

A monocentric retrospective analysis of 10-year overall survival after stereotactic body radiotherapy for medically inoperable non-small cell lung cancer

JÖRG ANDREAS MÜLLER¹, SEVERIN GUTTENBERGER², CHRISTINE KORNUHUBER¹,
CLARA PITZSCHEL^{1,3} and DIRK VORDERMARK¹

¹Department of Radiation Oncology, University Hospital Halle (Saale), D-06120 Halle (Saale), Germany;

²Department of Radiation Oncology, Klinikum Fürth, D-90766 Fürth, Germany; ³Institute of Computer Science, Martin-Luther-University Halle-Wittenberg, D-06120 Halle (Saale), Germany

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Abstract. Stereotactic body radiation therapy (SBRT) is widely used to treat inoperable non-small cell lung cancer (NSCLC). The present study analyzed the long-term (10-year) survival outcomes of patients with NSCLC treated with SBRT in a real-world setting. Patients with NSCLC treated with SBRT between 2009 and 2013 were retrospectively identified from institutional databases at the Department of Radiation Oncology, University Hospital Halle (Saale) [Halle (Saale), Germany]. Comorbidities were assessed using the Charlson comorbidity index (CCI) and the age-adjusted CCI. Kaplan-Meier curves were generated to estimate overall survival (OS) and group comparisons were performed using the log-rank test. Prognostic factors including age, sex, Karnofsky performance status (KPS), histological subtype, tumor grading, T- and N-stage, PET-based treatment planning, mean biologically effective dose (BEDmean/Gy₁₀), gross tumor volume (GTV) and CCI were analyzed. Cox proportional hazards regression was used to estimate hazard ratios (HR) and 95% confidence intervals (CI).

Variables that were significant in the univariate analysis were entered into a multivariate stepwise regression model. A sensitivity analysis with multiple imputations was performed to assess the robustness of the findings. $P < 0.05$ was considered to indicate a statistically significant difference. A total of 58 patients with NSCLC with M0-status were included in the present analysis. The 3-, 5- and 10-year OS rates were 35.09, 24.56 and 8.77%, respectively. The median OS was 32 months (95% CI, 10-35). In the univariate Cox regression, age ≥ 75 years was significantly associated with improved survival (HR, 0.54; 95% CI, 0.31-0.92; $P = 0.025$), though this effect was not statistically significant in the multivariate model (HR, 0.55; 95% CI, 0.30-1.01; $P = 0.057$). The KPS (≤ 70 vs. $> 70\%$), sex and the age-adjusted CCI showed no significant association with OS. BEDmean, dichotomized at 120.31 Gy₁₀, was not significantly associated with OS in the multivariate model ($P = 0.2$), although the Kaplan-Meier analysis showed a significant survival difference ($P = 0.011$). By contrast, larger GTV (> 25.6 cm³) was independently associated with worse survival in both the univariate (HR, 1.01; 95% CI, 1.00-1.02; $P = 0.041$) and multivariate (HR, 1.01; 95% CI, 1.00-1.02; $P = 0.024$) analyses. These findings were confirmed in a sensitivity analysis using multiple imputations, supporting the robustness of age and GTV as prognostic factors for NSCLC patients treated with SBRT. SBRT provides moderate long-term survival in patients with NSCLC. Older patients (≥ 75 years) showed favorable outcomes. Tumor volume was the strongest prognostic factor, while BEDmean and performance status were not independently associated with survival.

Correspondence to: Dr Jörg Andreas Müller, Department of Radiation Oncology, University Hospital Halle (Saale), 40 Ernst-Grube Street, D-06120 Halle (Saale), Germany
E-mail: joerg-andreas.mueller@uk-halle.de

Abbreviations: BED, biologically effective dose; CCI, Charlson comorbidity index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; FDG-PET, fluorodeoxyglucose positron emission tomography; FEV₁, forced expiratory volume in 1 second; HR, hazard ratio; KPS, Karnofsky performance status; SCLC, small cell lung cancer; NSCLC, non-SCLC; OS, overall survival; PFS, progression-free survival; RT, radiotherapy; SBRT, stereotactic body radiation therapy; UICC, Unité Internationale Contre Le Cancer; VATS L-MLND, video-assisted thoracoscopic surgical lobectomy with mediastinal lymph node dissection

Key words: early-stage lung cancer, 10-year survival, SBRT, BED, CCI, gross tumor volume

Introduction

According to recent global cancer statistics, lung cancer is the second most frequently diagnosed malignancy, accounting for ~2.3 million new cases annually (11.7%). Despite this, it remains the leading cause of cancer-related mortality, responsible for an estimated 1.8 million deaths worldwide (18%) (1). Tobacco smoking is well established as the primary risk factor for lung cancer (2). However, additional contributors include genetic susceptibility, environmental pollutants, occupational exposures, socioeconomic status and biological sex (3).

Although lung cancer continues to be associated with a poor prognosis, the 5-year relative survival rate for all types has improved significantly over the past four decades, increasing from 10.7 to 19.8% (4). This improvement is largely attributed to advances in diagnostic and therapeutic strategies, including earlier detection, molecular profiling, refined staging methods and enhanced treatment approaches, such as surgery, radiotherapy, targeted therapies and immunotherapy (5,6).

For cases deemed medically inoperable or for patients those who decline surgery, stereotactic ablative radiotherapy (SABR) has emerged as a highly effective alternative (7,8). SABR is a non-invasive, image-guided radiotherapy technique that delivers high-dose radiation with sub-millimeter precision, allowing for maximal tumor control while minimizing damage to surrounding healthy tissues (9). Clinical studies have demonstrated excellent local control rates with SABR, reaching up to 98% at 3 years, and a favorable toxicity profile (10,11).

