Stereotactic Ablative Radiotherapy for Operable Stage I Non-Small Cell Lung Cancer: Long-Term Results of the Single-Arm STARS Prospective Trial

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Summary

Background: A previous pooled analysis of the STARS/ROSEL trials showed higher survival after stereotactic ablative radiotherapy (SABR) compared to surgery for operable early-stage non-small cell lung cancer (NSCLC), but that analysis had notable limitations. This study reports long-term results of the STARS trial, in which the SABR arm was re-accrued with greater sample size, along with a protocol-specified propensity matched comparison with a prospectively registered, contemporary institutional cohort of patients who underwent video-assisted thoracoscopic surgical lobectomy with mediastinal lymph node dissection (VATS L-MLND).

Methods: Patients were ≥ 18 years of age and Zubrod performance status of 0–2, with newly-diagnosed and histologically confirmed ≤ 3 cm NSCLC with N0M0 disease (squamous cell, adenocarcinoma, large cell, or NSCLC not otherwise specified). This trial (NCT02357992) completed enrollment and did not include patients from the prior pooled analysis. Operability was defined as candidacy for lobectomy as determined by a thoracic surgeon using several objective criteria. PET/CT was required, and EBUS was strongly recommended for all patients. SABR dosing was 54 Gy in three fractions (for peripheral lesions) or 50 Gy in four fractions (for central tumors; simultaneous integrated boost to gross tumor totaling 60 Gy). The primary endpoint was the 3-year overall survival (OS) rate. Non-inferiority could be claimed if the 3-year OS rate after SABR was lower than that after VATS L-MLND by ≤ 12% and the upper bound of the 95%

confidence interval (CI) of the hazard ratio (HR) was <1.965. Propensity matching consisted of determining a propensity score using a multivariable logistic regression model encompassing several covariates (age, tumor size, histology, performance status, and the interaction of age and sex); based on the propensity scores, one SABR patient was randomly matched with one VATS L-MLND patient using a 5-to-1 digit greedy match algorithm.

Findings: Enrollment was from September 1, 2015 and completed on January 31, 2017. The median follow-up time for the 80 SABR patients was 5.1 years (IQR, 3.9 – 5.8 years). SABR was tolerated well, with no grade 4–5 toxicity and one case (1.3%) of grade 3 dyspnea. The OS was 91% (95% CI, 85–98%) at 3 years and 87% (95% CI, 79–95%) at 5 years. The OS in the propensity-matched VATS L-MLND cohort was 91% (95% CI 85%–98%) at 3 years and 84% (95% CI 76%–93%) at 5 years. There were no significant OS differences between groups (HR 0.86, 95%CI 0.45–1.65, p=0.65).

Interpretation: Long-term survival after SABR is non-inferior to VATS L-MLND for operable stage IA NSCLC. SABR remains promising for such cases but multidisciplinary management is strongly recommended.

Keywords

Non-small cell lung cancer; stereotactic ablative radiotherapy; stereotactic body radiotherapy; operable; surgery; lobectomy

Introduction

Stereotactic ablative radiotherapy (SABR), also known as stereotactic body radiation therapy (SBRT), is now a standard of care for inoperable early-stage non-small cell lung cancer (NSCLC).[1–2] Its effectiveness, convenience, and noninvasiveness have led to substantial explorations as to whether SABR should be used for patients with operable disease. Although numerous retrospective evaluations have been undertaken, findings from most such analyses are largely unreliable given the many associated selection biases for which complete adjustment can never be made[3] Prospective evidence, however, suggests that survival for patients with operable disease who undergo SABR can be substantially longer than for those with inoperable disease.[4] Unfortunately, several randomized trials aiming to address the use of surgery versus SABR for patients with operable disease have failed to accrue, including RTOG 1021, ROSEL, STARS, and SABRTooth.

Despite this shortcoming, a pooled analysis of patients enrolled in the STARS and ROSEL trials revealed that SABR was associated with significantly higher survival than lobectomy with mediastinal lymph node dissection (L-MLND) (95% for SABR versus 79% for surgery at 3 years).[5] However, that study had several limitations, most notably the small number of patients, short follow-up, heterogeneity between study protocols, and lack of contemporary surgical techniques such as video-assisted thoracoscopic surgery (VATS).

To address these shortcomings as well as the ongoing controversy regarding the use of surgery versus SABR for operable early-stage NSCLC in a more robust manner, we now present the long-term (5 years) results of the revised STARS trial, in which the SABR arm was re-accrued with greater sample size, along with a protocol-specified propensity matched

comparison with a prospectively registered, contemporary institutional cohort of patients who had undergone VATS L-MLND.

Methods

Study design and participants

The original STARS trial and the revised STARS trial were approved by the MD Anderson Institutional Review Board and ethics committee; all patients provided written informed consent to participate. This trial enrolled an entirely new set of patients with similar primary/ secondary objectives, eligibility, SABR dose regimens/interventions but did not analyze the patients from the original STARS trial. The Thoracic and Cardiovascular Surgery research team was responsible for patient enrollment, clinical data collection, and storage. This trial used mostly the same methods as the original trial,[5] with the few exceptions mentioned below.

Inclusion criteria were 18 years of age, Zubrod performance status of 0–2, newly diagnosed and histologically confirmed NSCLC (squamous cell carcinoma, adenocarcinoma with or without lepidic features, large cell carcinoma with or without neuroendocrine features, or NSCLC not otherwise specified), and tumor diameter 3 cm (cT1a or cT1b and cN0 cM0 according to the American Joint Committee on Cancer staging manual, 7th edition). Operability was defined based on candidacy for undergoing lobectomy -- baseline forced expiratory volume in 1 second (FEV1) >40% predicted, postoperative predicted FEV1 of >30%, diffusion capacity of the lungs for carbon monoxide >40% predicted, exercise oxygen consumption >50% predicted, no baseline hypoxemia or hypercapnia, no pulmonary hypertension, and no evidence of severe cerebral, cardiac, or peripheral vascular disease. Every patient was evaluated by a thoracic surgeon to confirm operability. There were no laboratory tests required to assess eligibility.

Exclusion criteria were carcinoid histology, synchronous primary lung cancer, prior lung/ mediastinal radiotherapy, prior malignancy within 3 years before enrollment (other than in situ cancers or nonmelanomatous skin cancers), any additional planned upfront local therapy, and (for women) being pregnant or lactating.

