic surgeon. Most patients had combinations of cardiac, pulmonary, and other comorbidities as reason for inoperability. The mean pre-SABR lung function, measured as the forced expiratory volume in 1 second, was 68.0% of predicted (range: 25–118%).

TABLE 1. Patient, Tumor, and Treatment Characteristics

Patients	63
Gender	Male: 42 (67%)
	Female: 21
Median age	74 (range: 47–87)
COPD GOLD score[a]	
No COPD	16 patients
I—mild	6
II—moderate	20
III—severe	19
IV—very severe	2
WHO performance score	
0	5 patients
I	38
II	19
III	1
Histology	24 patients
Squamous	8
Adeno	4
NSCLC not specified	12
No histology	39
Tumor diameter, median (range)	36 (15–74)
0–2 cm	5
>2–3 cm	12
>3–5 cm	29
>5–7 cm	15
>7 cm	2
PTV size, median (range)	43.6 ml (9.7–189.2 ml)
Fields (noncoplanar), median (range)	10 (7–11)

[a] The severity of chronic obstructive pulmonary disease (COPD) using the GOLD scoring system (http://goldcopd.com).

NSCLC, non-small cell lung cancer; PTV, planning target volume; WHO, World Health Organization.

4DCT Scanning Procedure

The 4DCT scanning procedure used at our center has been reported in detail previously.[19,20] Briefly, respiration-correlated 4DCT scans were performed during uncoached quiet respiration using the Real-Time Position Management system (RPM, Varian medical systems, Palo Alto, CA) and a

16-slice computed tomography (CT) scanner (Lightspeed 16 GE Medical Systems, Waukesha, WI). Data were acquired for each couch position for at least the duration of a full respiratory cycle. Retrospective sorting of the images into spatiotemporally coherent volumes was performed using Advantage 4D software (GE Medical Systems, Waukesha, WI). Each reconstructed image was assigned to a specific respiratory phase (or "bin"), resulting in 10 CT sets each reflecting 10% of the respiratory cycle.[21]

Generating Target Volumes

Internal target volume (ITV; ICRU 62) was delineated on a single maximum intensity projection CT set (MIP), which is derived from the 4DCT.[22] As an overlapping trajectory of the tumor with an adjacent high-density structure can lead to problems especially in centrally located tumors with overlapping bronchi, large blood vessels, and mediastinal structures, delineated MIPs were reviewed by projecting the ITV onto the other 4DCT bins or at least checked with the CT bins corresponding to the extreme inhale and exhale positions of the tumor. In difficult cases with overlapping hilar structures, a second 4DCT scan limited to the tumor area was performed after administration of intravenous contrast to facilitate delineation.[23] Isotropic margins of 3 mm were used to derive the PTV from the ITV. No separate margins were used to account for microscopic tumor extension.[7] Staging FDG-PET scans were not used for purposes of target delineation.

Dose Schemes and Treatment Delivery

All included patients were treated using a risk-adapted scheme of eight fractions of 7.5 Gy to a total dose of 60 Gy, prescribed at the 80% PTV encompassing isodose. At least 99% of the PTV volume was covered by the prescription isodose. Dose reductions of the PTV to spare overlapping critical structures were not used.

SABR was planned with Brainscan software (BrainLab AG, Heimstetten, Germany), and treatments were delivered using a Novalis linear accelerator using 7 to 11 (median 10) noncoplanar radiation beams with micromultileaf shielding. For patients reported in the current cohort, the ability to perform a conebeam CT with soft tissue setup was unavailable. Patient position was checked and corrected before each treatment fraction using orthogonal x-ray imaging devices integrated in the linear accelerator room (Exactrac system, Brainlab AG) and a Robotics treatment couch (Brainlab AG), which enables correction of both translational and rotational shifts.

Follow-Up

All patients underwent routine serial CT scans at 3, 6, and 12 months, followed by yearly CT scans thereafter.[8] FDG-PET scans were performed in case of suspected local, regional, or distant recurrence. If necessary, additional clinical follow-up information was obtained from the general practitioner and/or pulmonary physician. Complete survival data were obtained using Dutch civil records, which cover the entire Dutch population and contain all deaths since 1811.

Statistical Analysis

Statistical analysis was performed using SPSS 15.0.0 (SPSS Inc., Chicago, IL) and Microsoft Office Excel 2003 (Microsoft Corp., Redmond, WA) software. Survival was calculated from the date of first SABR treatment.

