Adverse Events Following Limited Resection versus Stereotactic Body Radiation Therapy for Early Stage Lung Cancer

Qian Wang[1], Kimberly Stone[2], Jeffrey A. Kern[3], Christopher G. Slatore[4,5,6,7], Scott Swanson[8], William Blackstock, Jr.[9], Rabia Saeed Khan[2], Cardinale B. Smith[1], Rajwanth R. Veluswamy[1], Mark Chidel[10], and Juan P. Wisnivesky[2,11]

[1]Tisch Cancer Institute, [2]Division of General Internal Medicine, and [11]Division of Pulmonary and Critical Care Medicine, Icahn School of Medicine at Mount Sinai, New York, New York; [3]Division of Oncology, National Jewish Health, Denver, Colorado; [4]Center to Improve Veteran Involvement in Care and [7]Section of Pulmonary and Critical Care Medicine, VA Portland Health Care System, Portland, Oregon; [5]Division of Pulmonary and Critical Care Medicine, Department of Medicine, and [6]Department of Radiation Medicine, Knight Cancer Institute, Oregon Health and Science University, Portland, Oregon; [8]Department of Thoracic Surgery, Brigham and Women's Hospital, Boston, Massachusetts; [9]Department of Radiology, Wake Forest Baptist Medical Center, Winston Salem, North Carolina; and [10]Department of Radiation Oncology, Colorado Permanente Medical Group, Denver, Colorado

ORCID ID: 0000-0002-1201-865X (Q.W.).

Abstract

Rationale: Approximately a quarter of patients with early stage lung cancer are not medically fit for lobectomy. Limited resection and stereotactic body radiation therapy (SBRT) have emerged as alternatives for these patients. Given the equipoise on the effectiveness of the two treatments, treatment-related adverse events (AEs) could have a significant impact on patients' decision-making and treatment outcomes.

Objectives: To compare the AE profile between SBRT versus limited resection.

Methods: Data were derived from a prospective cohort of patients with stage I-IIA non-small cell lung cancer who were deemed as high-risk for lobectomy recruited from five centers across the United States. Propensity scores and inverse probability weighting were used to compare the rates of 30- and 90-day AEs among patients treated with limited resection versus SBRT.

Results: Overall, 65% of 252 patients underwent SBRT. After adjusting for propensity scores, there was no significant difference in developing at least one AE comparing SBRT to limited resection (odds ratio [OR]: 1.00; 95% confidence interval [CI]: 0.65–1.55 and OR: 1.27; 95% CI: 0.84–1.91 at 30 and 90 days, respectively). SBRT was associated with lower risk of infectious AEs than limited resection at 30 days (OR: 0.05; 95% CI: 0.01–0.39) and 90 days posttreatment (OR: 0.41; 95% CI: 0.17–0.98). Additionally, SBRT was associated with persistently elevated risk of fatigue (OR: 2.47; 95% CI: 1.34–4.54 at 30 days and OR: 2.69; 95% CI: 1.52–4.77 at 90 days, respectively), but significantly lower risks of respiratory AEs (OR: 0.36; 95% CI: 0.20–0.65 and OR: 0.51; 95% CI: 0.31–0.86 at 30 and 90 days, respectively).

Conclusions: Though equivalent in developing at least one AE, we found that SBRT is associated with less toxicity than limited resection in terms of infectious and respiratory AEs but higher rates of fatigue that persisted up to 3 months posttreatment. This information, combined with data about oncologic effectiveness, can help patients' decision-making regarding these alternative therapies.

Keywords: early stage lung cancer; non-small cell lung cancer; limited resection; stereotactic body radiation therapy; adverse events

(Received in original form March 28, 2022; accepted in final form July 5, 2022)

Supported by the National Cancer Institute grant R01CA203193. C.G.S. is supported by resources from the Center to Involve Veteran Involvement in Care, VA Portland Health Care System, Portland, OR. The Department of Veterans Affairs did not have a role in the conduct of the study; in the collection, management, analysis, or interpretation of data; or in the preparation of the manuscript. The views expressed in this article are those of the authors and do not necessarily represent the views of the Department of Veterans Affairs or the US Government.

Author Contributions: Q.W. contributed to methodology, writing original draft, reviewing and editing; K.S. contributed to methodology, formal analysis, data curation, reviewing and editing; J.A.K. contributed to conceptualization, investigation, resources, writing original draft, reviewing and editing, and funding acquisition; C.G.S. contributed to conceptualization, investigation, resources, reviewing and editing the draft, and funding acquisition; S.S. contributed to reviewing and editing the draft; W.B. contributed to reviewing and editing the draft; R.S.K. contributed to methodology, and writing-reviewing and editing; C.B.S. contributed to contributed to conceptualization, writing-reviewing and editing; R.R.V. contributed to reviewing and editing, and supervision; M.C. contributed to reviewing and editing, and supervision; and J.P.W. contributed to conceptualization, methodology, investigation, resources, writing original draft, reviewing and editing, supervision, project administration, and funding acquisition.

Ann Am Thorac Soc Vol 19, No 12, pp 2053–2061, Dec 2022

DOI: 10.1513/AnnalsATS.202203-275OC
Internet address: www.atsjournals.org

While approximately half of lung cancers are at an advanced stage on diagnosis, the number of patients with early stage disease is growing with the implementation of low-dose chest computed tomography screening (1). Surgery with an anatomic lobar resection (i.e., lobectomy) via open or video-assisted thoracoscopic surgery is the standard of care for medically and physiologically fit patients with stage I-IIA non-small cell lung cancer (NSCLC). However, lung cancer is predominantly a disease of the elderly, with a mean age at diagnosis of 71 years, and patients frequently have other smoking-related comorbidities such as cardiovascular disease or chronic obstructive pulmonary disease (COPD) (2). As a result, approximately 25% of early stage lung cancer patients are determined to be not medically fit for lobectomy (3). These patients often have borderline lung function, multiple comorbidities, limited functional status, or are frail; and all of which are considered high-risk conditions for full lobectomy (4, 5).

Limited resection, segmentectomy or wedge resection, and stereotactic body radiation therapy (SBRT) are alternative treatment options for early stage NSCLC patients at high-risk for lobectomy (4, 6, 7). Wedge resection is nonanatomic surgery consisting of the removal of lung tumor with a surrounding margin of normal lung parenchyma. Technically more challenging, segmentectomy involves the anatomic removal of a complete lung segment (8). These limited surgical approaches for lung resection currently represent approximately 30% of all surgeries for stage I NSCLC (4, 6). Although not as effective as lobectomy (9), limited resection is associated with relatively good 5-year survival rates (8).