In addition to pulmonary function tests (PFTs), other mandatory staging studies were required within 10 weeks of study entry. ^{18}F-fluorodeoxyglucose positron emission tomography – computed tomography (PET-CT) was required for all patients. Use of endobronchial ultrasound bronchoscopy (EBUS) with hilar/mediastinal nodal fine-needle aspiration sampling was strongly recommended for all cases and required for patients with any mediastinal lymph node measuring >1.0 cm (short axis diameter) or a having maximum standard uptake value above that of the mediastinal blood pool. Brain CT or magnetic resonance imaging were recommended only for patients with cerebral symptoms.

Procedures

CT simulation was carried out with custom stereotactic immobilization and a four-dimensional (4D) CT scan. An internal gross tumor volume (iGTV) was delineated from the reconstructed maximum intensity projection and individual breathing phases of the 4D

CT or breath-hold CT images; an additional 5-mm isotropic expansion was used to construct the planning target volume (PTV). The prescribed radiation dose was 54 Gy in 3 fractions (for peripheral lesions, no intended boost to the iGTV), or 50 Gy in 4 fractions with a simultaneous integrated boost to the iGTV to 60 Gy (for central tumors, per the International Association for the Study of Lung Cancer [IASLC] definition[6]). The prescribed dose was to cover 100% of the iGTV and at least 95% of the PTV. To avoid exceeding the tolerance of critical normal tissues, cases with PTVs overlapping the tracheobronchial tree, esophagus, heart, or brachial plexus were not enrolled. Treatment planning (Pinnacle, Philips Medical Systems, Fitchburg, WI, USA) was conducted by using forward or inverse planning, accounted for tissue heterogeneity, and used 6–12 (coplanar or noncoplanar) 6 MV photon beams or two or more modulated arcs. All treatment planning was done in Pinnacle (v9.10 Philips Medical Systems, Fitchburg, WI, USA) using a convolution superposition algorithm (CC Convolve). Treatment delivery was either on a Varian 2100 linear accelerator with a standard multileaf collimator (MLC) or a Truebeam linear accelerator with a high-definition MLC (Varian Medical Systems, Palo Alto, CA). Treatment delivery was performed with one of two techniques based on tumor location and respiratory motion: 1) free-breathing; 2) breath-hold treatment with feedback guidance was used for patients with lesions moving more than 1 cm who could tolerate the procedure (3 breath-hold images were used to generate the iGTV). SABR was delivered in consecutive days, and image guidance with in-room or cone-beam CT was required before each treatment.

The surgical technique for VATS L-MLND is described elsewhere[7] and was conducted in a standardized manner at our institution. All patients underwent VATS L-MLND by high-volume (over 100 cases per year) thoracic surgeons specializing in thoracic cancer surgery.

Follow-up visits were scheduled every 3 months for the first 2 years, every 6 months for another 3 years, and annually thereafter. Each follow-up visit included a clinical examination and thoracic CT; at each visit, toxicity assessment was conducted using the Common Terminology Criteria for Adverse Events version 4.0. One PET-CT scan was recommended, at either 6 or 12 months after SABR, but was not required. PFTs were recommended at 12 months but not required. All patients were to be followed for a minimum of 3 years or until death.

Outcomes

The primary endpoint was the overall survival (OS) rate at 3 years; other assessed endpoints were progression-free survival (PFS) and cancer-specific survival (CSS) rates and the incidence of grade 3 toxicity. All endpoints were calculated from the SABR start date. OS was calculated to the date of death from any cause. PFS was calculated to the date of first recurrence (local, regional, or distant) or death. CSS was calculated to the date of lung cancer-associated death.

Local recurrence (LR), regional recurrence (RR), distant metastasis (DM), and second primary lung cancer (SPLC) were secondary or exploratory endpoints. Definitions of these terms are extensively described elsewhere[8] but briefly referred to failure within the same lobe (LR) and/or within 1 cm of the PTV (in-field recurrence), any intrathoracic lymph node

outside of the PTV (RR), and all other locations (DM). The definition of an SPLC was based on modified criteria of Martini and Melamed as described previously.[8]

Statistical analysis

Previously published results from the VATS L-MLND database indicated that the 3-year OS for patients with stage I NSCLC status after VATS L-MLND was 85.5%.[7] At the time of trial expansion, we hypothesized that SABR would achieve similar outcomes, and thus a non-inferiority design was implemented. With a target enrollment of 80 patients in this trial, a two-sided 95% confidence interval (CI) for the 3-year OS would extend ±7.7% from the observed rate given an expected rate of 85.5%. Non-inferiority could be claimed if the 3-year OS was not lower than the matched VATS L-MLND cohort by more than 12% (i.e., 3-year OS in the SABR arm of at least 73.5%). The corresponding hazard ratio (HR) between the SABR arm and the VATS L-MLND arm for a 3-year OS of 73.5% vs. 85.5% was calculated to be 1.965, indicating that non-inferiority could be claimed only if the upper bound of the observed 95% CI for HR was less than 1.965. The relatively larger OS difference between groups as a non-inferiority criterion was largely a result of the practical concern regarding premature closure of multiple randomized trials of SABR for operable patients; we sought an OS difference that was unequivocally clinically significant, yet not mandating an unobtainable sample size based on the estimated accrual at our institution during a reasonable length of time.

In addition to reporting each endpoint of all enrolled SABR patients, the protocol prespecified propensity score matching (PSM) by a set of important prognostic factors with a surgical cohort from the MD Anderson Department of Thoracic and Cardiovascular Surgery's prospectively registered, IRB-approved database of all patients with clinical stage I NSCLC who underwent VATS L-MLND during the period of enrollment in this trial (no patients were removed before matching). PSM analysis was undertaken in an attempt to adjust for potential bias associated with prognostic factors related to treatment (SABR vs. VATS L-MLND). This statistical methodology has often been used in observational studies to control for nonrandom treatment assignment of patients by adjusting for differences in covariates between treatment groups.[9–10] To control for factors that may confound the relationship between treatment and OS or PFS, we determined the propensity score to receive SABR for each patient, using multivariable logistic regression model that included the following covariates: age, tumor size, histology (adenocarcinoma vs. non-adenocarcinoma), performance status (0 vs. 1/2), and the interaction of age and sex. Given the propensity scores for all patients, we identified sets of patients and randomly matched one SABR patient with one VATS L-MLND patient using a 5-to-1 digit greedy match algorithm. We used absolute standardized mean differences (SMD; defined by $\frac{100 \times |\bar{x}_{SABR} - \bar{x}_{non-SABR}|}{\sqrt{\frac{s^2_{SABR} + s^2_{non-SABR}}{2}}}$) to assess balance on the prognostic variables between the two groups in the matched dataset because SMD is the most commonly used statistic to examine the balance of covariate distribution between treatment groups. An absolute SMD of less than 10% suggests a reasonable balance on a covariate between the two groups.[11]