Comparison with Peripheral Tumors

The survival outcomes of patients with central tumors were compared with the group of patients with peripheral tumors treated by SABR in our institute in the same period of time with identical treatment techniques except for the used dose schedules. Peripheral tumors were treated to three fractions of 20 Gy for T1 tumors; patients were treated to five fractions of 12 Gy for T2 tumors and for T1 tumors directly adjacent to the chest wall.

RESULTS

Sixty-three patients had tumors located in a high-risk location. Thirty-seven tumors were located in a hilar, central location within 2 cm of the proximal bronchial tree. The remaining 26 patients who had tumors located outside the region of the proximal bronchial tree were nevertheless considered to be at high risk due to overlap with other high-risk mediastinal structures (Table 2).

Early Toxicity

Fifty-six patients (89%) reported no or grade I toxicity (CTCAE V3.0); six patients (10%) reported grade II toxicity, and only one patient (2%) reported grade III acute toxicity (Table 3). The patient with grade III symptoms required temporary treatment for nonspecific chest wall pain with opioids, despite the fact that the tumor did not extend to the chest wall, and the high-dose regions were not in the chest wall.

Late Toxicity

Fifty patients (79%) reported no or grade I late toxicity (≥3 months after treatment); nine patients (14%) reported grade II toxicity, and four patients (6%) reported grade III toxicity (Table 3). One patient presenting with grade II toxicity had a bronchial stenosis with atelectasis and symptomatic cough 3.5 years after treatment. No evidence for tumor recurrence was found at bronchoscopy and on a FDG-PET, and no medical intervention was indicated in this patient. In two patients, grade III toxicity manifested due to increased dyspnea, one patient had a rib fracture and one

TABLE 2. Tumor Location

Tumor Location[a]	No. of Patients
Proximal bronchial tree	37
Pericardium	11
Overlap other mediastinal structures	15
Aorta	6
Near esophagus	2
Other	7

[a] Many tumors are near multiple structures. The area with predominant overlap was chosen as primary location.

TABLE 3. Early and Late Toxicity After SABR in 63 Patients with Central Stage Early-Stage NSCLC (Absolute Patient Numbers)

	Acute Toxicity			Late Toxicity (>3 mo)		
	I	II	III	I	II	III
Dyspnea	5	2	—	3	2	2
Chest wall pain	3	1	1	4	2	1
Fatigue	10	1	—	4	1	—
Coughing	5	—	—	—	—	—
Nausea	3	—	—	—	—	—
Radiation dermatitis	1	1	—	—	1	—
Hemoptysis	1	1	—	—	1	—
Esophagitis	1	—	—	—	—	—
Pleural effusion	—	—	—	—	1	—
Rib fracture	—	—	—	—	—	1
Bronchial stenosis	—	—	—	—	1	—
Total (% of patients)	29 (62)	6 (10)	1 (2)	11 (17)	9 (14)	4 (6)

SABR, stereotactic ablative radiotherapy; NSCLC, non-small cell lung cancer.

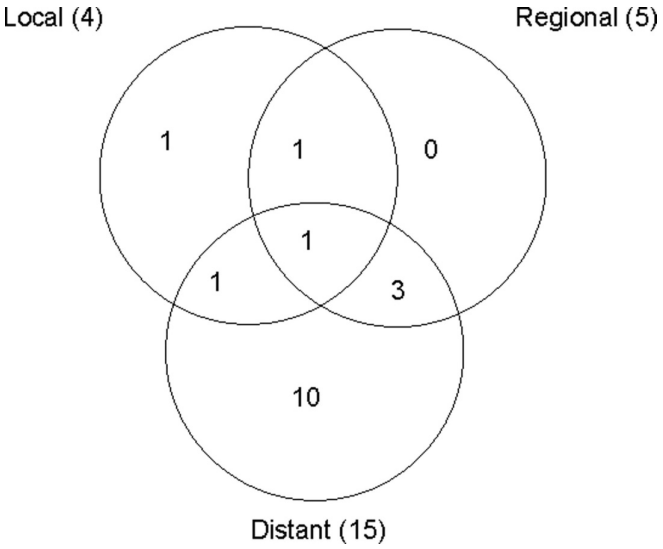

FIGURE 2. Local, regional, and distant failure rates for central early-stage lung tumors after stereotactic ablative radiotherapy (SABR).

presented with nonspecific chest wall pain. The latter is same patient who developed early grade III chest wall pain. Three patients with grade III toxicity had tumors below the median tumor size (36 mm), and the patient with the rib fracture had a tumor with a diameter of 7 cm extending from the central hilus up to the chest wall (Figure 1). No grade IV or clear grade V toxicity was observed.

