ORIGINAL ARTICLE

Use of Stereotactic Ablative Radiotherapy (SABR) in Non–Small Cell Lung Cancer Measuring More Than 5 cm

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ABSTRACT

Introduction: Stereotactic ablative radiotherapy (SABR) is currently not the guideline-recommended treatment for lung tumors measuring more than 5 cm. However, improvements in radiotherapy techniques have led to increasing use of SABR for larger tumors.

Methods: We analyzed the clinical outcomes in patients with a primary or recurrent NSCLC measuring more than 5 cm and treated with five or eight fractions of SABR at our center. Patients who had prior thoracic radiotherapy were excluded.

Results: A total of 63 consecutive patients with a median tumor diameter of 5.8 cm (range 5.1–10.4) were identified; 81% had T2N0 disease and 18% had T3N0 disease. The median Charlson comorbidity index was 2 (range 0–6). After a median follow-up of 54.7 months, median survival was 28.3 months. Disease-free survival at 2 years was 82.1%, and the local, regional, and distant control rates at 2 years were 95.8%, 93.7%, and 83.6%, respectively. An out-of-field distant recurrence at one or more sites was the most common pattern of failure (10%). Grade 3 or higher toxicity was recorded in 30% of patients, with radiation pneumonitis being the most common toxicity (19%). A likely (n = 4) or possible (n = 8) treatment-related death was scored in 19% of patients. There was preexisting interstitial lung disease in eight patients (13%), with fatal toxicity developing in five of them (63%).

Conclusions: Lung SABR in tumors larger than 5 cm resulted in high local control rates and acceptable survival outcomes in a patient population with appreciable comorbidity. Patients with interstitial lung disease should be considered a very high-risk population for SABR.

Keywords: NSCLC; SABR; Toxicity; Outcomes; Stage II; Large tumors

Introduction

The current guidelines of the European Society for Medical Oncology recommend stereotactic ablative radiotherapy (SABR) as the treatment of choice in patients presenting with peripheral stage I NSCLC who are medically inoperable or decline an operation.[1] Clinical trials of SABR have generally excluded lung tumors with a diameter exceeding 5 to 6 cm.[2–4] Because of the limited data available on toxicity of SABR, conventional radical radiotherapy schemes have been recommended by the European Society for Medical Oncology for lesions larger than 5 cm.[1,5–8]

Lung SABR was introduced at our institution in 2003, with good disease control and limited treatment toxicity reported.[9–11] Improvements in treatment planning and delivery have enabled better sparing of normal organs, leading to an increased use of SABR for tumors exceeding 5 cm.[12] A recent report on outcomes in 40 such tumors reported little toxicity, and failures mainly due to distant metastases, although the median follow-up was only 10 months.[5] Surgical data also indicate a higher risk for distant progression for larger tumors, as reflected in the eighth edition of the TNM, according to

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which tumors larger than 5 cm and 7 cm are classified as T3 and T4, respectively.[13]

As the available literature is limited, we retrospectively analyzed our institutional long-term outcomes in patients with primary or recurrent NSCLC measuring more than 5 cm in diameter that were treated with SABR delivered in five or eight fractions.

Material and Methods

Patient Selection and Definitions

All patients presenting with nonmetastatic lung cancer are discussed at a multidisciplinary tumor board. Our institutional SABR protocol was introduced in 2003 and specifies use of three risk-adapted SABR schemes based on tumor size and location.[9] Patients with peripheral tumors and an internal target volume (ITV) of 3 cm or less are treated with three fractions of 18 Gy. When there is broad contact with the chest wall or when the ITV diameter is between 3 and 7 cm, patients usually receive a scheme of five fractions of 11 Gy. The dose delivered per fraction for the three-fraction regimen was 20 Gy, and for the five-fraction schedule it was 12 Gy before the introduction of more advanced heterogeneity correction algorithms.[14] So-called moderately central tumors adjacent to and/or with minimal overlap with organs at risk are generally treated with eight fractions.[10] The eight-fraction schedule has consistently remained at 7.5 Gy per fraction. SABR was not considered contraindicated in tumors larger than 5 cm at our institution. In recent years, however, we have used a hypofractionated scheme to deliver 12 fractions of 5 Gy over 3 weeks in selected patients with tumors (or an ITV) more than 6 cm in diameter and/or tumors (or a PTV) significantly overlapping the central structures. For the five-fraction schedule, SABR was delivered in 2 weeks (every other day), and for the eight-fraction scheme, it was delivered in 2.5 weeks (using three or four fractions per week).