The chi-square test for categorical variables or t-test for continuous variables was used to assess the difference in distribution between the SABR and VATS L-MLND patients after PSM. The Kaplan-Meier method was used to estimate time-to-event outcomes such as OS and PFS, with comparisons made with the log-rank test. Recurrence outcomes were quantified by the cumulative incidence function considering death as a competing risk, with comparisons done using Gray's test. We used Weibull regression models for the multivariable analysis of OS and PFS given that the proportional hazard assumption did not hold for some covariates.[12–13] SAS (9.4, Cary, NC), S-Plus (8.2, Palo Alto, CA), and R (3.4.4, Vienna, Austria) software were used for all analysis, and statistical significance was set at $p<0.05$.

This trial is registered at clinicaltrials.gov, number NCT02357992.

Results

The last follow-up date of the original STARS trial was July 14, 2014, and the results were published in June 2015.[5] The current trial commenced enrollment on September 1, 2015, completed enrollment on January 31, 2017, and had a final follow-up date of September 30, 2020. No patient was ineligible, so all 80 enrolled patients were analyzed.

The CONSORT diagram for this trial is shown in Figure 1. The clinical characteristics of the patient population are displayed in Table 1. Most tumors were adenocarcinomas and were peripherally situated. The mean (± standard deviation) tumor size was 1.83 ± 0.56 cm. All patients completed SABR. The median follow-up time for all censored patients was 5.1 years (IQR, 3.9 – 5.8 years).

The OS, PFS, and CSS rates for the trial population are shown in Figure 2. At the time of data lock, 10 patients had died. The median OS time had not been reached (95% CI not reached-not reached), and the 3- and 5-year OS rates were 91% (95% CI 85%−98%) and 87% (95% CI 79%−95%) respectively. The median PFS time also had not been reached (95% CI not reached-not reached), and the 3- and 5-year PFS rates were 80% (95% CI 72%−89%) and 77% (95% CI 68%−87%) respectively. The median CSS time also had not been reached (95% CI not reached-not reached), and the 3- and 5-year CSS rates were 95% (95% CI 90%−100%) and 92% (95% CI 86%−98%) respectively.

With death as a competing risk, the 5-year cumulative incidence rate of any recurrence was 17.6% (95% CI 10.1%–26.7%), which included LR (same lobe; 5/80; 6.3%; 95% CI 2.3%–13.2%), RR (10/80; 12.5%; 95% CI 6.4%–20.8%), and DM (7/80; 8.8%; 95% CI 3.8%–16.2%) (Appendix P.2, Supplemental Figure 1). The 5-year cumulative incidence of SPLC was 6.9% (95% CI 2.5%–14.6%), corresponding to an incremental increase of 1.38% per year. All recurrences (LR, RR, DM) were confirmed by biopsy. The median time to progression had not been reached (95% CI not reached-not reached), and the median time to any recurrence was 16.6 months (IQR, 6.9 – 29.8 months).

SABR was tolerated well, with no grade 4–5 toxicity and a single case each (1/80, 1.3%) of grade 3 dyspnea, grade 2 pneumonitis, and grade 2 lung fibrosis. These are tabulated in Table 2.

All 352 patients in the surgical database of patients with clinical stage I NSCLC who underwent VATS L-MLND during the period of enrollment were used for 1:1 PSM with the SABR cohort. The results showed a satisfactory match with no significant differences between groups in terms of age, sex, performance status, tumor size, or histology (p values ranged from 0.61 to 0.87; Appendix P.3, Supplemental Table 1); all standardized mean differences were less than 8%, suggesting a reasonable balance on all covariates between the two groups.

Results comparing OS, PFS, and CSS for the SABR and surgery groups are shown in Figure 3. The OS rates between groups was not significantly different (p=0.49), and the 3-year OS rate was 91% (95% CI 85%–98%) in both arms. The 5-year OS rate was 87% (95% CI 79%–95%) in the SABR arm versus 84% (95% CI 76%–93%) in the VATS L-MLND arm. This corresponded to a HR of 0.858 (95% CI 0.446–1.651, p=0.65) for SABR with reference to the VATS L-MLND group with the adjustment of age and tumor size in the multivariable model. Thus, per the prespecified conditions in the protocol relating to the 3-year OS and the upper bound of the 95% CI for the HR, non-inferiority of SABR as compared with VATS L-MLND was claimed.

The PFS rates between groups was also similar (p=0.57) at 3 and 5 years, with 80% (95% CI 72%–89%) and 77% (95% CI 68%–87%) in the SABR group versus 88% (95% CI 81%–96%) and 80% (95% CI 71%–90%) in the VATS-L-MLND group, respectively. This corresponded to a HR of 1.380 (95% CI 0.698–2.725, p=0.35) for SABR with reference to VATS L-MLND with the adjustment of age and tumor size in the multivariable model. The CSS rates remained similar as well (p=0.69): the 3-year CSS rates were 95% (95% CI 90%–100%) for the SABR group versus 97% (95% CI 94%–100%) for the surgery group; the corresponding 5-year CSS rates were 92% (95% CI 86%–98%) versus 93% (95% CI 87%–99%), respectively. The multivariable model for CSS could not be fitted owing to the limited number of lung cancer-related deaths.

The comparative cumulative incidence of recurrences using death as a competing risk for both groups is shown in Appendix P.4, Supplemental Figure 2. No differences were found between groups in 5-year LR rates (6.3%, 95% CI 2.3%–13.2% for SABR versus 1.3%, 95% CI 0.1%–6.2% for VATS L-MLND, p=0.10) or DM rates (8.8%, 95% CI 3.8%–16.2% for SABR versus 4.0%, 95% CI 1.0%–10.2% for VATS L-MLND, p=0.19). However, a higher rate of RR was seen in the SABR arm (12.5%, 95% CI 6.4%–20.8% versus 2.7%, 95% CI 0.5%–8.5%, p=0.02). The cumulative incidence of any recurrence at 5 years was 8.0% (95% CI 3.2%–15.5%) with VATS L-MLND and 17.6% for SABR (95% CI 10.1%–26.7%) (p=0.051).