For inoperable peripherally located stage I lung cancer, stereotactic body radiation therapy (SBRT) can result in superior local control rates without increasing major toxicities compared with standard radiotherapy (12). However, the two randomized phase 3 trials on patients with operable stage I NSCLC (STARS and ROSEL) have closed early due to slow patient accrual. Chang *et al* (13) assessed the overall survival (OS) of patients treated with SBRT vs. surgery by pooling data from the STARS trial [NCT00840749] and the ROSEL trial [NCT00687986]. The estimated 3-year OS was 95% [95% confidence interval (CI), 85-100%] in the SBRT group compared with 79% (95% CI, 64-97%) in the surgery group; therefore, it was concluded that SBRT could be a suitable option for operable patients with stage I NSCLC (13). However, due to the small sample size and short-follow-up duration this analysis has notable limitations. A subsequent revised STARS trial, which provided a larger sample size of SBRT patients, along with a protocol-specified propensity-matched prospectively registered cohort of patients who underwent video-assisted thoracoscopic surgical lobectomy with mediastinal lymph node dissection (VATS L-MLND) (14). Long-term survival outcomes after SABR were found to be non-inferior to those achieved with VATS L-MLND in operable patients with stage IA NSCLC (14). Despite these promising results, lobectomy with mediastinal lymph node dissection remains the standard of care for operable patients with operable early-stage NSCLC (15).

According to the Californian Cancer Center registry data, long-term survival analysis of untreated patients with stage I NSCLC suggests that a large proportion patients die of lung cancer specific reasons; the 5-year OS of untreated patients with stage I NSCLC was 6% overall (16). There are numerous factors affecting treatment outcomes after SBRT in patients with NSCLC. Baine *et al* (17) investigated the role of histology on post-SBRT treatment outcomes such as local, regional and distant control; the multi-institutional analysis showed higher local, regional and distant recurrence rates and worse OS in NSCLC patients with squamous cell cancer after SBRT. The biologically effective dose (BED) affects the efficacy and the OS of patients with NSCLC treated with SBRT. Medium or medium to high BEDs have been associated with improved OS compared with high or low BEDs (18).

The assessment of frequency and severity of comorbidities also serves a critical role in terms of treatment outcomes after SBRT. In lung cancer, one of the most frequently used comorbidity scores is the Charlson comorbidity index (CCI) (19,20). The CCI includes 19 different diseases, each of which is weighted with scores ranging from 1 to 6 points according to the risk of long-term mortality (21).

For treatment planning, position emission tomography (PET) computed tomography (CT) scans with a fludeoxyglucose-18 tracer (FDG) can predict stage I and stage II disease, as well as the Tumor-Node-Metastasis (TNM) staging (22,23) (T- and N-status), among patients with NSCLC more effectively compared with dedicated PET alone (24). Furthermore, FDG-PET-CT may be a suitable diagnostic tool for predicting the therapeutic outcomes of patients with early-stage NSCLC treated with SBRT more accurately (25).

The specific aim of the present study was to provide data on the long-term (10-year) survival rates of patients with NSCLC treated with SBRT in a real-world setting. Specifically, the present study aimed to analyze clinical and treatment-related prognostic factors including age, performance status, comorbidities (CCI), BEDmean and gross tumor volume (GTV), as well as their associations with OS. Using Cox regression models and Kaplan-Meier survival analysis, the present study aimed to identify patient- and tumor-related factors influencing long-term outcomes, evaluate the prognostic impact of BEDmean and GTV and explore whether older patients experience comparable or superior outcomes compared with that of younger patients. The present analyses were conducted to support clinical decision-making and individual risk stratification in patients with early-stage NSCLC treated with SBRT outside of randomized controlled trials.

Patients and methods

Data and material. Patient recruitment was conducted retrospectively using the databases of the Department of Radiation Oncology at the University Hospital Halle [Halle (Saale), Germany]. Patient data were anonymized and retrieved from the hospital information system ORBIS (version 03.20.02.01; Moody's Analytics, Inc.). Information regarding diagnostic imaging and radiation treatment were obtained from Centricity PACS (Cytiva) and from Elekta Mosaiq (version 2.84; Elekta Instrument AB).

All patients (n=99) treated with SBRT between January 2009 and December 2013, were considered. After the initial screening process, further analysis focused on patients with NSCLC with M0-status according to the TNM staging system. Prior to any data collection, the present study was approved by the ethics committee of the Medical Faculty of Martin Luther University Halle-Wittenberg (ethics approval number 2025-006). A total of 64% of patients were male and 36% were female. The median age was 72 years, with a range of 44 to 91 years. Inclusion criteria comprised age >18 years, receipt of at least one SBRT treatment and curative treatment intent. The last date of follow-up was October 11, 2024.

Patient characteristics were categorized in multiple classifications for analysis. Sex was classified as male or female, while performance status was assessed using the Karnofsky performance status (KPS). The KPS is a widely used method

of assessing the functional status of patients with cancer. This scale allows clinicians to quantify a patient's functional impairment, facilitating comparisons of therapeutic effectiveness and prognostic assessments (26). Lower KPS scores correlate with decreased survival rates across various serious illnesses, including cancer, chronic obstructive pulmonary disease (COPD), congestive heart failure and advanced neurological disorders, such as stroke or dementia (27). In the present study, KPS scores were dichotomized into $>70\%$ (indicating superior physical condition) and $\leq 70\%$ (indicating poorer condition). T-status was grouped into T1, T2, T3, T4 and unknown stage based on the TNM staging system; nodal involvement (N-status) was categorized as N0 (no nodal involvement), N1, N2 or unknown. The Union for International Cancer Control (UICC) stage was recorded as stage I, II, III or unknown stage according to the 7th edition of the UICC classification (23).