Our institutional database was queried to identify consecutive patients with a primary or recurrent NSCLC who were treated using five or eight fractions between April 2003 and December 2014. Patients who had prior thoracic radiotherapy and/or simultaneous treatment for other lung tumors were excluded. The maximum tumor diameter in the axial, transversal, or sagittal planes was measured on lung window–level settings in the end-inspiratory phase of the 10-phase free-breathing four-dimensional planning computed tomography (CT) scan. A second physician randomly checked the measurements of the first observer. If required, diagnostic scans were used. Tumors with a diameter larger than 5 cm were selected for further analysis. Where necessary, the disease stage was reclassified according to the seventh version of the TNM classification by using pretreatment clinical information and imaging. In the Netherlands, approval from the medical ethics board is not required for retrospective studies of patient records.

Treatment Planning and Delivery

The treatment planning and delivery techniques used have previously been described.[15,16] A free-breathing 10-phase four-dimensional CT scan was consistently used to identify the ITV, with dose calculation performed on the average intensity projection. Between 2003 and 2008, SABR was delivered by using eight to 12 noncoplanar static conformal beams and stereoscopic radiographic image guidance, with a 3-mm planning target volume (PTV) margin added to the ITV. Volumetric modulated arc therapy (RapidArc [Varian Medical Systems, Palo Alto, CA]) was introduced in 2008 with online cone-beam CT– based positioning by using the tumor and a 5-mm ITV-PTV margin. At least 95% of the PTV had to receive the prescribed dose, and an inhomogeneous dose distribution with a maximum up to 140% of the prescribed dose was accepted. Since 2009, treatment planning has emphasized preferential sparing of the contralateral lung.[17,18]

Clinical Outcomes

Patients were generally followed up at 3, 6, 12, 18, and 24 months after treatment and yearly thereafter. Clinical data from hospital records, referring physicians, and general practitioners were used to evaluate clinical outcomes. All cases with potential severe toxicity (i.e., grade 3 [G3] or higher) were evaluated by a clinical panel consisting of three clinicians using the Common Terminology Criteria for Adverse Events, version 4.03; the evaluation was consensus based. Potential fatal toxicity was subclassified as *possibly* (when no other likely cause of death was identified and if a treatment-related cause could not be excluded) or *likely* (when the cause of death was considered radiation related) treatment related. A local failure was defined as a recurrence in or adjacent to the PTV. As recent data indicated that patients with coexisting interstitial lung disease (ILD) are at increased risk for high-grade pneumonitis,[19] a pulmonologist specialized in ILD retrospectively evaluated the pretreatment images of all patients and classified preexisting radiological ILD according to the current American Thoracic Society/European Respiratory Society guidelines.[20] The same pulmonologist scored the presence of emphysema, which was quantified by using a three-point scale as follows. Mild emphysema was defined by the presence of subtle centrilobular emphysema in apical segments of upper lobes; moderate emphysema was defined by a

Table 1. Baseline Patient and Treatment Characteristics (N = 63)

Patient Characteristics	n (%) or Median (Range)
Age at presentation for SABR, y	78 (49-92)
WHO performance status	
0/1	10 (16%)/31 (49%)
2/3	18 (29%)/4 (6%)
Age-adjusted Charlson comorbidity index	5 (1-10)
1-3	9 (14%)
4-5	23 (37%)
6-7	19 (30%)
8-10	12 (19%)
History of COPD	45 (71%)
GOLD status, I/II	11 (18%)/19 (30%)
GOLD status III/IV	12 (19%)/3 (5%)
Predicted FEV_1 before treatment[a], %	69 (25-177)
Current or former smoker	57 (91%)
Reasons for choice of SABR[b]	
Patient refusal	6 (10%)
Comorbidity	38 (60%)
Pulmonary	23 (37%)
Cardiovascular	11 (17%)
General condition (including age)	15 (24%)
Prior lung surgery[c]	3 (5%)
Pathological diagnosis of malignancy obtained	42 (67%)
Adenocarcinoma	11 (17%)
Squamous cell carcinoma	19 (30%)
Neuroendocrine carcinoma	1 (2%)
NSCLC NOS	10 (16%)
Squamous dysplasia suggestive of squamous cell carcinoma	1 (2%)
Disease stage (TNM classification, seventh edition)	
T2bN0M0 (stage IIA)	51 (81%)
T3N0M0 (stage IIB)	11 (18%)
Recurrent NSCLC	1 (2%)
Median tumor diameter (range), cm	5.8 (5.1-10.4)
Prior nonlung malignancy	12 (19%)
Any prior treatment for same lesion	1 (2%)
Prior lung surgery	6 (10%)
Chemotherapy after SABR[d]	1 (2%)
Thoracic irradiation after SABR	3 (5%)
Treatment characteristics	
PTV, cm^3	135.5 (47.0-290.6)
Dosimetric details	
PTV coverage	
≥95% of PTV received at least the prescription dose	63 (100%)
≥99% of PTV received ≥90% of the prescription dose	57 (90%)
Dose maximum within PTV	
≥110% of the prescription dose	62 (98%)
≤140% of the prescription dose	60 (95%)