Cause of Death

Thirty-nine of the 63 patients (62%) were still alive at time of analysis. Of the 24 patients who had died, 14 patients died of tumor progression, and one patient died of acquired immune deficiency syndrome-related complications. The remaining nine patients died at a median age of 79 years, and their deaths were attributed by their physician to cardiac events (five patients), respiratory failure (three patients), or unknown (one patient). Causes of death were not related to tumor location. Of five patients who died of possible cardiac failure, one had a target volume overlapping the pericardium, three were located in the proximal bronchial tree zone, and one was located against the upper mediastinum but not adjacent to the heart muscle or coronary vessels. The only patient who died of a cardiac cause and had overlap with the pericardium had chronic atrial fibrillation and a severe pretreatment aortic valve stenosis. His planned aortic valve replacement was postponed because of his lung cancer until his death almost 2.5 years after SABR. In the three patients who died of possible respiratory failure, only one tumor was located in the hilus, one was located next to the ascending aorta, and one next to the descending aorta. The pretreatment pulmonary function of these patients was comparable with the other patients. The patient with an unknown cause of death had a tumor located near the right hilus in the proximal bronchial tree zone.

Survival Outcomes

For the 63 patients with central tumors, 1, 2- and 5-year overall survival rates were 85.7%, 69.0%, and 49.5%, respectively. Four local failures were observed resulting in actuarial local control rates at 1, 2, and 5 years of 94.8%, 92.6%, and 92.6%, respectively. All four patients with local failure had a tumor diameter exceeding 3 cm. Only one patient had a suspected isolated local recurrence, the other three patients also had regional or distant metastases (Figure 2). The suspected local recurrence in the single patient with an isolated local recurrence was based on a growing lesion at CT investigation. Nevertheless, this patient died of respiratory insufficiency without further investigations being performed, or pathological proof of recurrence, 6 months later at the age of 84 years.

Five regional failures were seen, resulting in actuarial regional control rates at 1, 2, and 5 years of 93.0%, 91.1%, and 91.1%, respectively. No isolated regional recurrences were observed. Fifteen patients had distant failure, with actuarial distant control rates at 1, 2, and 5 years of 85.7%, 76.0%, and 72.7%, respectively. Disease-free survival rates at 1, 2, and 5 years were 82.3%, 74.3%, and 71.0%, respectively. Univariate analysis of possible predictive factors for overall survival showed improved survival for women, with 2-year overall survival of 79.6% versus 34.8% for men ($p = 0.045$). All other studied predictive factors and outcome measures (proof of malignancy, T stage, tumor location, GOLD class, comorbidity scores, World Health Organization performance score, and earlier malignancies) did not show significant correlations, although the lack of histological proof of malignancy showed a trend toward inferior disease-free survival.

Comparison with Peripheral Tumors Treated with SABR

Clinical outcomes of the 63 patients with central tumors were compared with 445 patients with peripheral early-stage lung tumors. The median follow-up was 35 months for both groups (range: 13–86 months). Both groups were well bal-

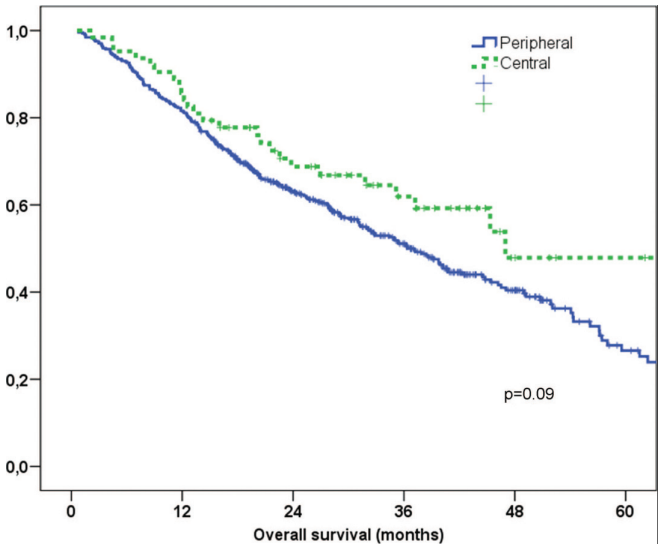

FIGURE 3. Overall survival for central and peripheral early-stage lung tumors after stereotactic ablative radiotherapy (SABR).