Histological grading was documented as either known or unknown, while tumor histology was categorized into adenocarcinoma, large cell lung carcinoma, squamous cell carcinoma, not otherwise specified (NOS) or unknown histology. PET-based treatment was recorded as performed or not performed. Radiation dose was reported as single dose (such as 7, 8 and 12.5 Gy) and number of fractions delivered. Furthermore, treatment regimens and prescription isodoses were recorded.

COPD is a common comorbidity in patients with lung cancer and is classified into four grades based on the severity of airflow limitation, as defined by the Global Initiative for Chronic Obstructive Lung Disease (28). These grades are determined using spirometry, specifically assessing the post-bronchodilator forced expiratory volume (FEV) in a 1-sec duration (FEV₁), as a percentage of the predicted value. Grade I (mild) is characterized by an FEV₁ $\geq 80\%$ of the predicted value. Symptoms may include chronic cough and sputum production, but airflow limitation is mild. Grade II (moderate) corresponds to an FEV₁ between 50-79% of the predicted value. Patients typically experience shortness of breath on exertion, along with cough and sputum production. Grade III (severe) includes an FEV₁ between 30-49% of the predicted value, often accompanied by significant shortness of breath, reduced exercise capacity, fatigue and frequent exacerbations. Grade IV (very severe) is defined as a FEV₁ $<30\%$ of the predicted value or $<50\%$ with chronic respiratory failure. Grade IV diseases is associated with severe airflow limitation, a significant decline in quality of life and life-threatening exacerbations (29).

For analysis, COPD status of each patient was categorized into COPD unspecified, COPD I, COPD II, COPD II-III, COPD III, COPD IV or unknown status. Overall comorbidities were evaluated using the CCI and the age adjusted CCI. The CCI is a widely used tool to estimate the prognosis and 10-year survival of patients based on their comorbidities. Table I provides an overview of CCI estimation based on different comorbidities and their weight in the score (21).

The age-adjusted CCI incorporates the age of the patient to provide a more refined assessment of prognosis. In this approach, one additional point is added to the total CCI score for each decade of life starting from 50 years of age. For

example, patients aged 50 to 59 years receive one additional point, those aged 60 to 69 years receive two points, those aged 70 to 79 years receive three points and patients aged ≥ 80 years receive four points. This adjustment reflects the increasing risk of mortality associated with aging, independent of the presence or severity of comorbid conditions (21,30). By accounting for age, the age-adjusted CCI provides a more accurate prediction of outcomes, particularly in older populations where age serves a significant role in overall health and survival (30). In the present study, CCI was used to evaluate the burden of comorbidities in the patient population. The CCI was analyzed in two forms: The original version (without age adjustment) and the age-adjusted version. The CCI without age-adjustment was categorized into 3 groups: Low comorbidity (<4), moderate comorbidity (4-5) and high comorbidity (>5). The age-adjusted CCI was further stratified into 4 groups: Very low (<3), low (3-5), moderate (6-8) and high (>8).

Stereotactic radiation treatment. Treatment plans were carried out in accordance with the national recommendations in place at the time of data collection. The equipment consisted of a 'Light Speed RT' (GE Healthcare) for scanning the patient geometry, the 'Oncentra Master Plan' treatment planning system (Elekta Instrument AB) and two linear accelerators ('MXE' and 'Primus'; Siemens Healthineers), each equipped with a collimator offering 1-cm leaf width in the center part (measured at isocenter distance) and a portal imaging system for position verification.

Patients were immobilized by means of a vacuum mattress on a stereotactic board to which a stereotactic frame (acrylic box) was attached (Fig. 1). A radiopaque coordinate system embedded in the acrylic glass was used for patient alignment under the treatment machine. Several CT series were collected with a slice thickness of 2.5 mm using different scan techniques to visualize the tumor's movement during a breathing cycle. Target volume was defined as this movement space enlarged by 5 mm in all directions to account for overall geometrical uncertainties of the treatment chain. Dose was calculated using the 'collapsed cone algorithm' on the 'slow' CT series. This series was scanned with a gantry rotation time of 4 sec and therefore displayed an averaged anatomy during ~1 breathing cycle.

Dose was prescribed in 1 to 6 fractions onto the 65% isodose enclosing the target volume, with the dose rising steeply to a maximum of 100% in the center of the target (Fig. 2). All treatment plans consisted of 6-13 fixed beams of 6 MV acceleration potential and were created using 3D-conformal technique with the beam isocenter in the center of the tumor. Prior to each irradiation session, a control CT examination (slow series) of the movement space of the tumor was taken in which the center coordinates of the tumor, as documented in the treatment plan, were localized relative to the origin of the stereotactic frame. The beam isocenter of the treatment device was then set to that location and orthogonal MV images were taken. Finally, these images were compared with the respective digitally reconstructed radiographs from the treatment planning system to verify correct patient position. Patients were irradiated daily, unless if three fractions were applied. Those patients were irradiated every other day.

Table I. Charlson comorbidity index calculation chart.