[a]In six patients, there was no information available about the predicted FEV_1 value.
[b]More than one reason was present in some patients.
[c]Patients had a history of prior bilobectomy, a bilobectomy plus lobectomy, or a lobectomy of the right upper lobe.
[d]Patient received carboplatin/paclitaxel for ovarian cancer.
SABR, stereotactic ablative radiotherapy; COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; FEV_1, forced expiratory volume in the first second; NOS, not otherwise specified; PTV, planning target volume.

cluster of centrilobular and paraseptal emphysema, with a preference for upper lobes; and severe emphysema was defined by generalized centrilobular and paraseptal emphysema in both upper and lower lobes.

Statistics

Descriptive statistics were performed with IBM SPSS for Windows, version 20.0 (IBM, Armonk, NY). Kaplan-Meier estimates were generated for all clinical outcomes and compared by using the log-rank test. Median follow-up time was calculated by the reverse Kaplan-Meier method.[21]

Results

Patient and Tumor Characteristics

In total, 63 patients with 63 tumors were eligible for further analysis (Table 1 and Fig. 1). Only eight patients (13%) had undergone treatment before January 2009. Median tumor diameter was 5.8 cm (range 5.1–10.4, SD = 1.0). Eleven patients (17%) had a tumor diameter exceeding 7 cm; all of them were treated before 2013. The median patient age was 78 years (range 49–92); the median Charlson comorbidity index was 2 (range 0–6); and when corrected for age, the median Charlson comorbidity index was 5 (range 1–10). A histopathological confirmation of NSCLC could not be obtained in 21 patients (33%), most (19) of whom had been treated before 2011. Among the former, biopsy yielded inconclusive results in 12 patients, was not performed in two others on account of their poor general condition, and was abandoned in one patient in whom a pneumothorax developed during the procedure. In the 21 patients who underwent SABR without a pathological diagnosis, the median calculated risk for malignancy, which was calculated by using a model validated in the Dutch population, was 97.2% (range 97.1–97.6).[22] A positron emission tomography (PET) scan was performed in all but two patients because of claustrophobia, but a pathological diagnosis had been obtained in both. Invasive mediastinal staging was performed by endoscopic ultrasonography or endobronchial ultrasonography in seven patients and by mediastinoscopy in one patient. All patients staged T3N0 had a tumor diameter