anced regarding gender, age, GOLD class, proof of malignancy, and World Health Organization performance scores. Median tumor diameter was larger for the central tumor group (median: 36 mm versus 26 mm; $p < 0.001$). No significant differences were observed in survival outcomes between the 63 patients with central and the 445 patients with peripheral tumors (Figure 3). The 3-year overall survival rates for patients with central versus peripheral tumors were 64.3% and 51.1%, with median survival rates of 47 and 36 months, respectively ($p = 0.09$). Three-year local control rates were 92.6% and 90.2% ($p = 0.9$), regional control 91.1% and 86.2% ($p = 0.47$), distant control 72.7% and 75.2% ($p = 0.72$), and 3-year disease-free survival rates were 69.9% and 67.8% ($p = 0.91$), respectively.

DISCUSSION

The treatment of patients with early stage, centrally located lung tumors who are unfit for surgery is challenging. Outcomes of conventional radiotherapy are poor due to high rates of local failure, but the use of SABR for centrally located tumors has been reported to be associated with increased toxicity when the SABR schedules commonly used for peripheral tumors were applied.[10] Nevertheless, the available data on SABR for centrally located tumors has largely been limited to small series with generally limited follow-up (summarized in Table 4), and most of these series consist of a mix of patients with NSCLC in central and peripheral locations, or patients with centrally located pulmonary metastasis, without reporting separate data for central lung tumors. Our present report on long-term results in 63 patients with early-stage NSCLC using a standardized schedule of 60 Gy in eight fractions, represents the largest such report to date. Our main conclusion is that SABR can achieve cures in patients with central, high-risk tumors with a low incidence of high-grade toxicity.

The relatively high local control rates and low toxicity observed in our series is consistent with the known relationships between local control, toxicity and biological effective doses (BED) as shown in Figure 4. The data were extrapolated from the published series summarized in Table 4. Despite the small patient numbers, Figure 4*A* reveals the same trend toward higher local control at higher BEDs as was reported for peripheral tumors, with local control rates more than 90% using schedules with a BED_{10} above 100 Gy. The BED_{10} of our 60 Gy in eight fraction schedule is equivalent to 105 Gy for tumor tissue. Figure 4*B* shows the trend toward higher toxicity rates at higher doses. The BED_3 for normal tissue in our series was 210 Gy, equivalent to 126 Gy in 2 Gy fractions, which is at the low end of the fractionation schedules reported in the literature.

In a group of 22 patients, Timmerman et al.[10] reported an actuarial 2-year severe toxicity rate of 46% for centrally located primary lung tumors. Nevertheless, these authors used an estimated BED_{10} far in excess of the approximately 100 Gy required for local control in early-stage NSCLC,[9,12,24] as 60 to 66 Gy was delivered in three fractions (BED_{10} = 180–211 Gy for tumor; BED_3 460–550 Gy for normal tissue). If one assumes that the linear-quadratic model for BED calculation is appropriate for high fraction doses, these schedules were equivalent to more than 275 Gy in 2 Gy fractions for normal tissue, which is more than twice that delivered in our eight-fraction schedule. Nevertheless, a subsequent publication by the same authors with longer follow-up, reported no statistically significant differences in toxicity between central and peripheral tumors, and an identical survival for the group of 22 central tumors to their group of patients with peripheral tumors.[25]

Song et al.[11] also reported increased toxicity when treating central tumor locations with a short schedule of three to four fractions on consecutive days. Grades III to V toxicity was seen in three of nine patients, and eight of nine patients had radiological evidence of partial or complete bronchial strictures after a median time of 20 months. One patient died after an intervention for a complete bronchial stenosis. Nevertheless, no significant location-dependent differences in overall survival were found, with a 2-year overall survival rate of 50% versus 35%, in favor of the group of patients with central tumors. In the series reported by Bral et al.,[26] one patient with a central lesion died after an intervention for a bronchial stenosis, which suggests that invasive procedures in highly irradiated bronchial tissues after SABR carries an increased risk of toxicity.