SBRT has emerged as a noninvasive alternative to limited resection for stage I lung cancer (7). In single arm phase I and II trials, (10–12) SBRT has been shown to provide 3-year survival rates between 50% and 70%, similar to outcomes achieved with limited resection (10, 11). However, there is no data comparing the oncologic outcomes of SBRT versus surgery from well-powered, randomized controlled trials (RCT) (13–15). While a meta-analysis of two RCTs (STARS and ROSEL) showed that SBRT led to better survival than lobectomy, the sample size was very small ($n = 58$) and the included trials were discontinued before follow-up was completed due to lack of recruitment (15, 16). Furthermore, systematic reviews of observational studies comparing limited resection to SBRT for early stage lung cancer have shown mixed results (13, 14, 17–23). As a consequence, there is currently no clear guidance in terms of oncologic outcomes defining the best treatment approach for early stage NSCLC patients who are at high-risk for lobectomy.

Besides the oncological outcomes, treatment-related adverse events (AEs) are important patient-centered outcomes that may be highly relevant in the case of equipoise between therapeutic approaches. Both limited resection and SBRT are potentially associated with major AEs (24). However, AE data from well-matched patients with early stage lung cancer treated with limited resection or SBRT are limited. In this study, we used data from a well-characterized, prospective cohort to compare the rate of 30- and 90-day AEs in patients with early stage NSCLC treated with limited resection versus SBRT.

Material and Methods

Study Participants

The study cohort was enrolled in a prospective observational trial recruited from five sites across the United States, including New York City, New York (Mount Sinai Health System), Portland, Oregon, (Oregon Health and Science University/Veterans Affairs Portland Health Care System), Boston, Massachusetts (Brigham and Women's Hospital and Dana Farber Cancer Institute), Denver, Colorado, (National Jewish Health and St. Joseph's Hospital), and Wake Forest, North Carolina, (Wake Forest Baptist Health) from September 2016 to May 2021. The study was approved by the Institutional Review Board of all participant institutions and all patients signed informed consent. The study methods were compliant with the STROBE checklist for cohort study. English- or Spanish-speaking patients who were potential candidates for limited resection and SBRT were eligible to participate in the study if they: *1*) had primary stage IA, IB, or IIA NSCLC with tumor size $\leqslant 5$ cm and no lymph node involvement based on information available prior to curative-intent therapy; *2*) were high-risk for lobectomy based on the assessment of the treating provider (e.g., thoracic surgeon, radiation oncologist, etc.); and 3) ability to be contacted for longitudinal follow-up. Patients with *1*) severe cognitive impairment or dementia; *2*) history of prior radiation to the lung; and *3*) prior history of cancer within the last 5 years (except for non-melanoma skin cancer) were excluded from the study.

Study Measures

In person and/or virtual (during the COVID-19 pandemic) interviews were used to collect information regarding sociodemographic features including age, sex, race, ethnicity, education, income, and insurance status. Tobacco use, including smoking status and pack-years of smoking, was obtained by self-report. A self-reported comorbidity profile was also collected on study entry including any history of COPD, hypertension, hypercholesterolemia, cardiovascular disease (CVD, including myocardial infarction [MI], coronary artery disease, valvular heart disease, atrial fibrillation, peripheral vascular disease) diabetes, and kidney disease. Body mass index (BMI, m/kg^2) was calculated based on measurements of height and weight. Symptoms of depression and anxiety were assessed with the Patient Health Questionnaire for Depression and Anxiety (PHQ-4) (25) and the 15-item short form of the Geriatric Depression Scale (GDS-15) (26). The 4-item cognitive function (Mini-Cog) Test was used to assess cognitive domains including memory, language comprehension, visual-motor skills and executive function (27). The 5-item Medical Research Council (MRC) dyspnea scale was used for grading the impact of breathlessness on daily activities (28). Pre-treatment pulmonary function including the forced expiratory volume in one second (FEV_1) and the FEV_1 to forced vital capacity ratio (FEV_1/FVC) were measured by spirometry

Correspondence and requests for reprints should be addressed to Qian Wang, M.D., M.P.H, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, Box 1079, New York, NY 10029. E-mail: dr.qian.wang@gmail.com.

This article has a related editorial.

or obtained from review of the electronic medical record (EMR). Performance status and self-care capability was evaluated using the Eastern Cooperative Oncology Group (ECOG) score (range 0–5) (29). Additionally, the 6-item Patient-reported Outcomes Measurement Information System (PROMIS) scale was used to measure physical functional status (30). Health-related quality-of-life was self-reported using the 8-item Short-Form Survey (SF-8) (31) and the lung-cancer specific Functional Assessment of Cancer Therapy-Lung (FACT-L) scale (32).

Diagnostic, staging and pretreatment workup including chest tomography, bronchoscopy, fine needle aspiration, endoscopic ultrasound, positron emission tomography, ventilation/perfusion scan, and cardiac testing were abstracted from the EMR using a standardized instrument. We recorded tumor histology (adenocarcinoma, squamous cell carcinoma, and other), size, and pretreatment clinical stage (IA, IB, and IIA) according to the American Joint Committee on Cancer eighth edition criteria based on review of the EMR. Treatment plans (i.e., therapeutic intention) were obtained by interviewing treating physicians about each case and complemented by EMR review of pretreatment notes.

Participants were followed at 30 and 90 days to obtain information about AEs using the Common Terminology Criteria for Treatment-related AE (version 4.0) which includes classification of severity (grade 1 to 5) and causality (related or no-treatment related) (33). These data were supplemented by review of the EMR. AEs were classified as: *1*) constitutional (fatigue); *2*) cardiovascular (MI, atrial fibrillation, ventricular arrythmia, transient ischemic attack, cerebrovascular accident and venous thromboembolism [VTE]); *3*) respiratory (dyspnea, bronchospasm, atelectasis, pleural effusion, pneumonitis, hemoptysis, pneumothorax, bronchopleural fistula, postoperative thoracic procedure complication, acute respiratory distress syndrome, and respiratory failure); *4*) gastrointestinal (esophagitis); *5*) musculoskeletal (chest wall pain, rib pain, and rib fracture); *6*) cutaneous (rash and skin burn); *7*) infectious (urinary tract infection and other infections); *8*) hematological (including anemia requiring transfusion); *9*) neurological (brachial plexopathy and other neurological events); and *10*) other (e.g., weight loss, sleeping disturbance, discomfort, etc.).