Comorbidity	Weight	Criteria
Myocardial infarction	1	History of myocardial infarction or coronary artery disease
Congestive heart failure	1	History of heart failure
Peripheral vascular disease	1	Claudication, peripheral artery disease or previous vascular surgery
Cerebrovascular disease	1	Stroke, transient ischemic attack or history of cerebral hemorrhage
Dementia	1	Clinical diagnosis of dementia
Chronic pulmonary disease	1	Chronic obstructive pulmonary disease or asthma
Connective tissue disease	1	Rheumatoid arthritis or systemic lupus erythematosus
Peptic ulcer disease	1	History of gastric or duodenal ulcer
Mild liver disease	1	Chronic liver disease without liver failure (for example, cirrhosis without ascites)
Diabetes without complications	1	Diabetes mellitus without end-organ damage
Diabetes with complications	2	Diabetes with end-organ damage, such as retinopathy or nephropathy
Hemiplegia or paraplegia	2	Paralysis due to stroke, spinal cord injury or other causes
Moderate or severe renal disease	2	Chronic kidney disease with creatinine >3 mg/dL or dialysis-dependent
Cancer (non-metastatic, active treatment)	2	Any solid tumor without metastasis, currently treated
Leukemia	2	Chronic or acute leukemia
Lymphoma	2	Non-Hodgkin's or Hodgkin's lymphoma
Moderate or severe liver disease	3	Cirrhosis with complications (ascites, encephalopathy)
Metastatic solid tumor	6	Any solid tumor with metastasis
HIV/AIDS	6	HIV infection with AIDS or opportunistic infections

Adapted from Charlson *et al* (21). HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome.

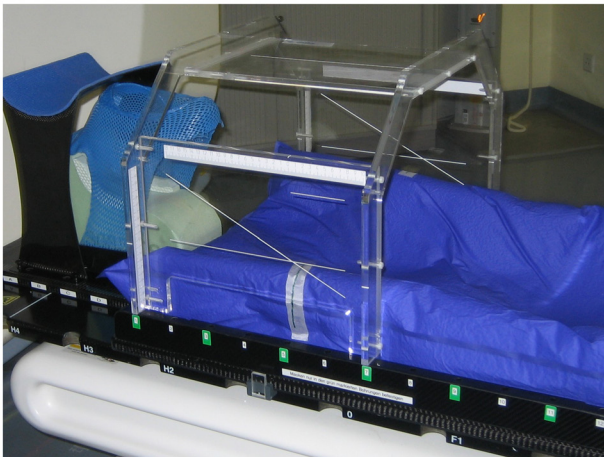


Figure 1. Stereotactic board with vacuum mattress, headrest, armrest and stereotactic frame (acrylic box).

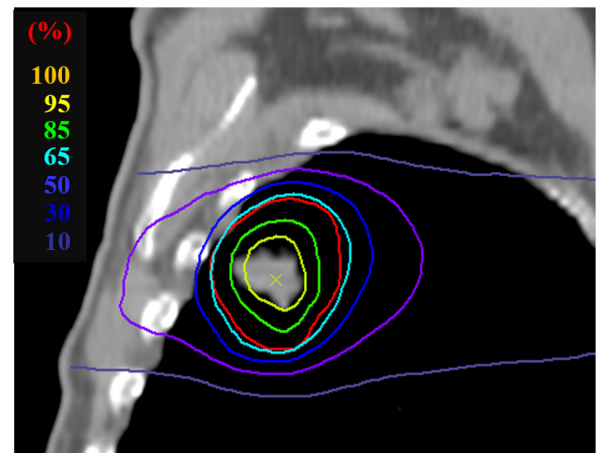


Figure 2. Dose distribution of lung irradiations with 65% isodose (light blue contour) enclosing the target volume (red contour).

Calculation of biologically equivalent dose. The varying effectiveness of the different dose concepts can be partially explained by the use of a biologically equivalent dose BED according to the linear quadratic model (31):

$$BED = n \cdot d \left(1 + \frac{d}{\alpha/\beta} \right)$$

Where n , d and α/β are the number of treatment sessions, their dose and the characteristic parameter of the linear quadratic

model, which is inversely proportional to the repair capacity of the tissue under consideration, respectively (1). As per previous research for the stereotactic irradiation of lung tumors (32) the arithmetic mean was calculated from the prescription BED_{min} and the isocenter BED_{max} with $\alpha/\beta=10$ Gy:

$$BED_{mean} = \frac{1}{2}(BED_{min} + BED_{max})$$

In the present study, the BED is given in units of Gy_{10} in order to visualize the numerical value of α/β used in the calculation.

GTV was defined based on the radiotherapy planning CT acquired prior to the start of SBRT.

Statistical analyses. Proportional hazard Cox regression models were used to assess the association of cancer-related parameters with OS and computed hazard ratios (HR) with 95% confidence intervals (CI). In the univariate analysis, each clinical factor was evaluated individually. All significant predictors, as well as CCI and KPS, from the univariate models were subsequently considered in a multivariate analysis.

To identify the best-fitting model, a stepwise variable selection approach was applied (both forward inclusion and backward elimination) based on the Akaike Information Criterion (33). The final multivariable model was derived from this stepwise selection procedure. The primary endpoint of the analysis was OS, defined as the time interval between the end of radiotherapy and either death or the last known follow-up as documented in the local citizen registration.

Survival curves were generated using the Kaplan-Meier method to analyze cumulative patient survival. Differences between groups were assessed using the log-rank test. $P < 0.05$ was considered to indicate a statistically significant difference. Cut-off values for both BEDmean and GTV were defined as the thresholds that provided the best separation in OS, as determined by the log-rank test. To assess the robustness of the findings in the presence of missing data, a sensitivity analysis using five imputations was performed. All statistical analyses were conducted using RStudio (version 2024.04.2+764; Posit Software, PBC).