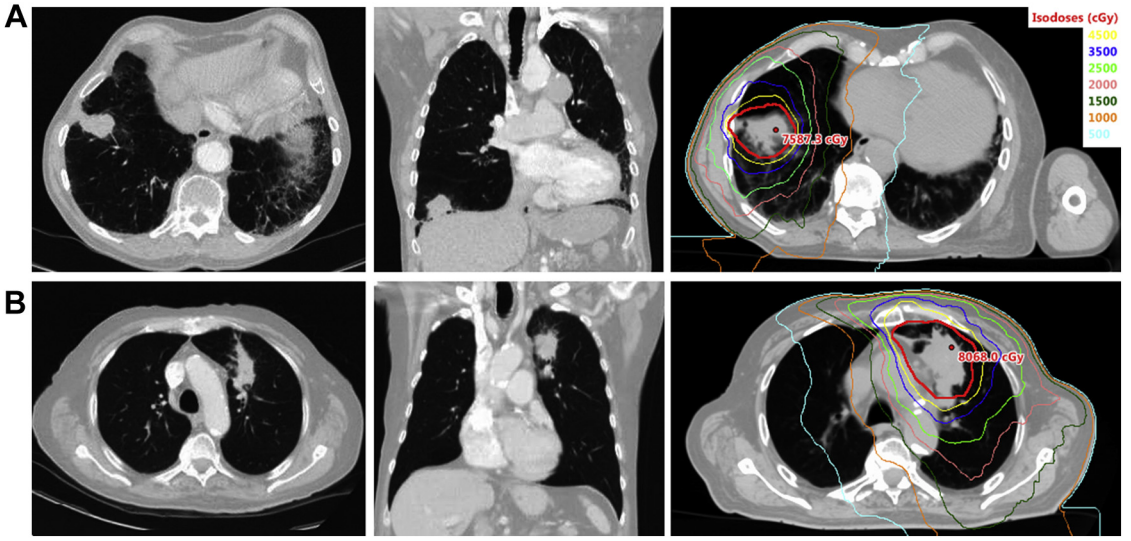

Figure 1. Diagnostic and treatment planning computed tomography scans of two patients. (*A*) A patient with a nonclassifiable fibrosis who died of cardiac failure and possible radiation pneumonitis 12 months after stereotactic ablative radiotherapy. (*B*) A patient with mild emphysema who died of an unknown cause 30 months after stereotactic ablative radiotherapy. The planning target volumes are shown in red.

exceeding 7 cm, except for one patient with chest wall invasion. Three patients (5%) had very centrally located tumors (so-called ultracentral tumors).[23]

In total, eight patients (13%) had radiological evidence of ILD preceding SABR. In four of them, the diagnosis was clinically recognized before SABR. In two patients retrospective analysis indicated that there were certain features consistent with ILD mentioned in the radiology report; however, the term *ILD* was not used and there was no record of a formal diagnosis subsequently being made. In the remaining two patients, ILD was detected only on a retrospective imaging review for the purposes of this study. In four patients who were identified as having ILD, the corresponding radiological diagnosis was possible *usual interstitial pneumonia* (UIP) with a clinical working diagnosis of interstitial lung fibrosis (IPF). Two other patients had nonclassifiable fibrosis, and nonspecific interstitial pneumonia was diagnosed in one. The remaining patient had systemic lupus erythematosus and a radiological UIP, with a