Statistical Analysis

Baseline characteristics of patients treated with limited resection versus SBRT were compared using a *t* test, Wilcoxon test or chi-square test for continuous and categorical variables, as appropriate. Unadjusted cumulative rates of AEs occurring within 30 and 90 days of treatment initiation in patients that underwent SBRT versus limited resection were compared using the chi-square test.

We used propensity scores methods to adjust for differences in the baseline characteristics of early stage NSCLC patients treated with SBRT versus limited resection. We first fitted a logistic regression model predicting treatment type conditional on sociodemographic characteristics, smoking history, baseline comorbidity profile, BMI, psychiatric assessment (PHQ4 and GDS scores), Mini-Cog test, patient-reported respiratory symptoms (MRC scale), pulmonary function test (FEV_1 and FEV_1/FVC ratio), quality of life (PROMIS, SF-8 and FACT-L scores), and pretreatment lung cancer characteristics (clinical stage and tumor size). Using this model, we calculated weights representing the inverse of the probability of receiving limited resection or SBRT based on the final therapeutic plans of the treating team. Then we used logistic regression with the calculated inverse probability weightings to compare rates of AEs among patients treated with limited resection versus SBRT. We used multiple imputation (proc MI with 10 imputations) approaches to address missing data.

Sample size calculations showed that with a cohort of 250 patients, the study had >80% power to identify a 12% absolute difference in the rates of AE following limited resection versus SBRT. All analyses were conducted with SAS statistical software version 9.4 (SAS Institute) and using two-sided *P* values.

Results

A total of 509 patients considered for limited resection (79% video assisted thoracoscopic resection and 10% robotic assisted surgery) or SBRT were approached for participation in the study. A total of 122 (24%) declined participation. A total of 387 patients with lung cancer consented to study participation. Of these, 2 (<1%) withdrew before treatment initiation and 47 (12%) were excluded because they underwent a treatment other than limited resection or SBRT. Of the 338 participants in the study cohort, 252 (75%) reached the relevant assessments at the time of these analyses and were included in the study.

Overall, 88 (35%) of participants underwent limited resection while 164 (65%) received SBRT. Baseline characteristics according to treatment are shown in Table 1. Compared with patients who underwent limited resection, those who were treated with SBRT were older ($P < 0.0001$), more likely to be White ($P < 0.0001$), less likely to have an advanced education degree ($P = 0.04$), and less likely to have private insurance ($P < 0.0001$). Physiologically, patients treated with SBRT were more likely to have COPD ($P < 0.0001$), hypertension ($P = 0.04$), CVD ($P < 0.01$); and lower FEV_1 value ($P < 0.0001$), lower FEV_1/FVC ratio ($P < 0.0001$), and an ECOG score of ≥ 1 ($P < 0.0001$) than patients treated with surgery. Functionally, and from a quality-of-life standpoint, patients treated with SBRT reported a higher GDS score ($P = 0.01$), a lower Mini-Cog score ($P = 0.03$), a higher MRC score ($P < 0.001$), a lower PROMIS T-score ($P < 0.0001$), lower SF-8 score ($P < 0.0001$) and FACT-L scores ($P < 0.0001$). Finally, patients who were treated with SBRT were less likely to have stage IA lung cancer ($P < 0.001$).

Overall, unadjusted analyses (Table 2) showed that there were no significant differences in the proportion of patients treated with SBRT versus limited resection that developed at least one AE (25.6% versus 29.6%, $P = 0.50$) 30 days posttreatment. Most 30-day AEs after SBRT (85.8%) and limited resection (88.5%) were mild (grades I and II). However, the number of patients with grade III/IV respiratory AEs was low in both the SBRT and surgical groups (2 [1.2%] versus 1 [1.1%]. However, one patient in the surgical group died within 30 days of surgery. The most common 30-day AEs for both groups were respiratory (70% dyspnea, 22% atelectasis, 13% pneumothorax, and 11% pleural effusions), with a higher risk found among those who underwent limited resection (58.3% versus 41.7% for SBRT, $P = 0.002$). In addition, patients that underwent limited resection were more likely to develop infectious AE than SBRT-treated patients (8.0% versus 0.6%, $P = 0.003$), and fatigue was more frequently reported in patients who had SBRT than limited

resection (17.7% versus 8.0%, $P = 0.04$). No statistically significant difference in the 30-day rate of neurological, cardiovascular, cutaneous, gastrointestinal, hematological or musculoskeletal AEs were found between the treatment modalities ($P > 0.05$ for all comparisons).

Similarly, there was no significant difference in the proportion of patients treated with SBRT versus limited resection that developed at least one AE at 90 days post treatment (34.2% versus 34.1%, $P = 0.99$). The proportion of grade I and II AEs were 89.3% for SBRT and 90.0% for surgery. Respiratory complications remained the most common 90-day AE for both procedures and were more common among patients treated with limited resection than SBRT (53.3% versus 46.7%, P 0.004). The number of severe respiratory AEs at 90-days was low in both groups (3 [1.8%] versus 1 [1.1%] in the SBRT and surgical group, respectively). Prevalence of fatigue remained higher at 90 days among patients who underwent SBRT than limited resection (21.3% versus 9.1%, $P = 0.01$). There were no statistically significant differences in the rates of infectious AEs between SBRT and limited resection (4.3% versus 8.0%, $P = 0.25$). Limited resection was again associated with a higher risk of 90-day cardiovascular complications than SBRT (4.6% versus 0.6%, $P = 0.05$). No significant 90-day differences were observed in neurological, cutaneous, gastrointestinal, hematological, or musculoskeletal AEs between SBRT versus limited resection($P > 0.05$ for all comparisons). Most AEs at 390 days posttreatment in both arms were also not severe (grades I and II).

In propensity scored adjusted analyses (Table 3), at 30 days, there were no statistically significant differences in the odds of experiencing at least one AE (OR, 1.00; 95% CI, 0.65–1.55) when comparing SBRT to limited resection. When stratified by organ system, patients treated with SBRT had 2.47 greater odds of developing fatigue (OR, 2.47; 95% CI, 1.34–4.54) than those who underwent limited resection. In addition, patients treated with SBRT were at lower risk of developing infectious (OR, 0.05; 95% CI, 0.01–0.39) and respiratory complications (OR, 0.36; 95% CI, 0.20–0.65) than those treated with limited resection.