Results

Case selection. The present retrospective study cohort was initially comprised of 99 patients who were treated with SBRT at the radiation oncology department of the University Hospital Halle (Saale) between 2009 and 2013. However, 31 patients that were treated for lung or bone metastasis caused by various primary tumors (such as melanoma, laryngeal, oropharyngeal, parotid, renal cell, thyroid, colorectal carcinoma or sarcoma) were excluded. The remaining 68 patients were diagnosed with lung cancer. Subsequently, 10 of these 68 patients were excluded due to M1-status, resulting in a final cohort of 58 patients with M0-status that were included in the present analysis (Fig. 3).

Patient characteristics. The baseline characteristics of all patients with lung cancer are presented in Table II, stratified by age groups (<75 and ≥ 75 years). Among patients aged <75 years ($n=28$) and ≥ 75 years ($n=30$), the proportion of females was comparable (32 vs. 33%), with the majority of patients in both groups being male (68 vs. 67%). A higher KPS ($>70\%$) was observed more frequently among older patients (53 vs. 29%), whereas lower KPS ($\leq 70\%$) occurred more often in the younger group (71 vs. 47%).

T1 tumors were the most common in both groups (43 vs. 47%), while T2 tumors were slightly more frequent among older patients (25 vs. 40%). T3 and T4 stages were rare in both groups. Unknown T-status was more common in the <75 years group (17 vs. 10%). Regarding nodal status, most patients were N0, particularly in the older group (83 vs. 64%). N1 and N2

involvement was observed only in younger patients (N1: 7%; N2: 11%), while N-status remained unknown in 18 and 14% of the <75 and ≥ 75 groups, respectively.

UICC stage I was the most frequent stage in both age groups (57 vs. 70%). Stage II and III cases were similarly distributed, and unknown stage was slightly more frequent in the younger group (18 vs. 14%). Histological grading was unknown in the majority of patients in both age groups, slightly more so in younger patients (75 vs. 70%).

A PET-based treatment approach was used more often in older patients (77 vs. 64%). Squamous cell carcinoma was the most frequent histological subtype (46 vs. 33%), followed by adenocarcinoma (25 vs. 30%). Large cell lung carcinoma occurred only in the younger group (4%). Tumors NOS were found exclusively in older patients (10%).

Regarding comorbidities, COPD IV was substantially more frequent in younger patients (36 vs. 3%), while unspecified COPD was more frequent in the older group (23 vs. 14%). The proportion of patients with unknown COPD status was higher among older patients (51 vs. 25%). Age-adjusted CCI values were higher in the ≥ 75 years group: 73% had a score of 6-8 and 20% had a score of >8 , compared with 50 and 14% in the <75 years group, respectively.

The most commonly prescribed treatment regimen was 37.5 Gy in 3 fractions (52 vs. 68%), followed by 48 Gy in 6 fractions (32 vs. 28%). Most patients received a mean biological effective dose (BEDmean) of 126.51 Gy₁₀ (50%). The second most frequent BEDmean was 125.57 Gy₁₀, administered in 24% of patients. All other regimens (e.g., 118.11, 120.31, 100.24, 83.71 and 68.53 Gy₁₀) accounted for $<5\%$ of patients.

Survival analysis. For OS, the 3-, 5- and 10-year OS rate was 35.09, 24.56 and 8.77%, respectively. The overall median survival of all patients without metastasis was 32 months (95% CI, 10-35 months). Median survival estimates for the respective patient subgroups are summarized in Table SI.

The results of the univariate and multivariate Cox regression analyses are summarized in Table III. Although the CCI and KPS showed a statistically significant but weak correlation (Pearson's $r=0.29$; $P=0.029$), both variables were retained in the univariate Cox regression analyses. This decision was based on clinical reasoning, as comorbid burden and performance status represent distinct yet complementary aspects of the general health of a patient and may independently influence survival. Furthermore, considering their relevance within different age groups, their inclusion allows for a more nuanced assessment of age-related heterogeneity in the prognosis of patients with non-metastatic NSCLC.

In the univariate analysis, age ≥ 75 years was significantly associated with decreased OS (HR, 0.54; 95% CI, 0.31-0.92; $P=0.025$). However, age ≥ 75 years was not statistically significant in the multivariate stepwise model (HR, 0.55; 95% CI, 0.30-1.01; $P=0.057$), although a similar trend was observed. Sex (male vs. female) was not significantly associated with OS in the univariate analysis (HR, 1.12; 95% CI, 0.64-1.97; $P=0.7$) and was not selected for the multivariate stepwise model.

The CCI did not show a significant association with survival in either the univariate analysis or the stepwise model ($P=0.6$). When compared with patients with a CCI