The moderate and severe surgical complications of the propensity-matched VATS L-MLND group that required significant medical interventions are listed in Appendix P.5, Supplemental Table 2. There were no instances of 90-day mortality. The most common adverse effects were pulmonary (11/80, 13.8% for chest tube placement; 5/80, 6.3% for air leak; 1/80, 1.3% each for tracheostomy, ventilation, re-incubation, embolization, etc.) and cardiovascular (10/80, 12.5%) in nature. Other complications included acute renal failure (1/80, 1.3%), gastrointestinal/genitourinary complications (3/80, 3.8% each), post-

operative transfusion (4/80, 5%), bleeding requiring re-admission (1/80, 1.3%), and wound complications (4/80, 5%). One of 80 (1.3%) patients required postoperative admission to the intensive care unit (ICU), 5/80 (6.3%) patients were re-admitted to the hospital, and 2/80 (2.5%) were re-admitted to the ICU. Altogether, 69/80 (86%) patients were discharged with some degree of activity limitations, and all discharged patients required pain and other medications.

In the SABR arm, there were 5 instances of LR in the involved lobe (one in-field (within 1 cm of the PTV) and four out-of-field), 10 RRs, and 7 DMs. One isolated LR in the involved lobe was salvaged with a second course of SABR, with no evidence of disease at last follow-up. Four patients had isolated RRs salvaged with chemoradiotherapy, of whom two had no evidence of disease at last follow-up. The remainder of the LRs and RRs occurred simultaneously with DMs.

Of the 80 patients in the matched VATS L-MLND cohort, 8 (10%) had occult hilar (n=4) or mediastinal (n=4) lymph node involvement that was not detected by preoperative staging procedures but was found on final pathology analysis. All patients with N1 disease (except one) received adjuvant chemotherapy; all patients with N2 disease received adjuvant chemotherapy and radiotherapy (except one who declined radiotherapy). Of the 8 patients with occult lymph node involvement, only 2 experienced subsequent failure in the regional lymphatics.

Discussion

The results of the revised STARS trial illustrated that SABR was non-inferior to VATS L-MLND for operable stage IA NSCLC. These results are important because the pooled analysis of the STARS and ROSEL trials had notable limitations; as a result, the SABR arm of the STARS trial was re-accrued with greater sample size, long-term follow-up was achieved and compared per protocol with that of a contemporary institutional cohort of VATS L-MLND cases. This trial, however, is not a substitute for phase 3 trials (e.g., VALOR (NCT02984761), which could take at least another 5 years for enrollment, along with additional time for follow-up).

The outcomes for the SABR patients herein are among the best results reported in other literature but consistent with published randomized studies, such as the pooled STARS/ROSEL study, wherein the 3-year OS was 95%. However, the 3-year OS rates for patients in both RTOG 0618 and JCOG 0403 were just under 80%.[4,14] This could result from several factors. First, patients in the more contemporary RTOG 0618 trial were slightly older, had stage IB and poorer PFT findings than those in STARS. However, the Zubrod performance status was similar between trials, and our trial had a higher proportion of central lesions (excluded in RTOG 0618). Second, this trial strongly recommended/mandated thorough pathologic nodal sampling using EBUS (>90%), thereby minimizing the number of patients with occult node–positive disease. Third, patients in this trial were treated with the most contemporary SABR techniques, including not only high-quality volumetric image guidance but also careful attention to the technical nuances of SABR treatment planning.

It is also worth mentioning that most published data of SABR in medically inoperable stage I NSCLC have observed considerably poorer OS at 5 years (ranging from just 32–55%), in part owing to advanced age and comorbidities of those populations.[8] The toxicity rates in those data also tend to be numerically higher than those observed herein (no grade 4/5 toxicity and only 1/80 (1.3%) grade 3 toxicity), which is also related to age, comorbidities, tumor size/location, and the use of modern technologies for SABR planning and delivery. As a result, given the comparable OS and much fewer side effects, the current study particularly supports the use of SABR in younger operable stage IA NSCLC cases.

In the propensity-matched VATS L-MLND cohort, the rate of occult lymph node involvement was 10%. Discovery of occult nodal disease mandated additional adjuvant chemotherapy with or without radiotherapy, which was effective and associated with lower RR rates than that achieved with SABR (2.7% vs. 12.5% at 5 years). Notably, only about 60% of the VATS L-MLND group underwent EBUS as part of disease staging before scheduled surgical resection, a rate lower than the >90% in the SABR cohort. Despite this imbalance, it is unlikely that there was a bias. The role of EBUS in patients who will eventually have a MLND remains without consensus based on the existing literature; as a result, it was neither mandated in this trial nor mandated in contemporary practice. There always exists a proportion of SABR and surgical patients with a false-negative EBUS; however, occult disease will only be detected in patients undergoing MLND. Conversely, in SABR patients, the lack of confirmatory MLND results in the proportion of patients with a false-negative EBUS to continue harboring disease and could have contributed to the greater RRs. However, notably, the higher RRs in the SABR arm did not translate into compromised PFS or OS, most likely because isolated LR or RR can be effectively salvaged. Our experience and that of others have demonstrated that the survival of patients with salvaged isolated LRs (most commonly with surgery or repeat SABR) is similar to that of newly diagnosed patients; furthermore, the survival of patients with salvaged isolated RRs (most commonly with chemoradiotherapy) is similar to that of patients with *de novo* stage III NSCLC.[15–16] The current study also supports this conclusion. Therefore, we strongly encourage close follow-up after SABR and the use of salvage therapy for isolated LRs and RRs after SABR according to the guidelines set forth by the IASLC.[17]

Although SABR was non-inferior to VATS L-MLND in this study population, extrapolation of these results is not recommended. For instance, tumors >3 cm were excluded from this trial, and larger tumors are known to be not only more difficult to control locally with a given dose but are also associated with higher rates of occult nodal involvement and DM.[18–19] Moreover, "ultra-central" cases were also excluded from this trial, because their close abutment to organs-at-risk limits the ability to deliver high biologically effective doses such as those used in this trial.[20] Finally, these data may not precisely apply to patients receiving lower biologically effective doses than those of our institutional practice (typically >130 Gy_{10}).[21–22] Taken together, the proportional benefit from surgery may be directly correlated with tumor size and the degree of abutment with organs at risk.