Our study found low levels of grade III, no grade IV, and no clear grade V toxicity. We only saw one grade II bronchial stricture, and no intervention was needed. Nevertheless, nine patients died of cardiac or pulmonary causes without tumor progression. Although we could not relate tumor location to the probable cause of death, we cannot completely exclude grade V toxicity as cause of death in these nine patients. Had the use of SABR for central lesions been as dangerous as was suggested previously, the resulting median survival in patients with central tumors after SABR would be expected to be much lower than for patients with

TABLE 4. Published Data on Local Control and Toxicity in Centrally Located Stage Early-Stage Lung Tumors

Author	Year	Central Stage I NSCLC	Central Other[a]	Location Peripheral	FU (mo)	Schedules	BED Tumor	Local Control	BED Normal	Toxicity > Grade III	OS
Joyner[32]	2006	1	8	99	10.6[b]	36/3	79	100[b]	180	1 grade III: 1 bronchial stenosis in metastasis patient	NR
Milano[33]	2009	7	46	—	28[b]	Wide range, most common 40/10	Most common schedule: 56	1 yr: 84[b]; 2 yr: 73[b]	Most common schedule: 93	1 grade III pneumonia (no pneumonitis)	2 yr: 72
Onimaru[34]	2003	[c]/9	[c]/9	48	NR	48/8	57	3 yr: 69.6[b]	100	1 grade V Esophagitis in metastasis patient; No other toxicity	2 yr: 41.5
Song et al.[11]	2009	9	—	23	27[b]	40/4	80	2 yr: 88.9	173	8/9 radiological strictures	2 yr: 50
						48/4	106		240	2 grades III–IV obstructive pneumonia (40 Gy/4)	
						60/3	180		460	1 grade V bronchial stricture (48 Gy/4)	
Xia[35]	2006	[c]/9	[c]/9	34	NR	50/10	75[d]	3 yr: 96[b]	133	No severe toxicity	2 and 3 yr: 91[b]
Chang[36]	2008	[c]/13	[c]/27	—	17[b]	40/4	80	57[e]	173	Dermatitis/pain grades II–III in 3 patients[b]	NR
						50/4	113	100	258		
Zimmerman[37]	2006	16	—	52	17[b]	Range most common 35/5	60	3 yr: 88[b]	117	1 grade III pneumonitis[b]	2 yr: 71; 3 yr: 51[b]
Bral et al.[26]	2011	17	—	23	16[b]	60/4	150	1 local failure	360	8 grade >2 pneumonitis[b]; Including 1 grade V bronchial stenosis	2 yr: 52[b]
Fakiris et al. and Timmerman et al.[10,25]	2009	22	—	48	50[b]	60/3	180	2 yr: 95[b]	460	6 grades III–V (central)	3 yr: 43
						66/3	211	3 yr: 88[b]	550	5 possible grade 5[b]	
Nuyttens[f][38]	2010	38	20	—	15[b]	Range: most common 60/5	132	2 yr: 93[b]	300	No severe toxicity	2 yr: 55
Present study	2011	63	—	—	34	60/8	105	2 yr: 93; 3 yr: 93	210	2 grade III chest wall pain; 2 grade III dyspnea	3 yr: 65

As most series also include noncentral tumors and metastasis, data for centrally located stage early-stage lung tumors have been extracted where possible.
[a] Central other: metastasis, recurrent NSCLC, stages II to III NSCLC, or near plexus/vertebral body.
[b] Data for whole group, including noncentral or nonstage I patients with NSCLC.
[c] Unclear, not fully reported.
[d] Gamma-knife system, dose prescribed at 50%: BED for tumor at isocenter is 200 Gy.
[e] Crude number: three of seven patients treated to 40 Gy had local recurrences.
[f] Abstract only.
NR, not reported; NSCLC, non-small cell lung cancer; BED, biologically effective dose; OS, overall survival.