Similarly, at 90 days there were no statistically significant differences in the risk of developing at least one AE (OR, 1.27; 95% CI, 0.84–1.91). Compared with patients who underwent limited resection, patients treated with SBRT had higher odds of developing fatigue (OR, 2.69; 95% CI, 1.52–4.77) but lower odds of respiratory (OR, 0.51; 95% CI, 0.31–0.86) AEs. Patients who underwent SBRT remained at lower risk of developing infectious AEs than patients treated with limited resection (OR, 0.41; 95% CI, 0.17–0.98). No differences were found in the adjusted risk of cardiovascular or musculoskeletal 90-day AEs. We were not able to compare the adjusted risk of neurological, cutaneous, gastrointestinal, and hematological AEs due to the overall low rates of these complications.

Table 1. Baseline characteristics of study patients treated with stereotactic body radiation therapy versus limited resection*

Characteristic	SBRT *N* = 164	Limited Resection *N* = 88
Age, years, mean (SD)	74.3 (7.6)	69.7 (8.3)
Female, No. (%)	82 (50.0)	50 (56.8)
Race/ethnicity, No. (%)		
White	141 (86.0)	57 (64.8)
Black	15 (9.2)	12 (13.6)
Hispanic	3 (1.8)	15 (17.1)
Other	5 (3.1)	4 (4.6)
Education, No. (%)		
High school or below	51 (31.1)	31 (35.2)
Some college	38 (23.2)	11 (12.5)
Completed college	44 (26.8)	23 (26.1)
Advanced degree	17 (10.4)	19 (21.6)
Annual income, No. (%)		
<$50,000	80 (48.8)	37 (42.1)
Insurance, No. (%)		
Private	45 (27.4)	49 (55.7)
Medicare	52 (31.7)	28 (31.8)
Medicaid	5 (3.1)	2 (2.3)
Other	47 (28.7)	6 (6.8)
Missing	15 (9.2)	3 (3.4)
Smoking status, No. (%)		
Current	29 (17.7)	12 (13.6)
Pack-years, mean, SD	43.5 (31.0)	47.0 (70.3)
Comorbidities, No. (%)		
COPD	105 (64.0)	27 (30.7)
Hypertension	100 (60.1)	43 (48.9)
High cholesterol	71 (43.3)	49 (55.7)
Cardiovascular disease	94 (57.3)	33 (37.5)
Diabetes	36 (22.0)	16 (18.2)
Chronic kidney disease	13 (7.9)	5 (5.7)
BMI, kg/m^2, mean (SD)	26.9 (6.0)	28.6 (6.7)
Characteristic	**SBRT**	**Limited Resection**
PHQ-4, median, IQR†	2 (1–4)	2 (0–4)
GDS, median, IQR‡	7 (6–8)	6 (5–7)
Mini Cog, median, IQR§	3 (1)	5 (1)
MRC scale, median, IQR‖	2 (1–3)	1 (1–3)
FEV_1% predicted, mean, SD	64.9 (25.4)	85 (24.8)

(*Continued*)

Discussion

Limited resection and SBRT are the main treatment options for patients with early stage lung cancer who are not good candidates for lobectomy. In this prospective cohort of patients with stage I-IIA NSCLC, we found that SBRT and limited resection were associated with similar risks of developing at least one AE at the 30-day and 90-day landmarks. When stratifying AEs by organ system, SBRT was associated with a higher risk of fatigue; whereas the risks of respiratory complications were significantly higher among patients treated with limited resection. Limited resection was associated with higher risk of 30-day infectious AEs

Table 1. (*Continued*)

Characteristic	SBRT	Limited Resection
FEV_1/FVC ratio, mean, SD	58.6 (16.2)	68.0 (12.6)
ECOG Performance status, No. (%)		
0	55 (33.5)	61 (69.3)
1	77 (47.0)	16 (18.2)
2	21 (12.8)	3 (3.4)
3	5 (3.1)	1 (1.1)
Missing	6 (3.7)	7 (8.0)
PROMIS (T score), mean, SD[¶]	28.6 (7.9)	37.1 (8.0)
SF8 physical scale, mean, SD[**]	40.1 (9.2)	48.0 (9.4)
SF8 mental scale, mean, SD[††]	50.3 (9.5)	52.8 (9.1)
FACT-L, mean, SD[‡‡]	19.0 (3.2)	20.7 (2.8)
Tumor information		
Clinical stage, No. (%)		
IA	103 (63.2)	74 (85.1)
IB	56 (34.4)	13 (14.9)
IIA	4 (2.5)	0 (0.0)
Tumor size, No. (%)		
<3 cm	103 (63.2)	74 (85.1)

Definition of abbreviations: BMI = body mass index; COPD = chronic obstructive pulmonary disease; ECOG = Eastern Cooperative Oncology Group; FACT-L = Functional Assessment of Cancer Therapy-Lung; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; GDS = Geriatric Depression Scale; IQR = interquartile range; MRC = Medical Research Council dyspnea scale; PHQ-4 = Patient Health Questionnaire for Depression and Anxiety; PROMIS = Patient-reported Outcomes Measurement Information System; SBRT = stereotactic body radiation therapy; SD = standard deviation; SF8 = 8-item Short-Form Survey.

*The percentage of participants with missing data for specific covariates were: education = 7%, Income = 28%, Insurance = 7%, Smoking Status = 9%, BMI = 8%, PHQ-4 = 8%, GDS = 10%, Mini-Cog = 37%, Medical Research Council Scale = 10%, FEV_1% predicted = 19%, FEV_1/FVC ratio = 22%, ECOG = 5%, PROMIS = 6%, SF8 physical scale = 16%, SF8 mental scale = 16%, FACT-L = 7%, Clinical stage = 1%, and Tumor Size = 1%. All other variables had no missing data.

[†]The PHQ-4 measures symptoms of anxiety and depression. Scores are rated as: no (0–2), mild (3–5), moderate (6–8), or severe (9–12) symptoms.

[‡]GDS score measures symptoms of depression. Scores of 0–4 suggest no symptoms; 5–8 indicate mild depression symptoms; 9–11 indicate moderate depression symptoms; and 12–15 indicate severe symptoms of depression.

[§]The Mini cog test is used to screen for dementia; scores of 3–5 indicates a negative screen.

[‖]The MRC scale measures the extent to which patients' breathlessness affects their mobility.