SABR may be preferred over surgery for cases such as those reported here for several reasons. The first of these reasons pertains to toxicity: the SABR group had no grade 4–5 toxicity, and a grade 3 toxicity rate of only 1.3%. Conversely, L-MLND has been associated

with significant postoperative morbidity (19%−50%) and 90-day mortality (0%−5%), which may be more pronounced for older patients and/or at low-volume hospitals[7,23], which is the reason VATS has rapidly gained popularity in the contemporary era. Second, the dose and normal tissue tolerance associated with image and computer-based SABR planning and delivery stand in contrast to the more significant heterogeneity in surgical techniques in community hospitals, which not only affect surgical complications but also lead to variations in the quality and quantity of dissection or sampling of systemic hilar/mediastinal lymph nodes. Notably, in the current study the comparative OS curves crossed over at 3 years, favoring VATS L-MLND in earlier years but favoring SABR later; this may indicate that long-term complications of lobectomy could have negative effects on long-term survival. This notion is supported by an update of the randomized JCOG 0802/WJOG4607L trial (presented at the 2021 meeting of the American Association for Thoracic Surgery), which compared segmentectomy with lobectomy for stage IA1–2 (2 cm) NSCLC. The finding of fewer toxicities in the segmentectomy arm could have driven some portion of the differences in OS, and hence for this unique population with small tumors, it seems that "less" (extent of surgery) is "more" (OS and quality of life). Third, SABR can potentially galvanize the immune system by means of tumor antigen release, which then addresses residual and occult tumor cells[24–25] (unlike surgery, which could cause immune depression from surgical-related trauma[26]). This notion may not be fully appreciated in the shorter term (just 60% of SABR cases in the MISSILE study[27] achieved a complete pathological response at 8 weeks), and we believe that a much longer interval is needed to evaluate pathological response after SABR due to ongoing immune activity causing "delayed tumoricide".[28] These effects may produce more durable responses and reduce future recurrences.[28] The interaction between SABR-mediated antigen release and immune activation may also explain the enhanced outcomes of patients with advanced NSCLC undergoing immunotherapy when SABR is delivered for immunostimulatory purposes.[29] To further explore this emerging concept, several randomized investigations of SABR with or without immunotherapy for high-risk node-negative NSCLC are underway (e.g., NCT03110978, NCT03446547, NCT03833154, NCT03924869, NCT04214262).

Several limitations of this trial merit discussion. First, this was not a randomized study; although the PSM analysis was protocol-specified, biases cannot be excluded because matching for all possible variables is not feasible. Second, unlike the SABR arm, the VATS L-MLND patients were not treated under a fixed protocol (e.g., with standardized preoperative workup, treatment, and follow-up); it typically had less frequency of follow up visits and images (potentially delay detecting recurrences) thus further limiting comparison with a protocol-specified cohort. Third, "enrollment bias" regarding the selection of patients who enrolled in STARS also cannot be excluded, including the role of both physicians' and patients' personal preferences. Fourth, allowance of a longer interval between PET-CT and the start of SABR can cause further tumor spread and upstaging[30], but longer intervals reflect a wide variety of "real world situations", especially at community and/or rural facilities where longer intervals are not uncommon. Finally, because there is no single accepted definition of "operability," the definitions used herein may not be universally applicable. These limitations notwithstanding, findings from this trial will require corroboration from ongoing randomized trials (e.g., NCT02984761, NCT02468024).

In summary, although not randomized, the long-term results of the STARS trial demonstrate that SABR was non-inferior to VATS L-MLND in terms of OS and PFS for patients with operable stage IA NSCLC. Although SABR is an option for operable early-stage lung cancer, the role of SABR versus surgery for such patients should continue to be debated, studied, and verified until corroborated by a randomized trial.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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Research in context

Evidence before this study

We searched PubMed for published studies until June 16, 2021 on the role of surgery or stereotactic ablative radiotherapy (SABR; also known as SBRT) for operable early-stage non-small cell lung cancer (NSCLC). Searches were intentionally broad and contained the terms "lung cancer" AND "stereotactic radiation" OR "stereotactic radiotherapy" AND "operable" OR "surgery" OR "lobectomy" OR "sublobar". Many retrospective studies of institutional, multi-institutional, or national/population databases were found. The three notable prospective trials were JCOG 0403, a multi-arm nonrandomized trial; RTOG 0618, a single-arm nonrandomized trial; and the STARS-ROSEL pooled analysis of two incompletely accrued randomized trials. These studies collectively showed satisfactory outcomes with SABR for operable early-stage NSCLC, which were comparable to surgery. The quality of evidence was moderately high (level 2). Neither long-term prospective data nor direct randomized evidence were found.

Added value of this study

To our knowledge, no long-term data evaluating the roles of SABR vs surgery exist to date. Long-term results of this trial extend the results of the aforementioned prospective studies, namely by confirming that both surgery and SABR yield similar long-term survival for patients with operable early-stage NSCLC.