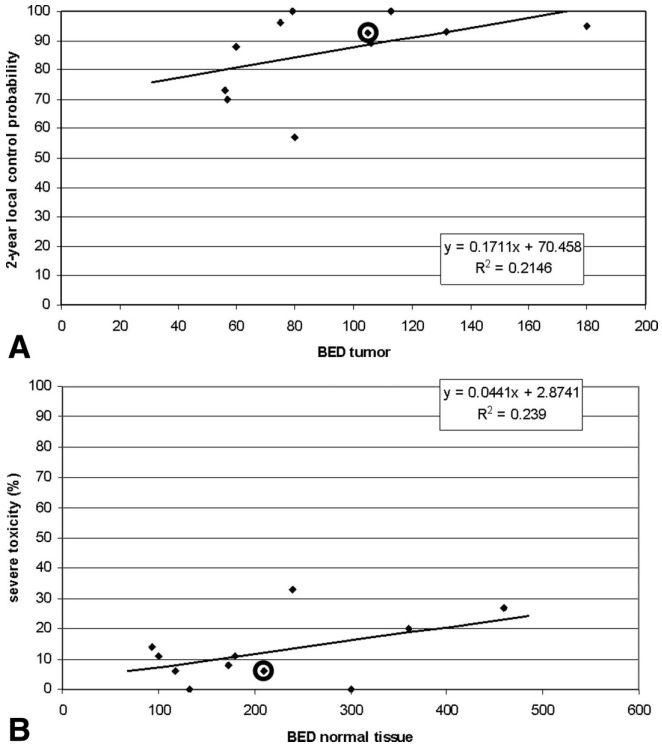

FIGURE 4. Biological effective doses (BED) tumor (α/β = 10) versus 2-year local control probability (*A*), and BED normal tissue (α/β = 3) versus severe toxicity (*B*), data derived from Table 4; present study marked by circle. BED, biologically effective dose; BED = D (1 + d/(α/β)), where D is total dose, d is dose per fraction, and the α/β ratio is assumed to be 10 for tumor tissue and 3 for normal tissues.

peripheral tumors. When comparing our results for central tumors with that seen for 445 SABR patients treated in the same time period for peripheral tumors in our institute, no survival decrease was seen for patients treated for central tumors (Figure 3). These findings are reassuring, particularly in the light of comparable SABR results from peripheral tumors in 13 reports using BED values above 100 Gy.[27] The survival observed in our patients with central tumors is higher than in 9 of 13 of these series in the review, with only the four Japanese series reporting higher survival rates.

Dose-dependent late bronchial, cardiac, and esophageal toxicity has been reported after conventionally fractionated high-dose radiotherapy or chemoradiotherapy for lung tumors.[28,29] The toxicity risk after SABR in our series is acceptable at a median follow-up of 35 months, but we acknowledge that late bronchial stenosis or cardiac problem might still arise after even longer follow-up. Nevertheless, medically inoperable patients with centrally located tumors have few alternative treatment options. In addition, the results have to be viewed in the light of the alternative scenarios, specifically the surgical mortality of centrally located lung cancer of up to 10% for pneumonectomies,[30] the unacceptable death rate from tumor progression after conventional radiotherapy,[31] or no curative treatment.

A shortcoming of this study, and most studies in SABR literature, is the lack of histological proof of malignancy in a majority of patients, although surgical series show that the chance of treating benign disease in the Netherlands is below 5% as pointed out earlier.[16–18] Our study population reflects current clinical practice where pathological proof is preferred but not obtained at all costs in our frail, inoperable patient groups. This issue is important in areas with a higher prevalence of benign disease and will become extra important in future when more very small lesions will be detected by screening. As routine screening has not yet been implemented in the Netherlands, the smallest lesion in our series was 15 mm.

Safety data from our study indicate that SABR should continue to be evaluated for centrally located tumors using optimal 4DCT-based treatment planning and delivery, in conjunction with schemes with a BED_{10} for tumor of around 100 to 110 Gy, and a relatively low BED_3 for normal tissues. The Radiation Therapy Oncology Group 0813 study is currently accruing patients with central, pathology-proven early-stage lung tumors in a dose escalation approach and will take several years to accrue and attain long enough follow-up to estimate long-term toxicity. The European Organization for Research and Treatment of Cancer is also planning a similar study including pathology-proven central tumors, based on the preliminary results of this study. A recent population-based study indicates that an increasing number of elderly, unfit patients are referred for potentially curative SABR therapy than when only conventional radiotherapy is available.[6] The growing experience with SABR for central tumors can also be expected to lead to further improvements in population-based survivals in early-stage lung cancer.