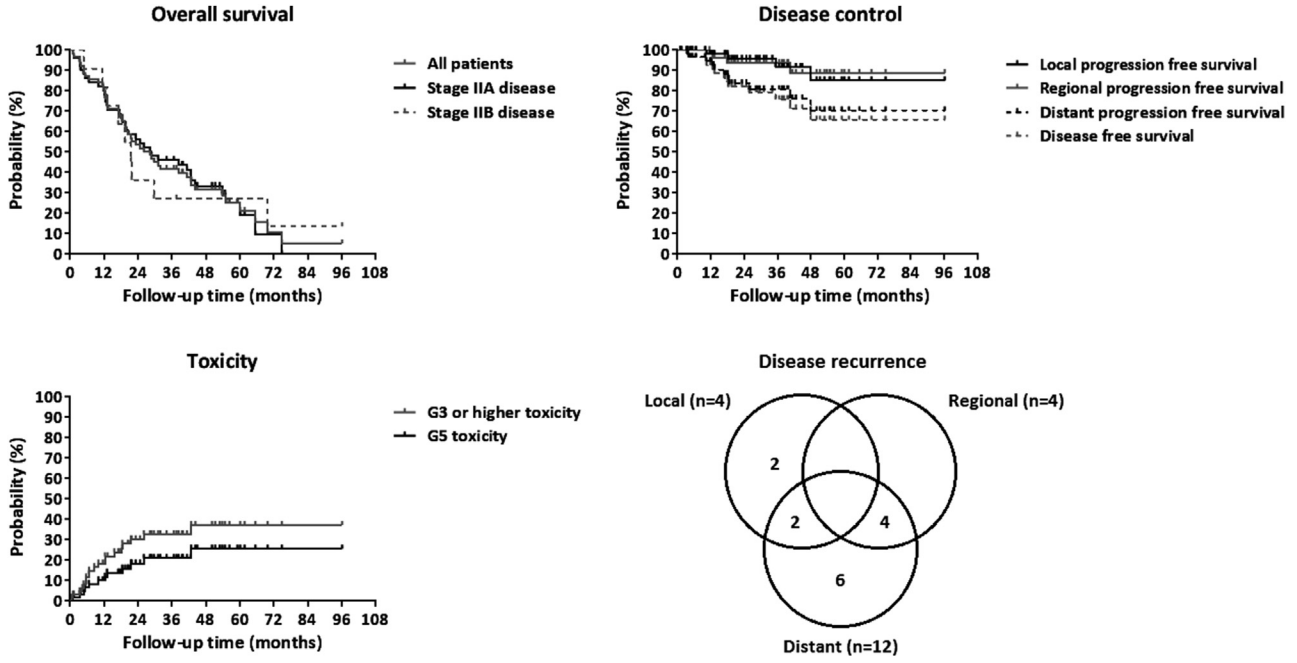

Figure 2. Overall survival, disease control, and toxicity outcomes of all patients.

Table 2. Details of Patients with a Likely or Possible Fatal Toxicity

Cause of Death	Reason for SABR	Pulmonary Comorbidity before SABR	Pre-SABR FEV_1 Absolute (L)/FEV_1 Predicted (%)/DLCO (%)	Treatment and Tumor Details	Clinical Outcomes
Likely grade 5					
Fatal lung hemorrhage	Prior lung surgery: left lobectomy and right bilobectomy	COPD GOLD stage II	2.24/67/69	SABR: 8 × 7.5 Gy T2bN0M0, RUL TD: 5.5 cm PTV: 135.5 cm^3	Survival: 13.1 mo No disease progression documented Grade 3 radiation pneumonitis
Radiation pneumonitis, cardiac failure, and myocardial infarction	Cardiac comorbidity and general condition	COPD GOLD stage I Radiological possible UIP (clinical IPF)	2.30/77/69	SABR: 5 × 12 Gy T2bN0M0, RLL TD: 6.3 cm PTV: 139.1 cm^3	Survival: 6.6 mo No disease progression documented
Radiation pneumonitis	Cardiac comorbidity	COPD GOLD stage II Radiological possible UIP (clinical IPF) Mild emphysema	2.36/82/—	SABR: 5 × 11 Gy T3N0M0, LLL TD: 10.4 cm PTV: 161.3 cm^3	Survival: 4.8 mo No disease progression documented
Sudden death with pleural effusion leading to mechanical compromise of heart and cardiac failure	Pulmonary comorbidity	COPD GOLD stage II Moderate emphysema	1.56/61/—	SABR: 5 × 11 Gy T2bN0M0, RLL TD: 5.8 cm PTV: 290.6 cm^3	Survival: 10.0 mo No disease progression documented
Possible grade 5					
Fatal lung hemorrhage	Pulmonary comorbidity	COPD GOLD stage II Severe emphysema	2.89/87/33	SABR: 8 × 7.5 Gy T2bN0M0, LUL TD: 5.1 cm PTV: 94.1 cm^3	Survival: 18.4 mo No in-field radiological progression but possible intrathoracic progression
Fatal lung hemorrhage	Cardiac comorbidity and general condition		2.19/79/—	SABR: 5 × 11 Gy T3N0M0, LLL TD: 7.1 cm PTV: 215.5 cm^3	Survival: 21.5 mo Regional and distant relapse with possible local recurrence
Respiratory insufficiency due to a possible radiation pneumonitis and COPD	General condition and age	COPD GOLD stage II Nonclassifiable fibrosis Mild emphysema	1.80/69/—	SABR: 5 × 11 Gy T2bN0M0, RUL TD: 5.1 cm PTV: 108.0 cm^3	Survival: 26.1 mo No disease progression documented
Cardiac failure and possible radiation pneumonitis	General condition	COPD GOLD stage II Moderate emphysema	1.12/57/72	SABR: 5 × 11 Gy T2bN0M0, RUL TD: 5.9 cm PTV: 144.4 cm^3	Survival: 12.3 mo Local recurrence (pathological confirmed)
Terminal respiratory failure, unable to exclude radiation pneumonitis	Pulmonary comorbidity and general condition	COPD GOLD stage IV Severe emphysema	0.75/31/—	SABR: 8 × 7.5 Gy T2bN0M0, RLL TD: 5.9 cm PTV: 194.0 cm^3	Survival: 3.4 mo No disease progression documented Grade 3 pleural effusion

(continued)