Implications of all the available evidence

Collectively, the long-term data corroborate previously published results and illustrate that SABR remains a viable approach for the management of operable early-stage NSCLC. However, properly accrued randomized trials directly comparing surgery and SABR are required for definitive conclusions.
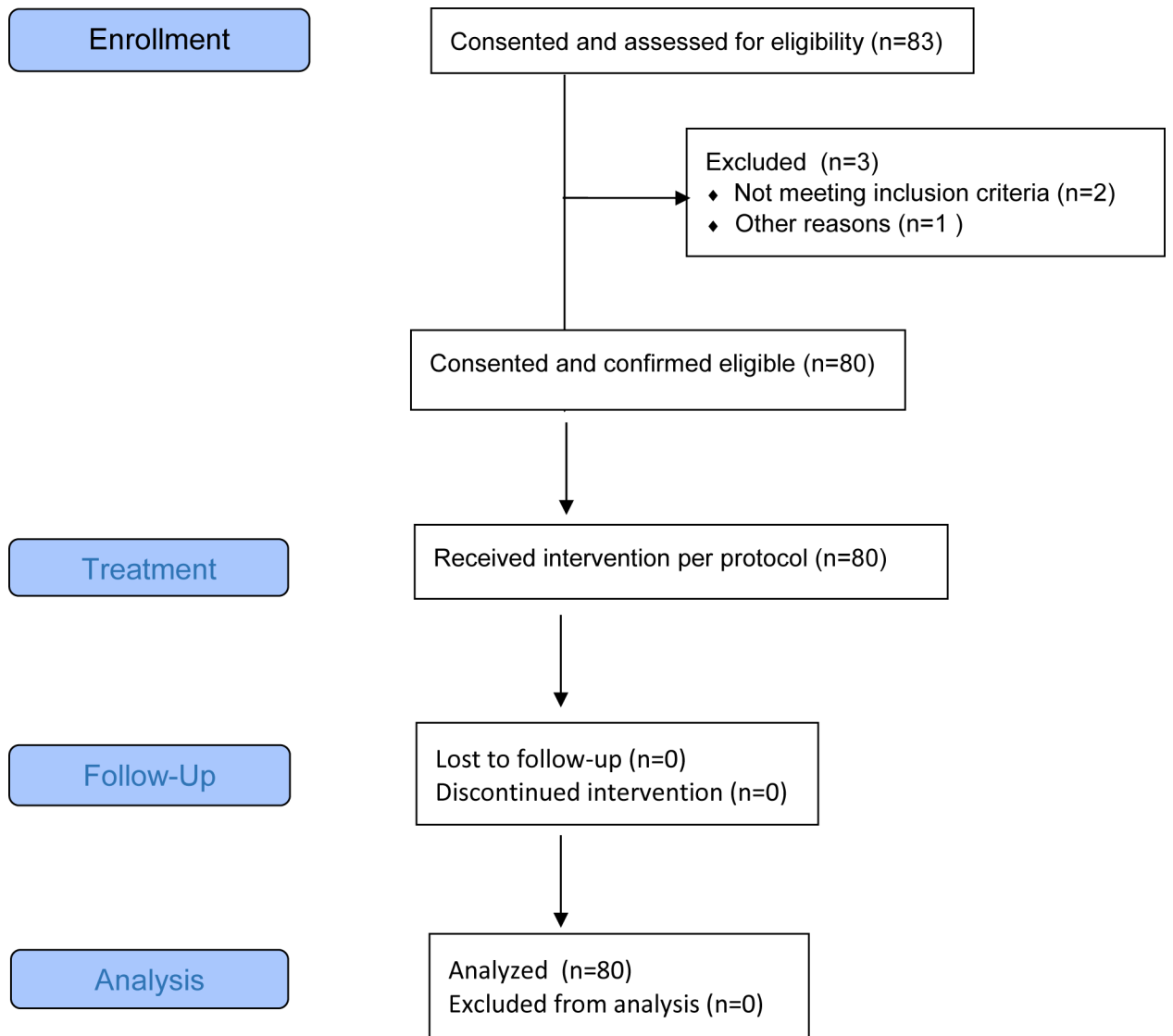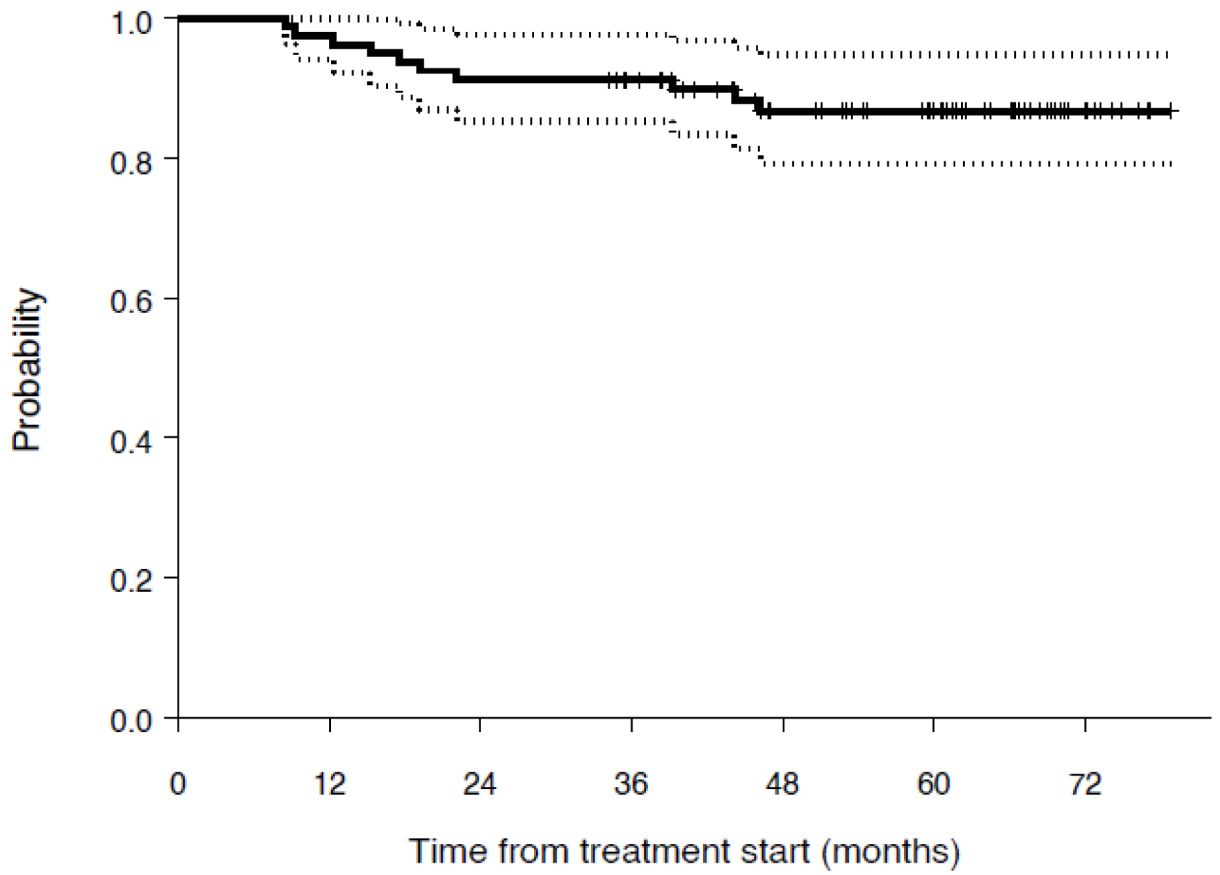
Figure 1.
CONSORT diagram.