CONCLUSIONS

In medically inoperable patients with a centrally located early-stage lung cancer, the use of risk-adapted stereotactic radiation therapy using a dose scheme of eight fractions of 7.5 Gy is an effective treatment with acceptable toxicity.

REFERENCES

1. Parkin DM. Global cancer statistics in the year 2000. *Lancet Oncol* 2001;2:533–543.
2. Crino L, Weder W, van Meerbeeck J, et al. Early stage and locally advanced (non-metastatic) non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010;21:v103–v115.
3. Haasbeek CJ, Senan S, Smit EF, et al. Critical review of nonsurgical treatment options for stage I non-small cell lung cancer. *Oncologist* 2008;13:309–319.
4. Chi A, Liao Z, Nguyen NP, et al. Systemic review of the patterns of failure following stereotactic body radiation therapy in early-stage non-small-cell lung cancer: clinical implications. *Radiother Oncol* 2010;94: 1–11.
5. Palma D, Senan S. Stereotactic radiation therapy: changing treatment paradigms for stage I nonsmall cell lung cancer. *Curr Opin Oncol* 2011;23:133–139.
6. Palma D, Visser O, Lagerwaard FJ, et al. Impact of introducing stereotactic lung radiotherapy for elderly patients with stage I non-small-cell lung cancer: a population-based time-trend analysis. *J Clin Oncol* 2010;28:5153–5159.
7. Potters L, Steinberg M, Rose C, et al. American Society for Therapeutic Radiology and Oncology and American College of Radiology practice