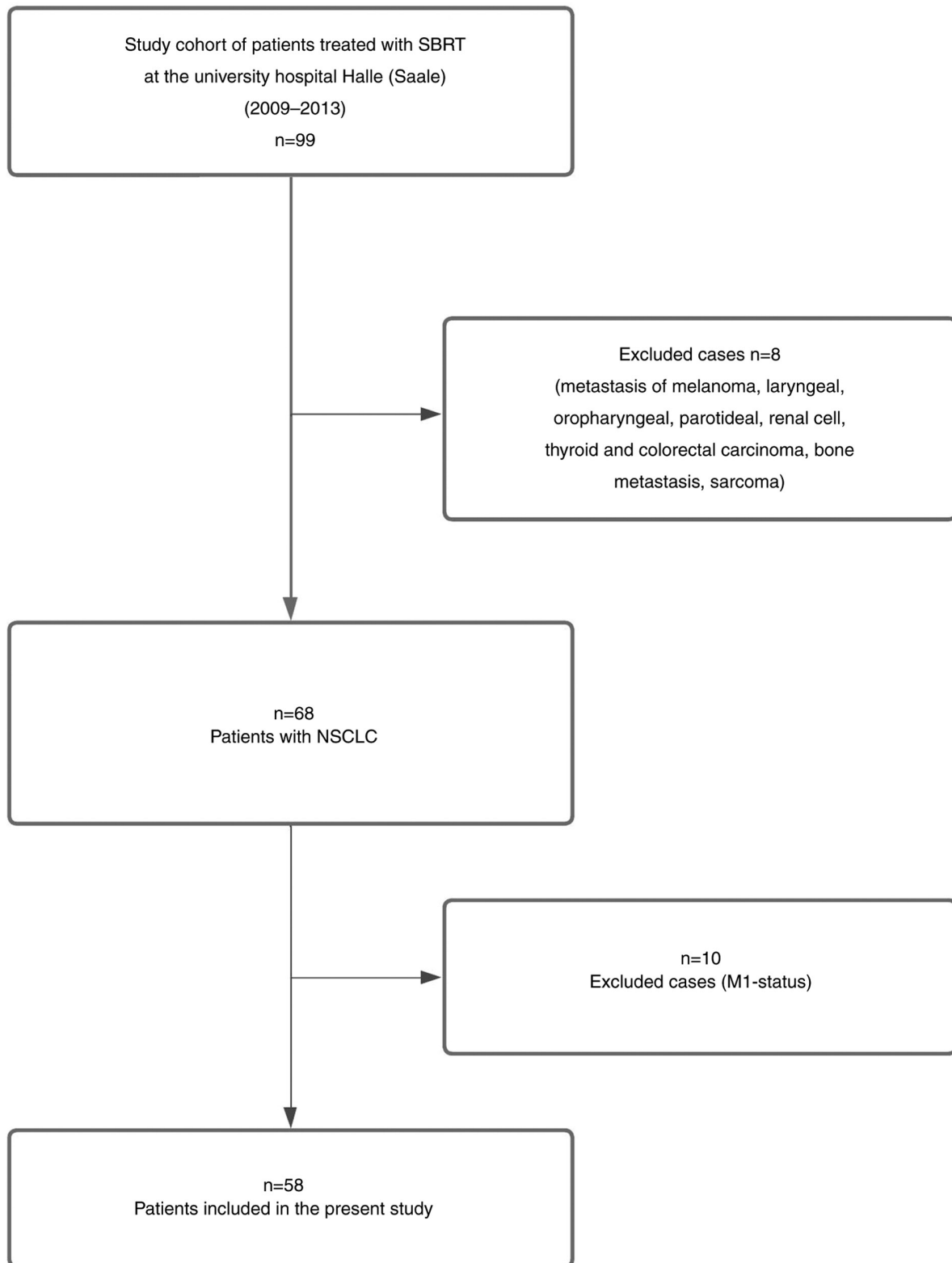


Figure 3. Flowchart of inclusion and exclusion criteria.

<4, those with scores of 4-5 (HR, 1.36; 95% CI, 0.73-2.53) and >5 (HR, 1.11; 95% CI, 0.53-2.30) did not differ significantly in mortality risk. The KPS (≤ 70 vs. $>70\%$) was also not significantly associated with survival (HR, 1.33; 95% CI, 0.77-2.30; $P=0.3$) and was excluded from the multivariate stepwise model. The mean BED (BEDmean/Gy₁₀) showed

no significant association with survival in the univariate analysis (HR, 0.99; 95% CI, 0.97-1.00; $P=0.2$) and was not retained in the multivariate model. The GTV was significantly associated with survival in both the univariate (HR, 1.01; 95% CI, 1.00-1.02; $P=0.041$) and multivariate (HR, 1.01; 95% CI, 1.00-1.02; $P=0.024$) analyses. This indicates

Table II. Baseline patient characteristics (n=58)^a.

Characteristic	Total, n (%)	Patients aged <75 years, n (%)	Patients aged ≥75 years, n (%)
Sex			
Female	19 (33)	9 (32)	10 (33)
Male	39 (67)	19 (68)	20 (67)
Age, years			
<75	28 (48)		
≥75	30 (52)		
Karnofsky-performance-status, %			
>70	24 (41)	8 (29)	16 (53)
≤70	34 (59)	20 (71)	14 (47)
T-status			
1	26 (45)	12 (43)	14 (47)
2	19 (33)	7 (25)	12 (40)
3	2 (3)	1 (4)	1 (3)
4	3 (5)	3 (11)	0 (0)
Unknown	8 (14)	5 (18)	3 (10)
N-status			
0	43 (74)	18 (64)	25 (83)
1	2 (3)	2 (7)	0 (0)
2	4 (7)	3 (11)	1 (3)
Unknown	9 (16)	5 (18)	4 (13)
UICC-stage			
I	37 (64)	16 (57)	21 (70)
II	8 (14)	4 (14)	4 (13)
III	4 (7)	3 (11)	1 (3)
Unknown	9 (16)	5 (18)	4 (13)
Grading			
Known	16 (28)	7 (25)	9 (30)
Unknown	42 (72)	21 (75)	21 (70)
PET-based treatment			
No	15 (26)	9 (32)	6 (20)
Yes	41 (71)	18 (64)	23 (77)
Unknown	2 (3)	1 (4)	1 (3)
Histology			
Adenocarcinoma	16 (28)	7 (25)	9 (30)
Large cell lung carcinoma	1 (2)	1 (4)	0 (0)
Not otherwise specified	3 (5)	0 (0)	3 (10)
Squamous cell carcinoma	23 (40)	13 (46)	10 (33)
Unknown	15 (26)	7 (25)	8 (27)
COPD			
COPD unspecified	11 (19)	4 (14)	7 (23)
COPD I	1 (2)	0 (0)	1 (3)
COPD II	8 (14)	6 (21)	2 (7)
COPD II-III	1 (2)	0 (0)	1 (3)
COPD III	4 (7)	1 (4)	3 (10)
COPD IV	11 (19)	10 (36)	1 (3)
Unknown	22 (38)	7 (25)	15 (50)
CCI without age adjustment			
<3	1 (2)	1 (4)	0 (0)
>8	10 (17)	4 (14)	6 (20)
3-5	11 (19)	9 (32)	2 (7)
6-8	36 (62)	14 (50)	22 (73)