A

Overall Survival

number at risk (number censored)

80 (0)   78 (0)   73 (0)   69 (4)   51 (15)   39 (12)   11 (28)
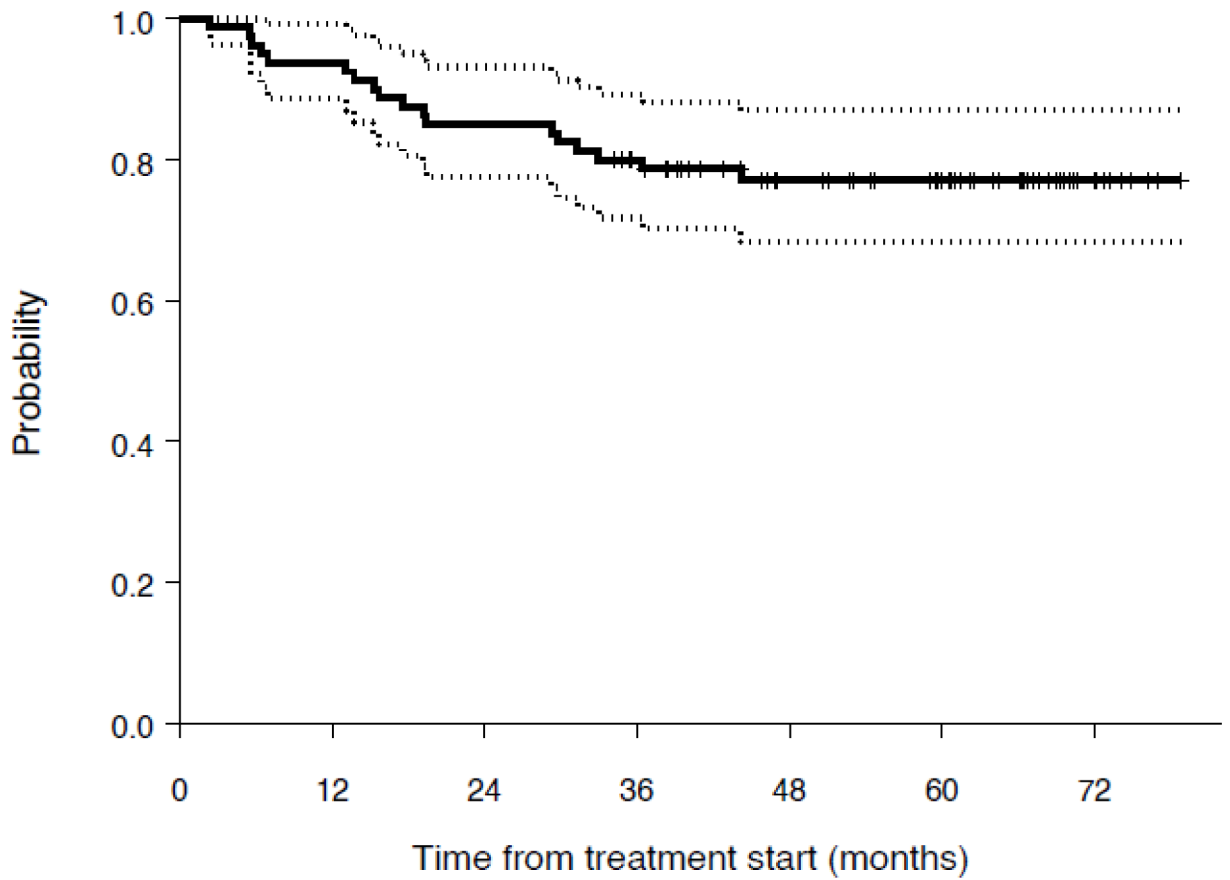
B

Progression Free Survival
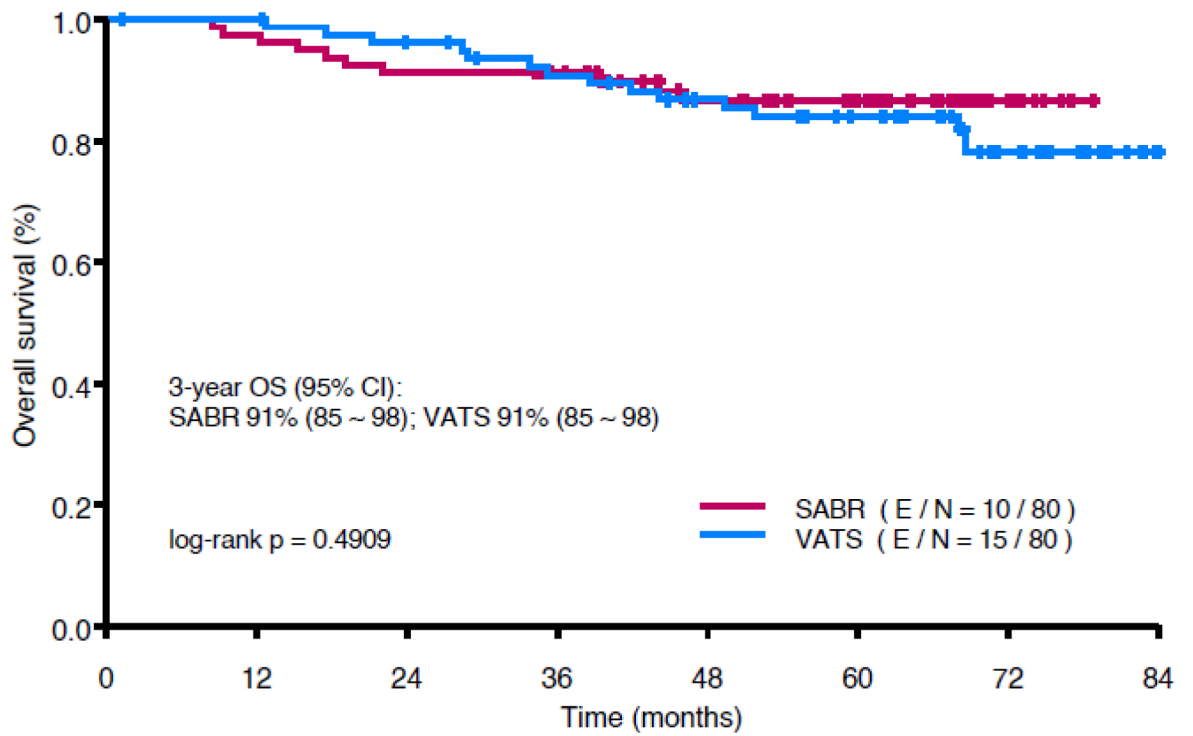

number at risk (number censored)

80 (0)   75 (0)   68 (0)   60 (4)   45 (13)   35 (10)   9 (26)

Figure 2.
Kaplan-Meier curves illustrating overall survival (A), progression-free survival (B), and lung cancer-specific survival (C) among patients treated with stereotactic ablative radiotherapy (SABR).