Table 2. Continued

Cause of Death	Reason for SABR	Pulmonary Comorbidity before SABR	Pre-SABR FEV_1 Absolute (L)/FEV_1 Predicted (%)/DLCO (%)	Treatment and Tumor Details	Clinical Outcomes
Pneumonia, unable to exclude late radiation pneumonitis/fibrosis	Cardiovascular comorbidity	Radiological possible UIP (clinical IPF)	2.20/88/71	SABR: 8 × 7.5 Gy T2bN0M0, RUL TD: 5.4 cm PTV: 115.7 cm^3	Survival: 42.8 mo No disease progression documented
Sudden death	Cardiac comorbidity	COPD GOLD stage II Severe emphysema	1.50/75/—	SABR: 8 × 7.5 Gy T2bN0M0, LLL TD: 6.0 cm PTV: 170.2 cm^3	Survival: 5.4 mo No disease progression documented Grade 3 radiation pneumonitis
Sudden death, after episodes of severe dyspnea, diarrhea, clinical deterioration	Pulmonary comorbidity	COPD GOLD stage III Radiological possible UIP (clinical IPF) Moderate emphysema Chronic oxygen use	—	SABR: 8 × 7.5 Gy T2bN0M0, LLL TD: 5.3 cm PTV: 140.8	Survival: 1.0 mo No disease progression documented

SABR, stereotactic ablative radiotherapy; L, litre; FEV_1, forced expiratory volume in the first second; DLCO, diffusion capacity of lung for carbon monoxide; COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; TD, tumor diameter; PTV, planning target volume; UIP, usual interstitial pneumonia; IPF, idiopathic pulmonary fibrosis; RUL, right upper lobe; RLL, right lower lobe; LLL, left lower lobe; LUL, left upper lobe.

working diagnosis of collagen tissue disease–associated UIP. In total, 38 patients (60%) had radiological signs of emphysema, including 15 with mild emphysema, 11 with moderate emphysema, and 12 with severe emphysema.

The median PTV was 135.5 cm^3 (47.0–290.6), with 18 patients having a PTV of less than 100 cm^3 and 10 patients having a PTV of more than 200 cm^3. A total of 22 patients (35%) were treated with five fractions (median tumor diameter 5.7 cm, median PTV 131.5 cm^3), and the remainder were treated in eight fractions (median tumor diameter 5.8 cm, median PTV 135.5 cm^3). The prescribed dose was delivered to the PTV in all but one patient, in whom the esophagus tolerance doses would have otherwise been exceeded.[10] Thirteen patients (21%) had been included in a previous study on short-term outcomes in large-volume tumors and 21 others (33%) had been included in our previous dosimetric study on moderately central tumors.[10,17]

OS and Disease Control

At a median follow-up of 54.7 months (95% confidence Interval [CI]: 48.5–61.0), the median overall survival (OS) was 28.3 months (95% CI: 18.3–38.2) for all patients. The 1-, 2-, 3-, and 4-year OS rates were 81.0%, 53.5%, 41.8%, and 31.5%, respectively, for all patients (Fig. 2). For T2b tumors, median OS was 28.7 months (95% CI: 12.2–45.3), and for T3 tumors, it was 21.5 months (95% CI: 16.4–26.6). Eight patients (13%) died within 6 months after start of treatment (survival range 1.0–5.4 months), with four of the deaths due to causes considered related to treatment (Table 2).

Details of follow-up CT scans were unavailable in 12 patients (19%), with five patients in this group having a survival of less than 6 months. Disease progression at any location was recorded in 14 patients (22%) (see Fig. 2). A local recurrence was reported in four patients (4%) in whom a growing lesion was observed on the follow-up CT scans. Three of these patients also had a local increase in fludeoxyglucose F 18 PET uptake, with a pathologically proven recurrence obtained in two of them. A regional recurrence and a distant failure were reported in four patients (6%) and 12 patients (19%), respectively. An out-of-field distant recurrence at one or more sites was the most common first manifestation of failure (10%). The disease-free survival rate at 2 years was 82.1%, and the local, regional, and distant control rates at 2 years were 95.8%, 93.7%, and 83.6%, respectively.

Toxicity

Late treatment-related toxicity could not be evaluated in seven patients (11%). Five of these patients died within 3 months of the start of treatment. Details about the cause of death were available for all of these five

patients, with two patients scored as a possible treatment-related death (Table 2). One patient had emigrated and no follow-up details were obtained in the remaining patient, who died after a fall and multiple fractures 31 months after treatment.