[¶]The PROMIS scale measures physical functional status; population-based reference T-scores (mean: 50, standard deviation: 10) are used to evaluate patients' responses.

[**]The SF-8 physical scale measures the physical component of health-related quality of life. A higher score indicates better quality of life.

[††]The SF-8 mental health scale measures the mental health component of health-related quality of life. A higher score indicates better self-reported reported quality of life.

[‡‡]The FACT-L measures lung cancer-specific health-related quality of life. A higher score indicates better quality of life.

than SBRT, but such difference was less pronounced at 90 days. These data suggest that while common, most AEs following these treatments are not severe. This information can facilitate patient-provider discussions regarding patient preferences for these procedures.

There is currently equipoise in terms of oncologic outcomes for treating patients who are not candidates for lobectomy due to the lack of RCT results comparing alternative therapies. AEs may play an important role in selecting the treatment of patients with stage I-IIA NSCLC who are at high risk for treatment-related complications. Data regarding AEs from randomized trials comparing SBRT to surgery are limited. Pooled analysis of the STARS and ROSEL trials (15) examined grade 3 or higher severe acute and chronic AEs in patients with adequate performance status randomized to SBRT ($n = 31$) versus anatomic lobectomy ($n = 27$). During a median follow-up of 35 to 40 months, 3 (10%) patients in the SBRT group versus 13 (48%) patients in the surgery group had severe AEs, including 1 death in the surgery group. Previous meta-analyses of observational studies (13, 14, 18, 20, 22, 23) focused on comparing survival outcomes between SBRT versus surgery with only a few reporting AEs (17, 19). In a meta-analysis by Cao and colleagues that included 23 studies (19), the most common 30-day AEs after SBRT were fatigue (0–27%), radiation pneumonitis (1–20%), chest pain (0–11%), and rib fractures (0–12%), whereas air leak (0–12%), pneumonia (0–13%), cardiac arrhythmia (0–12%), and MI (0–2%) were more common after surgery (including lobectomy and limited resection). Periprocedural mortality was 0% for SBRT but up to 8% postsurgery in the studies included in the meta-analysis. A more recent meta-analysis of cohort studies reported similar 30-day and 90-day mortality between SBRT versus sublobar resections (17). Although meta-analyses summarized the available literature, the heterogeneity in study design, patient population, and surgical techniques, including lobectomy, limited the validity of the AE pooled estimates (17, 19). In this study, we evaluated AEs at two time points after limited resection or SBRT in a well-characterized cohort of patients that underwent a standardized evaluation before treatment. We found that most AEs were not severe, with the exception of the death of a patient due to cardiomyopathy at Day 27 post limited resection. Additionally, patients treated with limited resection were at increased risk of pulmonary and cardiovascular AEs. Our results add to the existing literature by providing adjusted estimates controlling for several predictors that are not usually collected in observational studies and that may confound the relationship between procedure type and risk of AEs.

Constitutional AE

Fatigue is a complex symptom that is usually multifactorial in patients with cancer and is closely related to anxiety, depression, respiratory symptoms, and functional status (34). In an earlier study measuring quality of life after curative radiotherapy in patients with stage I NSCLC ($n = 46$), the frequency of fatigue was as high as 80% pretreatment with a gradual increase in severity over the 2 weeks following radiation therapy (35). While surgery, in general, is associated with a greater symptom burden than radiation therapy, large studies providing quantitative analyses of the prevalence of fatigue in the early postoperatively period in patients with stage I-II lung cancer are lacking. One single-center study ($n = 98$) showed that

Table 2. Unadjusted rates of adverse events among patients with early stage non-small cell lung cancer treated with stereotactic body radiation therapy versus limited resection

	30 d Post Treatment					90 d Post Treatment				
Adverse Event	SBRT No. (%)†	Grade III/IV No. (%)‡	Surgery No. (%)†	Grade III/IV No. (%)‡	*P* Value*	SBRT No. (%)†	Grade III/IV No. (%)‡	Surgery No. (%)†	Grade III/IV No. (%)‡	*P* Value*
At least 1 AE	42 (25.6)	6 (14.2)	26 (29.6)	3 (11.5)	0.50	56 (34.2)	6 (10.7)	30 (34.1)	3 (10.0)	0.99
Constitutional	29 (17.7)	0 (0.0)	7 (8.0)	0 (0.0)	0.04	35 (21.3)	0 (0.0)	8 (9.1)	0 (0.0)	0.01
Respiratory	15 (41.7)	2 (13.3)	21 (58.3)	1 (4.8)	<0.01	21 (46.7)	3 (14.3)	24 (53.3)	1 (4.1)	<0.01
Infectious	1 (0.6)	0 (0.0)	7 (8.0)	2 (28.5)	<0.01	7 (4.3)	2 (28.5)	7 (8.0)	2 (28.5)	0.25
Cardiovascular	1 (0.6)	1 (100.0)	2 (2.3)	0 (0.0)	0.28	1 (0.6)	1 (100.0)	4 (4.6)	0 (0.0)	0.05
Cutaneous	3 (1.8)	1 (33.3)	0 (0.0)	0 (0.0)	0.55	4 (2.4)	1 (25.0)	0 (0.0)	0 (0.0)	0.30
Musculoskeletal	4 (2.4)	1 (25.0)	2 (2.3)	0 (0.0)	0.99	5 (3.1)	1 (20.0)	2 (2.3)	0 (0.0)	0.99
Gastrointestinal	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0.99	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0.99
Neurological	1 (0.6)	1 (100.0)	0 (0.0)	0 (0.0)	0.99	1 (0.6)	1 (100.0)	0 (0.0)	0 (0.0)	0.99
Hematological	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	0.35	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	0.35

Definition of abbreviations: AE = adverse event; SBRT = stereotactic body radiation therapy.
**P* value compares the statistical significance for overall (i.e., all grades) AEs between SBRT vs. surgery.
†Indicates the percentage of participants in the treatment group that experienced AEs of any level of severity.
‡Indicates percentage of the total AEs that were grade III or IV.

approximately half of the patients reported fatigue 1 month after thoracotomy with the prevalence declining to 38% by Month 4 post-procedure (36). Fatigue can negatively impact quality of life, and is often undertreated (37). Thus, our findings that this symptom is more common after SBRT is important in guiding providers to assess for fatigue, provide counseling, and timely referral to rehabilitation for patients with more severe symptoms (37).