A

3-year OS (95% CI):
SABR 91% (85 ~ 98); VATS 91% (85 ~ 98)

log-rank p = 0.4909

SABR (E / N = 10 / 80)
VATS (E / N = 15 / 80)

number at risk (number censored)

SABR	80 (0)	78 (0)	73 (0)	69 (4)	51 (15)	39 (12)	11 (28)
VATS	80 (0)	79 (1)	74 (2)	68 (2)	61 (4)	54 (5)	37 (14)

B

number at risk (number censored)

SABR	80 (0)	75 (0)	68 (0)	60 (4)	45 (13)	35 (10)	9 (26)
VATS	80 (0)	78 (1)	71 (2)	66 (2)	60 (4)	51 (5)	35 (14)

C

Figure 3.
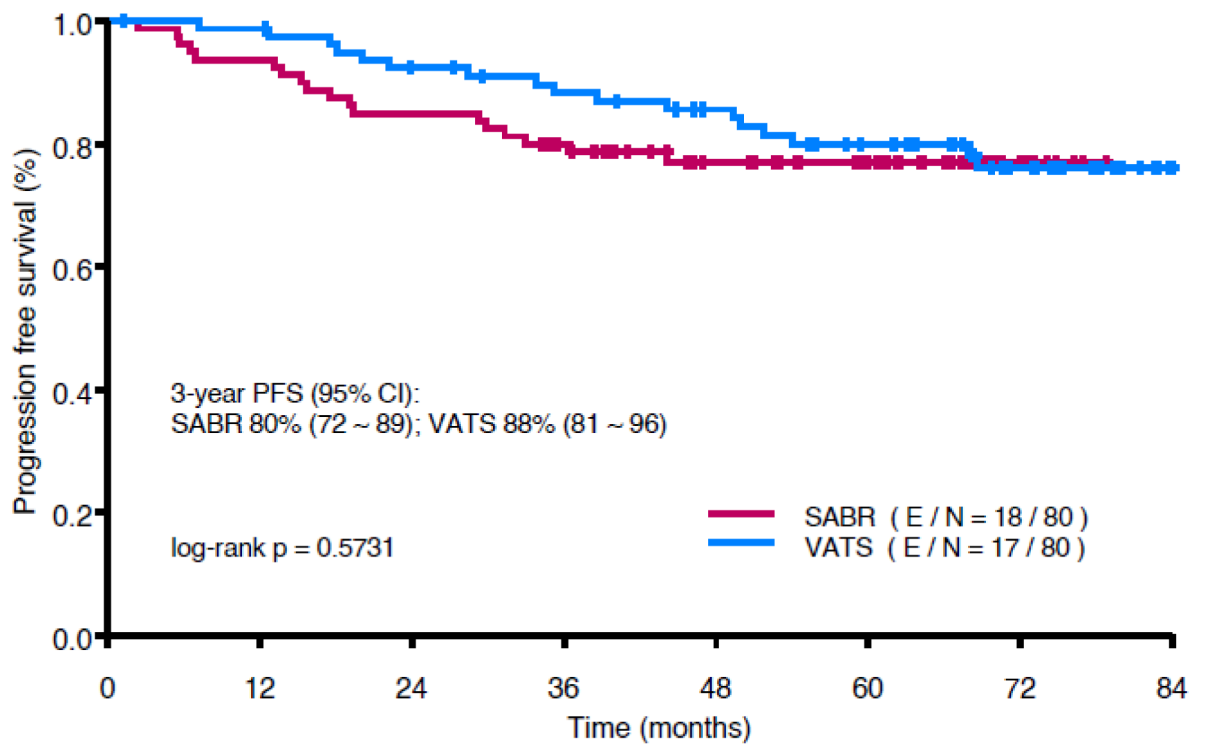Overall survival (A), progression-free survival (B), and lung cancer-specific survival (C) among patients treated with SABR or video-assisted thoracoscopic surgical lobectomy with mediastinal lymph node dissection (VATS L-MLND).

Table 1.

Clinical characteristics of the SABR study population.

Characteristic	Mean ± SD or No. (%)
Age (years)	
Mean ± SD	68.8 ± 7.9
Sex	
Male	44 (55%)
Female	36 (45%)
Zubrod performance status	
0	55 (69%)
1	25 (31%)
Histology	
Squamous cell carcinoma	13 (16%)
Adenocarcinoma	63 (79%)
NSCLC, not otherwise specified	4 (5%)
Tumor stage	
T1aN0M0	52 (65%)
T1bN0M0	28 (35%)
Tumor size, cm	
Mean ± SD	1.83 ± 0.56
Tumor site	
Left lower lobe	10 (13%)
Left upper lobe	18 (22%)
Right lower lobe	11 (14%)
Right middle lobe	3 (4%)
Right upper lobe	38 (47%)
Tumor location	
Central	26 (33%)
Peripheral	54 (67%)
Baseline smoking status	
Current	16 (20%)
Former	50 (63%)
Never	14 (18%)
Baseline FEV1 (% predicted)	
Mean ± SD	85.8 ± 19.1
Baseline FVC (% predicted)	
Mean ± SD	94.4 ± 16.5
Baseline DLCO (% predicted)	
Mean ± SD	81.4 ± 16.9

Abbreviations: SABR, stereotactic ablative radiotherapy; SD, standard deviation; NSCLC, non-small cell lung cancer; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; DLCO, diffusion capacity of the lungs for carbon monoxide

Table 2.

Toxicity of SABR in the 80 evaluable patients.

Adverse Event	Grade 2	Grade 3	Grade 4	Grade 5
Dyspnea	0	1 (1.3%)	0	0
Pneumonitis	1 (1.3%)	0	0	0
Pulmonary fibrosis	1 (1.3%)	0	0	0