Grade 3 or higher toxicity was recorded in 19 patients (30%). The actuarial incidence of the first G3 or higher toxicity event was 18.3% at 12 months and 30.3% at 24 months; 47% of the severe toxicity was observed within 6 months of the start of treatment and 26% was observed after 18 months or more. The most common G3 or higher toxicity was radiation pneumonitis (RP), which occurred in 12 patients (19%). There were a total of 12 grade 3 toxicity events, including RP (n = 6), chest wall pain (n = 3), dyspnea (n = 1), pleural effusion (n = 1), and stenosis of a main bronchus with complete atelectasis of the ipsilateral lung (n = 1). The latter patient remains disease-free 4.9 years after SABR.[24] No grade 4 toxicity events were recorded.

At the time of this analysis, 47 patients (75%) had died. Information about the cause of death was not available for eight of them (17%). Five patients died as a result of disease progression and two died as a consequence of euthanasia (both of the latter did not have proven disease progression). One patient had euthanasia 69.8 months after SABR; this patient had a coronary artery bypass graft, a history of severe chronic obstructive pulmonary disease (COPD) with oxygen use, severe valvular heart disease, and a pacemaker and requested euthanasia on account of severe dyspnea. The second patient died 13.1 months after SABR and requested euthanasia because of clinical deterioration as a consequence of severe dyspnea (preexisting COPD, Global Initiative on Obstructive Lung Disease stage IV), severe pelvic pain, and hypercalcemia due to probable bone metastases in the femur. Seven patients needed palliative sedation, including three as a consequence of disease progression and the remainder for reasons such as respiratory insufficiency after bacterial pneumonia, severe COPD, and complications of a talc pleurodesis. Other patients (n = 12) died from causes considered unrelated to lung cancer, such as a cerebrovascular accident, pulmonary hypertension, and severe peripheral vascular disease. A treatment-related death (grade 5 toxicity) was considered either possible (n = 8) or likely (n = 4) in 12 patients (19%) (Table 2). Three patients had a fatal lung hemorrhage considered possibly or likely related to treatment. Six patients died of a possible or likely treatment-related RP. A contribution of treatment to death could not be excluded in another three patients who experienced a sudden death. Among the patients with possible or likely fatal toxicity, eight (67%) had radiological signs of emphysema on pretreatment imaging, and five (42%) had signs of ILD. Fatal toxicity developed in five of the eight patients (63%) with radiological ILD. Four of the latter had fatal RP, and one patient had a sudden death possibly related to treatment. Grade 3 or higher RP was significantly more common in patients with ILD ($p = 0.01$) and a WHO performance score of 2 or 3 versus 0 or 1 ($p = 0.02$), but this difference was not observed in patients with emphysema ($p = 0.44$). Median survival was significantly worse in patients recorded to have any G3 or higher toxicity, with a median survival of 18.4 months (95% CI: 10.8–26.0) versus 38.3 months (95% CI: 22.0–54.7), respectively ($p < 0.01$).

Univariate Analyses

On univariate analysis, 1-cm increments in tumor size for the three largest groups (≥5 to 6 cm, >6 to 7 cm, and >7 to 8 cm) were not significantly associated with survival, local control, regional control, distant control, or G3 or higher toxicity ($p = 0.89$, $p = 0.66$, $p = 0.19$, $p = 0.39$, and $p = 0.97$, respectively). Survival and toxicity outcomes were similar between patients with a PTV of 200 cm^3 or less and those with a PTV larger than 200 cm^3 ($p = 0.51$ and $p = 0.94$, respectively). However, regional and distant tumor control were significantly worse in patients with a larger PTV. For patients with a PTV of 200 cm^3 or less, regional control at 2 years was 95.1%, and for patients with a PTV larger than 200 cm^3, the rate was 87.5% ($p = 0.02$). Distant control rates at 2 years were 89.9% and 54.0%, respectively ($p < 0.001$). Local control did not differ between the two PTV sizes ($p = 0.36$). For disease stage, survival, local control, regional control, and severe toxicity outcomes did not differ between stage IIA and IIB tumors ($p = 0.97$, $p = 0.61$, $p = 0.60$, and $p = 0.75$, respectively). Distant failure was significantly more frequent in patients with stage IIB tumors than in those with stage IIA tumors, with 2-year distant control rates of 58.9% and 89.4%, respectively ($p = 0.04$).