guideline for the performance of stereotactic body radiation therapy. *Int J Radiat Oncol Biol Phys* 2004;60:1026–1032.
8. Lagerwaard FJ, Haasbeek CJ, Smit EF, et al. Outcomes of risk-adapted fractionated stereotactic radiotherapy for stage I non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2008;70:685–692.
9. Onishi H, Shirato H, Nagata Y, et al. Hypofractionated stereotactic radiotherapy (HypoFXSRT) for stage I non-small cell lung cancer: updated results of 257 patients in a Japanese multi-institutional study. *J Thorac Oncol* 2007;2:S94–S100.
10. Timmerman R, McGarry R, Yiannoutsos C, et al. Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. *J Clin Oncol* 2006;24:4833–4839.
11. Song SY, Choi W, Shin SS, et al. Fractionated stereotactic body radiation therapy for medically inoperable stage I lung cancer adjacent to central large bronchus. *Lung Cancer* 2009;66:89–93.
12. Fowler JF, Tome WA, Fenwick JD, et al. A challenge to traditional radiation oncology. *Int J Radiat Oncol Biol Phys* 2004;60:1241–1256.
13. Kestin LL, Grills IS, Guckenberger M, et al. Substantial dose-response relationship with clinical outcome for lung stereotactic body radiotherapy (SBRT) delivered via online image guidance. *Int J Radiat Oncol Biol Phys* 2010;78:S14.
14. Kong FM, Ritter T, Quint DJ, et al. Consideration of dose limits for organs at risk of thoracic radiotherapy: atlas for lung, proximal bronchial tree, esophagus, spinal cord, ribs, and brachial plexus. *Int J Radiat Oncol Biol Phys* [published ahead of print October 7, 2010] doi:10.1016/j.ijrobp.2010.07.1977.
15. Goldstraw P. The 7th edition of TNM in lung cancer: what now? *J Thorac Oncol* 2009;4:671–673.
16. van Tinteren H, Hoekstra OS, Smit EF, et al. Effectiveness of positron emission tomography in the preoperative assessment of patients with suspected non-small-cell lung cancer: the PLUS multicentre randomised trial. *Lancet* 2002;359:1388–1393.
17. Herder GJ, Kramer H, Hoekstra OS, et al. Traditional versus up-front [18F] fluorodeoxyglucose-positron emission tomography staging of non-small-cell lung cancer: a Dutch cooperative randomized study. *J Clin Oncol* 2006;24:1800–1806.
18. Belgers EH, Siebenga J, Bosch AM, et al. Complete video-assisted thoracoscopic surgery lobectomy and its learning curve. A single center study introducing the technique in The Netherlands. *Interact Cardiovasc Thorac Surg* 2010;10:176–180.
19. Slotman BJ, Lagerwaard FJ, Senan S. 4D imaging for target definition in stereotactic radiotherapy for lung cancer. *Acta Oncol* 2006;45:966–972.
20. Underberg RW, Lagerwaard FJ, Slotman BJ, et al. Use of maximum intensity projections (MIP) for target volume generation in 4DCT scans for lung cancer. *Int J Radiat Oncol Biol Phys* 2005;63:253–260.
21. Rietzel E, Pan T, Chen GT. Four-dimensional computed tomography: image formation and clinical protocol. *Med Phys* 2005;32:874–889.
22. Underberg RW, Lagerwaard FJ, Slotman BJ, et al. Benefit of respiration-gated stereotactic radiotherapy for stage I lung cancer: an analysis of 4DCT datasets. *Int J Radiat Oncol Biol Phys* 2005;62:554–560.
23. Beddar AS, Briere TM, Balter P, et al. 4D-CT imaging with synchronized intravenous contrast injection to improve delineation of liver tumors for treatment planning. *Radiother Oncol* 2008;87:445–448.
24. Wulf J, Baier K, Mueller G, et al. Dose-response in stereotactic irradiation of lung tumors. *Radiother Oncol* 2005;77:83–87.
25. Fakiris AJ, McGarry RC, Yiannoutsos CT, et al. Stereotactic body radiation therapy for early-stage non-small-cell lung carcinoma: four-year results of a prospective phase II study. *Int J Radiat Oncol Biol Phys* 2009;75:677–682.
26. Bral S, Gevaert T, Linthout N, et al. Prospective, risk-adapted strategy of stereotactic body radiotherapy for early-stage non-small-cell lung cancer: results of a phase II trial. *Int J Radiat Oncol Biol Phys* 2011;80:1343–1349.
27. Nguyen NP, Garland L, Welsh J, et al. Can stereotactic fractionated radiation therapy become the standard of care for early stage non-small cell lung carcinoma. *Cancer Treatment Rev* 2008;34:719–727.
28. Miller KL, Shafman TD, Anscher MS, et al. Bronchial stenosis: an underreported complication of high-dose external beam radiotherapy for lung cancer? *Int J Radiat Oncol Biol Phys* 2005;61:64–69.
29. Stripp D, Glatstein E. The good, the bad, and the ugly. *Int J Radiat Oncol Biol Phys* 2005;61:3–4.
30. Damhuis R, Coonar A, Plaisier P, et al. A case-mix model for monitoring of postoperative mortality after surgery for lung cancer. *Lung Cancer* 2006;51:123–129.
31. Arriagada R, Le CT, Quoix E, et al. ASTRO (American Society for Therapeutic Radiology and Oncology) plenary: effect of chemotherapy on locally advanced non-small cell lung carcinoma: a randomized study of 353 patients. GETCB (Groupe d'Etude et Traitement des Cancers Bronchiques), FNCLCC (Federation Nationale des Centres de Lutte contre le Cancer) and the CEBI trialists. *Int J Radiat Oncol Biol Phys* 1991;20:1183–1190.
32. Joyner M, Salter BJ, Papanikolaou N, et al. Stereotactic body radiation therapy for centrally located lung lesions. *Acta Oncol* 2006;45:802–807.
33. Milano MT, Chen Y, Katz AW, et al. Central thoracic lesions treated with hypofractionated stereotactic body radiotherapy. *Radiother Oncol* 2009;91:301–306.
34. Onimaru R, Shirato H, Shimizu S, et al. Tolerance of organs at risk in small-volume, hypofractionated, image-guided radiotherapy for primary and metastatic lung cancers. *Int J Radiat Oncol Biol Phys* 2003;56:126–135.
35. Xia T, Li H, Sun Q, et al. Promising clinical outcome of stereotactic body radiation therapy for patients with inoperable Stage I/II non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2006;66:117–125.
36. Chang JY, Balter PA, Dong L, et al. Stereotactic body radiation therapy in centrally and superiorly located stage I or isolated recurrent non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2008;72:967–971.
37. Zimmermann FB, Geinitz H, Schill S, et al. Stereotactic hypofractionated radiotherapy in stage I (T1-2 N0 M0) non-small-cell lung cancer (NSCLC). *Acta Oncol* 2006;45:796–801.
38. Nuyttens J, Van der Voort van Zyp N, Hoogeman M, et al. Outcome of four-dimensional stereotactic radiotherapy for centrally located lung tumors. *Radiother Oncol* 2010;96:S132–S133; Supplement 1.