Respiratory AE

Respiratory complications were among the most common AEs observed in our cohort as well as in previous studies (19, 21, 38). It is important to point out that the types of respiratory AEs were different among patients treated with limited resection versus SBRT. As in prior reports, pneumonia and air leak were more common after surgical resection (19), while symptomatic radiation pneumonitis was almost exclusively associated with SBRT (38). In our study, while patients who underwent limited resection had a higher risk of respiratory complications, in general, the rates of severe (grade III/IV) AEs were low, and similar in both groups. Unfortunately, the low number of severe AEs did not allow for formal statistical comparisons across groups. Most patients with lung cancer treated with limited resection have reduced lung function or other severe smoking-associated comorbidities, which are independent risk factors for postoperative pneumonia (4, 6, 39). Moreover, postoperative pneumonia carries a high morbidity and mortality, and is associated with lower long-term survival (40). These findings highlight the need for aggressive postoperative management to reduce the risk of pulmonary infections. For then SBRT-associated respiratory AE profile, tumor location plays an important role (41).

Table 3. Propensity-score adjusted probability of adverse events among patients with early stage non-small cell lung cancer treated with stereotactic body radiation therapy versus limited resection

Adverse Events	30 d Post Treatment OR (95% CI)	90 d Post Treatment OR (95% CI)
At least 1 adverse event	1.00 (0.65–1.55)	1.27 (0.84–1.91)
Constitutional	2.47 (1.34–4.54)	2.69 (1.52–4.77)
Respiratory	0.36 (0.20–0.65)	0.51 (0.31–0.86)
Infectious	0.05 (0.01–0.39)	0.41 (0.17–0.98)
Cardiovascular	0.23 (0.03–1.89)	0.15 (0.02–1.12)
Musculoskeletal	0.67 (0.21–2.09)	1.11 (0.41–3.05)

Definition of abbreviations: CI = confidence interval; OR = odds ratio.

Rare and potentially lethal AEs such as pulmonary hemorrhage or airway necrosis have been reported in central tumors within 2 cm of the trachea or proximal bronchial tree (41). Radiation pneumonitis, which typically develops 1 to 3 months post-treatment, is one of the most common (15–40% incidence) and clinically challenging AEs after SBRT (38). In addition to a dose-response relationship with radiation, pre-existing pulmonary conditions such as COPD are independent risk factors for developing pneumonitis (38). 4D computed tomography planning-based thoracic radiation has shown promising results in reducing this rate (38). In addition to glucocorticoids, several therapies targeting free radical production, inflammatory cells, cytokine, and growth factors are under investigation as potential novel treatments for radiation pneumonitis (38).

Infectious AE

Extrapulmonary infection is more common in patients undergoing surgery than SBRT, especially within 30 days post-procedure. Previous reports showed that urinary tract infection (2–14% incidence) and surgical site wound infection (<1–6% incidence) are the second and third most common infectious AE, respectively, following pulmonary infections (40, 42). Extrapulmonary infections can lead to prolonged hospital stay, increased morbidity and worsen long-term survival (40). However, the incidence of extrapulmonary infections also increased in patients treated with SBRT after 30 days.

Prolonged (>4 wk) decrease in circulating lymphocytes and natural killer cells has been observed in patients treated with SBRT leaving these patients at higher risk of infections (43). Therefore, identifying high-risk patients, such as those with diabetes, and developing multidisciplinary strategies to reduce the risk of extrapulmonary infections are critical in this older and vulnerable population.

Other AE

Cardiovascular morbidity is a major concern when assessing eligibility for surgical resection. Prior studies showed that rates of cardiac arrhythmia post-lung resection range from 4 to 11% (19, 42). Similarly, a large study ($n = 9{,}033$) using data from the Society of Thoracic Surgeons reported between 1999 to 2006 found the rates of postoperative MI, deep venous thrombosis, and pulmonary embolism were <1% (42). However, the majority of patients in this study underwent lobectomy (42), which is used in patients with safer cardiovascular profile, potentially explaining the lower risk of complications (44).

Chest wall toxicities, which encompasses skin toxicity (1–14% incidence), chest wall pain (10–44% incidence), and rib fractures (5–17% incidence), can occur when SBRT is used to treat peripheral lung lesions (45, 46). Skin toxicity usually develops 3–6 weeks post-SBRT whereas chest wall pain and rib fractures are longer-term problems with a median onset of 13 months and 19 months posttherapy, respectively (45, 46). Peripheral nerve damage has been suggested as a potential cause of chest wall pain after SBRT, with obesity and higher radiation disease established risk factors (47). In our study, the rates of cutaneous AEs (rash and skin burn) associated with SBRT was 1.8% and 2.8% at 30 days and 90 days, respectively, consistent with previous literature (45, 46). We additionally found that the rates of short-term musculoskeletal AEs (including chest wall pain, rib pain, and rib fracture) post-SBRT were 2.4% and 3.1% at 30 days and 90 days, lower than reported long-term musculoskeletal AE rates (45, 46). Post thoracotomy pain is prevalent in patients who underwent thoracotomy (33–91%), and was more commonly associated with open thoracotomy than video-assisted thoracic surgery (48). The majority of the postthoracotomy pain was neuropathic with a median onset of 7 days and could last for months (49). Advanced age, duration of surgery (>2.5 h), and preoperative use of hypnotic medication were risk factors for post thoracotomy pain (49). No postsurgical neurological AEs were observed in our cohort, which could be due to a relatively younger patient population, surgical technique, and perioperative care.

Acute esophagitis is also commonly seen after SBRT (incidence of grade > 3: 5–20%) (46). This AE usually presents 2–3 weeks after SBRT and is a dose-limiting toxicity that varies in frequency by tumor location (46). The spectrum of esophagitis can range from mild disease to perforation and can lead to tracheoesophageal fistula formation and severely compromised nutritional status (45). We only observed 1 non-severe esophagitis (<1%) post-SBRT treatment at 30 days. Radiation-induced brachial plexopathy (RIBP) has been reported in up to 19% of cases months to years post-SBRT especially after treatment of apical lung tumors in proximity of the brachial plexus (46). Symptoms include upper extremity paresthesia, motor weakness and neuropathic pain (45). The severity of RIBP is positively associated with the dose delivered (50). No grade 3–4 neurological AE was observed in patients treated with SBRT, and only 1 patient developed non-severe AE. A more sophisticated risk model is under development to better quantify the dose tolerance of brachial plexus and potentially minimize the risk of RIBP (50).