Discussion

To the best of our knowledge, this is the first report on long-term follow-up after SABR for an early-stage lung tumor with a diameter measuring more than 5 cm. Although SABR is not currently recommended for such tumors, a growing group of frail elderly patients are now presenting with lung cancer, and 18% of patients in the SEER-Medicare population with early-stage NSCLC received no curative treatment in 2007.[1,25] Furthermore, larger tumors were associated with an increased use of radiation therapy as compared with surgery in the SEER-Medicare population, and unfit patients were less likely to accept conventional radiotherapy administered once daily for between 5 and 6 weeks.[25] Our caution in introducing

SABR for larger tumors is reflected by the fact that the 63 patients reported in this study constituted only 6% of the 1042 patients treated at our institution with SABR for a primary lung tumor since 2003.

Our patients had a median OS of 28.3 months after a median follow-up of 54.7 months. Out-of-field distant recurrence at one or more sites occurred in only 10% of patients. Although any retrospective scoring of toxicity can be challenging in a patient group with extensive comorbidity, the fact that grade 3 or higher toxicity was recorded in 30%, and a possible or likely treatment-related death was observed in 19% suggests that the risks of SABR are substantially higher than has been reported for peripheral tumors in fitter patients.[26] A substantial proportion of patients had COPD or radiological signs of either emphysema or ILD, findings that have been associated with higher overall mortality in patients with or without a diagnosis of lung cancer.[27–30] Such patients with inoperable, large-volume lung cancer are at a higher risk for grade 3 or higher toxicity, and they must be carefully counseled about treatment-related risks.[19,31] The fact that ILD was present on retrospective review in 13% of our patients, with fatal toxicity developing in 63% of the latter, suggests that tumor boards should pay particular attention to identifying underlying ILD in patients with early-stage NSCLC.

The median and 3-year OS rates of our patients compared favorably to those of 36 patients treated for a T2N0M0 tumor in a prospective dose escalation study.[26] Four recently published articles describing SABR for lung tumors larger than 5 cm reported similar median survival times (17.5–25.1 months) (Supplementary Table 1).[5–8] Grade 3 or higher toxicity was reported in 7.5% or less of patients after a median follow-up of 15 months or less. The relatively short follow-up in some reports may be relevant, as 42% of severe toxicity observed in our patients manifested after 12 months.

Although tumor diameter was not associated with clinical outcomes in our study, distant failure was significantly worse in patients with larger target volumes and higher disease stages. This is consistent with the findings of previous studies on SABR.[17,32] Survival in operable early-stage NSCLC is also significantly associated with tumor size and may be improved with use of adjuvant chemotherapy.[33,34] Prospective studies evaluating chemotherapy with SABR in NSCLC are not yet open for patient recruitment or have not completed accrual (NCT02417662 and NCT01446744). One trial has been terminated on account of poor accrual (NCT01300299). It is important to note that most of the patients in our series were not candidates for a surgical treatment or trials on account of comorbidities (60%), and it is unclear whether many would have been fit to receive conventional systemic therapy. Larger tumors may have a higher risk for development of occult regional nodal metastases. Despite invasive mediastinal staging being performed in only 13% of these patients, locoregional control rates were high. Ongoing studies are currently investigating the role of routine endoscopic mediastinal and hilar staging in patients without suggestive findings on PET/CT scan (NCT01786590 and NCT02719847).

Some limitations of our study deserve mention, including the limited numbers of patients. Patients in this analysis were treated with evolving radiotherapy techniques on account of the long treatment period. Although clinical outcomes were evaluated by a panel of experienced clinicians, the retrospective character and varying follow-up of these patients could make toxicity scoring inaccurate. Our liberal criteria for retrospectively scoring toxicity in patients who had incomplete follow-up details available may have led to overreporting of toxicity, as shown by survival outcomes that were comparable to those of patients treated in trials.

In conclusion, our cautious implementation of SABR for lung tumors larger than 5 cm resulted in the treatment of a selected group of patients. Nevertheless, survival outcomes for the whole group were not worse than those reported in recent trials using other radiotherapy schedules, suggesting that SABR could have a role in this patient group. Our findings again confirm that patients with ILD represent a group at very high risk for severe toxicity.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at http://dx.doi.org/10.1016/j.jtho.2017.02.021.

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