Table II. Continued.

Characteristic	Total, n (%)	Patients aged <75 years, n (%)	Patients aged ≥75 years, n (%)
CCI age-adjusted			
<3	1 (2)	1 (4)	0 (0)
3-5	11 (19)	9 (32)	2 (7)
6-8	36 (62)	14 (50)	22 (73)
>8	10 (17)	4 (14)	6 (20)
Treatment regimen (prescription isodose); BED _{mean} /Gy ₁₀			
37.5 Gy/3 fr. (65%); 126.51 Gy ₁₀	29 (60)	12 (52)	17 (68)
40 Gy/4 fr. (65%); 118.11 Gy ₁₀	1 (2)	1 (4)	0 (0)
28 Gy/4 fr. (65%); 68.53 Gy ₁₀	1 (2)	1 (4)	0 (0)
32 Gy/4 fr. (65%); 83.71 Gy ₁₀	1 (2)	0 (0)	1 (4)
36 Gy/4 fr. (65%); 100.24 Gy ₁₀	1 (2)	1 (4)	0 (0)
50 Gy/5 fr. (80%); 120.31 Gy ₁₀	1 (2)	1 (4)	0 (0)
48 Gy/6 fr. (65%); 125.57 Gy ₁₀	14 (29)	7 (30)	7 (28)

^aPercentages were calculated in relation to the total number of patients within each subgroup and are rounded. CCI, Charlson comorbidity index; BED, biologically effective dose; COPD, chronic obstructive pulmonary disease; GTV, gross tumor volume; fr, fractions; UICC, Unité International Contre Le Cancer.

Table III. Univariate and multivariate Cox-regression models.

Characteristic	Univariate Cox model			Multivariate stepwise model		
	HR	95% CI	P-value	HR	95% CI	P-value
Age, years			0.025			0.057
<75	-	-		-	-	
≥75	0.54	0.31-0.92		0.55	0.30-1.01	
Sex						
Female	-	-				
Male	1.12	0.64-1.97	0.762			
CCI			0.654			
<4	-	-				
4-5	1.36	0.73-2.53				
>5	1.11	0.53-2.30				
Karnofsky performance status, %			0.311			
>70	-	-				
≤70	1.33	0.77-2.30				
BED _{mean} /Gy ₁₀	0.99	0.97-1.00	0.257			
GTV	1.01	1.00-1.02	0.041	1.01	1.00-1.02	0.024

Results of the univariate and multivariate Cox proportional hazards regression analyses evaluating the association between clinical parameters and overall survival in the complete-case dataset. HR with 95% CI and P-values are reported. Variables with significant associations in the univariate analysis were included in the stepwise multivariate model. HR, hazard ratio; CI, confidence interval; CCI, Charlson comorbidity index; BED, biologically effective dose; GTV, gross tumor volume.

that larger tumor volumes were independently associated with increased mortality risk.

Kaplan-Meier survival analysis. Kaplan-Meier survival curves were generated to illustrate OS in the present study

cohort and stratified subgroups. The survival curve for the total cohort up to 10 years (120 months) is displayed in Fig. 4. OS was stratified by age group (<75 vs. ≥75 years), which demonstrated significantly reduced survival in older patients (P=0.023; Fig. 5). Survival rates were also analyzed stratified