Strengths and Limitations

Our prospective study design allowed us to collect detailed data regarding the baseline characteristics of study participants that could guide the use of limited resection versus SBRT. Additionally, prospective data collection minimized recall bias. We also used standardized definitions of AEs based on well-established criteria. The study was conducted in multiple sites across several geographic locations which increases the generalizability of our findings. However, lack of random treatment allocation can lead to systematic differences in the distribution of pretreatment characteristics and confound potential differences in AEs observed in the two treatment groups. Most participating medical centers routinely discuss in multidisciplinary tumor board meetings the treatment of patients with early stage lung cancer . However, it is possible that some patients may have not been evaluated by a surgeon and a radiation oncologist, potentially introducing biases in the treatment used. While we used propensity score methods to attenuate the impact of allocation bias, we could not adjust for unmeasured confounders. Although the study was powered to identify differences in the most frequent AE after limited resection versus SBRT, several complications (including perioperative mortality) and severe AEs had low frequency. Therefore, we cannot exclude potential associations with treatment type. Additionally, our follow-up did not allow us to capture long-term toxicities, such as secondary malignancies after chest radiation, or to compare the oncologic outcomes of patients treated with SBRT versus surgical resection.

In conclusion, our study found that among patients with stage I-IIA NSCLC with tumor size ⩽ 5 cm, SBRT was associated with lower risk of developing respiratory AEs compared with limited resection; however, SBRT was linked to a higher risk of fatigue up to 3 months posttreatment. Limited resection was associated with a higher risk of 30-day infectious AEs than SBRT, but this difference was less pronounced at 90 days. As lung cancer screening becomes increasingly adopted, the treatment of early lesions will become more critical. Understanding the postprocedure-related AE profile, in combination with data about oncologic effectiveness, especially among elderly and vulnerable population, could provide practical knowledge to directly inform patient-centered cancer care. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

References

1 Midthun DE. Early detection of lung cancer. *F1000 Res* 2016;5:739.
2 Weir HK, Thompson TD, Soman A, Møller B, Leadbetter S. The past, present, and future of cancer incidence in the United States: 1975 through 2020. *Cancer* 2015;121:1827–1837.
3 Wisnivesky JP, Bonomi M, Henschke C, Iannuzzi M, McGinn T. Radiation therapy for the treatment of unresected stage I-II non-small cell lung cancer. *Chest* 2005;128:1461–1467.
4 Wisnivesky JP, Henschke CI, Swanson S, Yankelevitz DF, Zulueta J, Marcus S, *et al.* Limited resection for the treatment of patients with stage IA lung cancer. *Ann Surg* 2010;251:550–554.
5 Zhang Y, Sun Y, Wang R, Ye T, Zhang Y, Chen H. Meta-analysis of lobectomy, segmentectomy, and wedge resection for stage I non-small cell lung cancer. *J Surg Oncol* 2015;111:334–340.
6 Brunelli A, Kim AW, Berger KI, Addrizzo-Harris DJ. Physiologic evaluation of the patient with lung cancer being considered for resectional surgery: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest J* 2013;143:e166S–e190S.
7 Tipton K, Launders JH, Inamdar R, Miyamoto C, Schoelles K. Stereotactic body radiation therapy: scope of the literature. *Ann Intern Med* 2011;154:737–745.
8 Bilfinger TV, Baram D. Sublobar resection in nonsmall cell lung carcinoma. *Curr Opin Pulm Med* 2008;14:292–296.
9 Ginsberg RJ, Rubinstein LV; Lung Cancer Study Group. Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer. *Ann Thorac Surg* 1995;60:615–622, discussion 622–623.
10 Fakiris AJ, McGarry RC, Yiannoutsos CT, Papiez L, Williams M, Henderson MA, *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.
11 Timmerman R, Paulus R, Galvin J, Michalski J, Straube W, Bradley J, *et al.* Stereotactic body radiation therapy for inoperable early stage lung cancer. *JAMA* 2010;303:1070–1076.
12 Baumann P, Nyman J, Hoyer M, Wennberg B, Gagliardi G, Lax I, *et al.* Outcome in a prospective phase II trial of medically inoperable stage I non-small-cell lung cancer patients treated with stereotactic body radiotherapy. *J Clin Oncol* 2009;27:3290–3296.
13 Zheng X, Schipper M, Kidwell K, Lin J, Reddy R, Ren Y, *et al.* Survival outcome after stereotactic body radiation therapy and surgery for stage I non-small cell lung cancer: a meta-analysis. *Int J Radiat Oncol Biol Phys* 2014;90:603–611.
14 Chen H, Laba JM, Boldt RG, Goodman CD, Palma DA, Senan S, *et al.* Stereotactic ablative radiation therapy versus surgery in early lung cancer: a meta-analysis of propensity score studies. *Int J Radiat Oncol Biol Phys* 2018;101:186–194.
15 Chang JY, Senan S, Paul MA, Mehran RJ, Louie AV, Balter P, *et al.* Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials. *Lancet Oncol* 2015;16:630–637.
16 Subramanian MP, Meyers BF. Surgical resection versus stereotactic body radiation therapy for stage I NSCLC: can randomized trials provide the solution? *Cancers (Basel)* 2018;10: 310.
17 Ijsseldijk MA, Shoni M, Siegert C, Wiering B, van Engelenburg AKC, Tsai TC, *et al.* Oncologic outcomes of surgery versus SBRT for non-small-cell lung carcinoma: a systematic review and meta-analysis. *Clin Lung Cancer* 2021;22:e235–e292.
18 Hamaji M, Matsuo Y, Chen-Yoshikawa TF, Mizowaki T, Date H. Surgery and stereotactic body radiotherapy for early stage non-small cell lung cancer: review of meta-analyses. *J Thorac Dis* 2019;11:S1646–S1652.
19 Cao C, Wang D, Chung C, Tian D, Rimner A, Huang J, *et al.* A systematic review and meta-analysis of stereotactic body radiation therapy versus surgery for patients with non-small cell lung cancer. *J Thorac Cardiovasc Surg* 2019;157:362–373.e8.
20 Yu XJ, Dai WR, Xu Y. Survival outcome after stereotactic body radiation therapy and surgery for early stage non-small cell lung cancer: a meta-analysis. *J Invest Surg* 2018;31:440–417.
21 Li C, Wang L, Wu Q, Zhao J, Yi F, Xu J, *et al.* A meta-analysis comparing stereotactic body radiotherapy vs conventional radiotherapy in inoperable stage I non-small cell lung cancer. *Medicine (Baltimore)* 2020;99:e21715.
22 Wang S, Wang X, Zhou Q, Xu Y, Xia W, Xu W, *et al.* Stereotactic ablative radiotherapy versus lobectomy for stage I non-small cell lung cancer: A systematic review. *Thorac Cancer* 2018;9:337–347.
23 Zhang B, Zhu F, Ma X, Tian Y, Cao D, Luo S, *et al.* Matched-pair comparisons of stereotactic body radiotherapy (SBRT) versus surgery for the treatment of early stage non-small cell lung cancer: a systematic review and meta-analysis. *Radiother Oncol* 2014;112:250–255.
24 Howington JA, Blum MG, Chang AC, Balekian AA, Murthy SC. Treatment of stage I and II non-small cell lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest J* 2013; 143:e278S–e313S.
25 Kroenke K, Spitzer RL, Williams JBW, Löwe B. An ultra-brief screening scale for anxiety and depression: the PHQ-4. *Psychosomatics* 2009;50:613–621.
26 Shah A, Phongsathorn V, Bielawska C, Katona C. Screening for depression among geriatric inpatients with short versions of the geriatric depression scale. *Int J Geriatr Psychiatry* 1996;11:915–918.
27 Borson S, Scanlan JM, Chen P, Ganguli M. The Mini-Cog as a screen for dementia: validation in a population-based sample. *J Am Geriatr Soc* 2003;51:1451–1454.
28 Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. *Thorax* 1999;54:581–586.
29 The ECOG-ACRIN Cancer Reesearch Group. [accessed 2019 Jun 21]. Available from: https://ecog-acrin.org/resources/ecog-performance-status.
30 Rothrock NE, Amtmann D, Cook KF. Development and validation of an interpretive guide for PROMIS scores. *J Patient Rep Outcomes* 2020;4:16.
31 Ware J Jr, Kosinski M, Keller SDA. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Med Care* 1996;34:220–233.
32 Cella DF, Bonomi AE, Lloyd SR, Tulsky DS, Kaplan E, Bonomi P. Reliability and validity of the Functional Assessment of Cancer Therapy-Lung (FACT-L) quality of life instrument. *Lung Cancer* 1995; 12:199–220.
33 Trotti A, Colevas AD, Setser A, Rusch V, Jaques D, Budach V, *et al.* CTCAE v3.0: development of a comprehensive grading system for the adverse effects of cancer treatment. *Semin Radiat Oncol* 2003; 13:176–181.
34 Huang X, Zhou W, Zhang Y. Features of fatigue in patients with early-stage non-small cell lung cancer. *J Res Med Sci* 2015;20:268–272.
35 Langendijk JA, Aaronson NK, de Jong JMA, ten Velde GPM, Muller MJ, Slotman BJ, *et al.* Quality of life after curative radiotherapy in Stage I non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2002;53:847–853.
36 Sarna L, Cooley ME, Brown JK, Chernecky C, Elashoff D, Kotlerman J. Symptom severity 1 to 4 months after thoracotomy for lung cancer. *Am J Crit Care* 2008;17:455–467, quiz 468.
37 Hsiao CP, Daly B, Saligan LN. The Etiology and management of radiotherapy-induced fatigue. *Expert Rev Qual Life Cancer Care* 2016; 1:323–328.
38 Jain V, Berman AT. Radiation pneumonitis: old problem, new tricks. *Cancers (Basel)* 2018;10:E222.
39 Schussler O, Alifano M, Dermine H, Strano S, Casetta A, Sepulveda S, *et al.* Postoperative pneumonia after major lung resection. *Am J Respir Crit Care Med* 2006;173:1161–1169.
40 Andalib A, Ramana-Kumar AV, Bartlett G, Franco EL, Ferri LE. Influence of postoperative infectious complications on long-term survival of lung cancer patients: a population-based cohort study. *J Thorac Oncol* 2013;8:554–561.
41 Andruska N, Stowe HB, Crockett C, Liu W, Palma D, Faivre-Finn C, *et al.* Stereotactic radiation for lung cancer: a practical approach to challenging scenarios. *J Thorac Oncol* 2021;16:1075–1085.
42 Boffa DJ, Allen MS, Grab JD, Gaissert HA, Harpole DH, Wright CD. Data from The Society of Thoracic Surgeons general thoracic surgery database: the surgical management of primary lung tumors. *J Thorac Cardiovasc Surg* 2008;135:247–254.
43 Maehata Y, Onishi H, Kuriyama K, Aoki S, Araya M, Saito R, *et al.* Immune responses following stereotactic body radiotherapy for stage I primary lung cancer. *BioMed Res Int* 2013;2013:731346.
44 Bédat B, Abdelnour-Berchtold E, Perneger T, Licker MJ, Stefani A, Krull M, *et al.* Comparison of postoperative complications between

segmentectomy and lobectomy by video-assisted thoracic surgery: a multicenter study. *J Cardiothorac Surg* 2019;14:189.
45 Kang KH, Okoye CC, Patel RB, Siva S, Biswas T, Ellis RJ, *et al.* Complications from stereotactic body radiotherapy for lung cancer. *Cancers (Basel)* 2015;7:981–1004.
46 Thompson M, Rosenzweig KE. The evolving toxicity profile of SBRT for lung cancer. *Transl Lung Cancer Res* 2019;8:48–57.
47 Welsh J, Thomas J, Shah D, Allen PK, Wei X, Mitchell K, *et al.* Obesity increases the risk of chest wall pain from thoracic stereotactic body radiation therapy. *Int J Radiat Oncol Biol Phys* 2011;81:91–96.
48 Arends S, Böhmer AB, Poels M, Schieren M, Koryllos A, Wappler F, *et al.* Post-thoracotomy pain syndrome: seldom severe, often neuropathic, treated unspecific, and insufficient. *Pain Rep* 2020;5:e810.
49 Homma T, Doki Y, Yamamoto Y, Ojima T, Shimada Y, Kitamura N, *et al.* Risk factors of neuropathic pain after thoracic surgery. *J Thorac Dis* 2018;10:2898–2907.
50 Kapitanova I, Biswas S, Divekar S, Kemmerer EJ, Rostock RA, Forster KM, *et al.* Estimating the tolerance of brachial plexus to hypofractionated stereotactic body radiotherapy: a modelling-based approach from clinical experience. *Radiat Oncol* 2021;16:98.