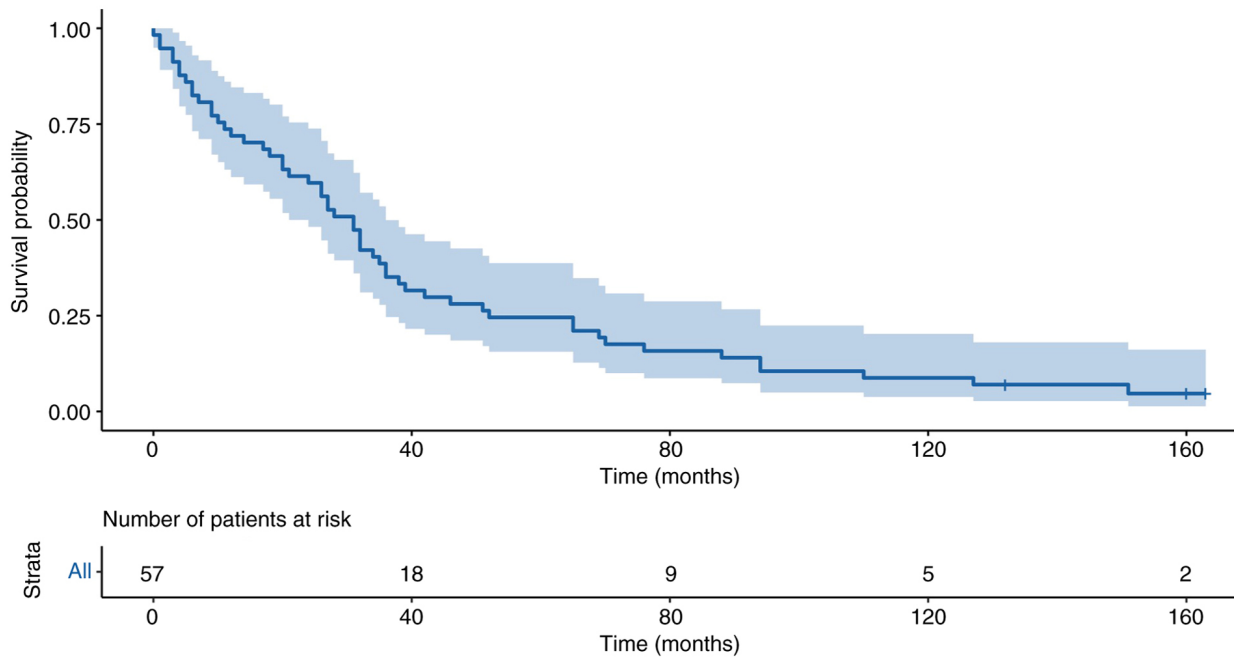


Figure 4. Kaplan-Maier curve of the survival outcome of all patients with lung cancer.

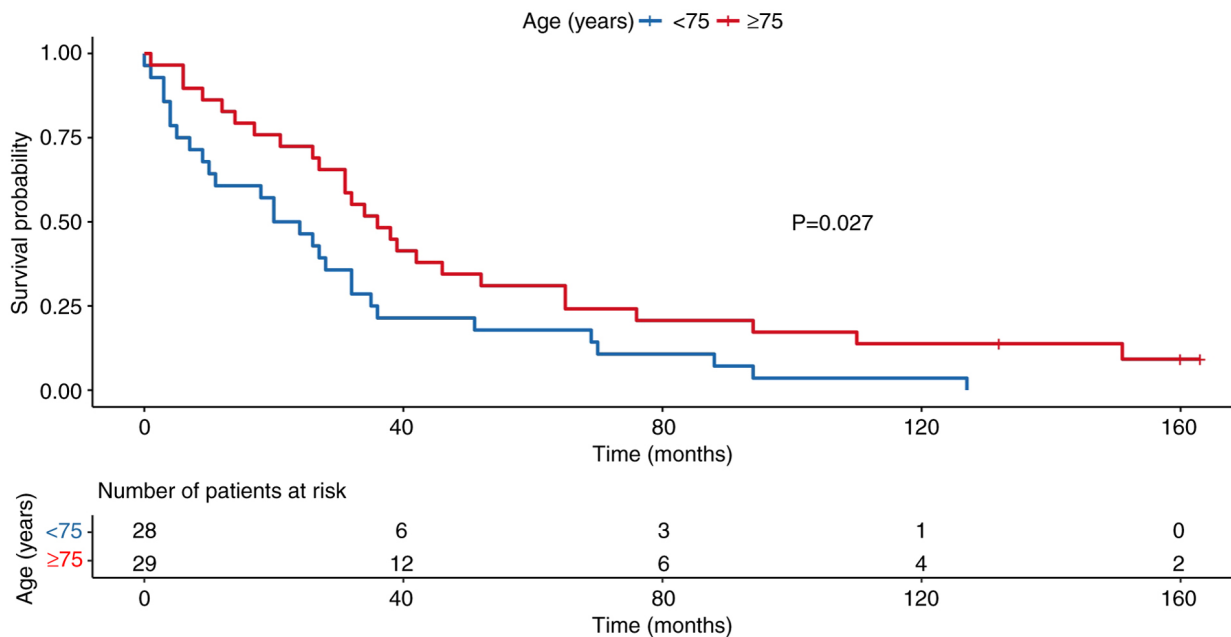


Figure 5. Kaplan-Maier curve of the survival outcome of all patients with lung cancer stratified by age group.

according to BEDmean, using a cut-off of 120.31 Gy₁₀ (Fig. 6). Patients with high BEDmean demonstrated significantly improved survival rates compared with those with lower doses (P=0.011). Survival was stratified by GTV, using a cut-off of 25.6 cm³ (Fig. 7). Patients with larger tumor volumes had significantly poorer survival outcomes (P=0.006).

Sensitivity analysis. To assess the robustness of the Cox regression results, a sensitivity analysis using multiple imputations was conducted and compared with the univariate and multivariate stepwise model based on complete-case analysis. The pooled results from the imputed datasets were compared

with the complete case analysis. The consistency of effect estimates between both models supported the validity of the present conclusions. Overall, the effect estimates were consistent between the imputed and stepwise models. The variable age ≥75 years remained significantly associated with improved survival across both approaches (univariate imputed, HR, 0.50; 95% CI, 0.29-0.88; P=0.016; multivariate stepwise, HR, 0.49; 95% CI, 0.29-0.85; P=0.012). Sex, CCI and KPS did not show any significant associations in either model.

Volume GTV remained significantly associated with worse survival in both the univariate imputed (HR, 1.01; 95% CI, 1.00-1.02; P=0.007) and multivariate stepwise model (HR,

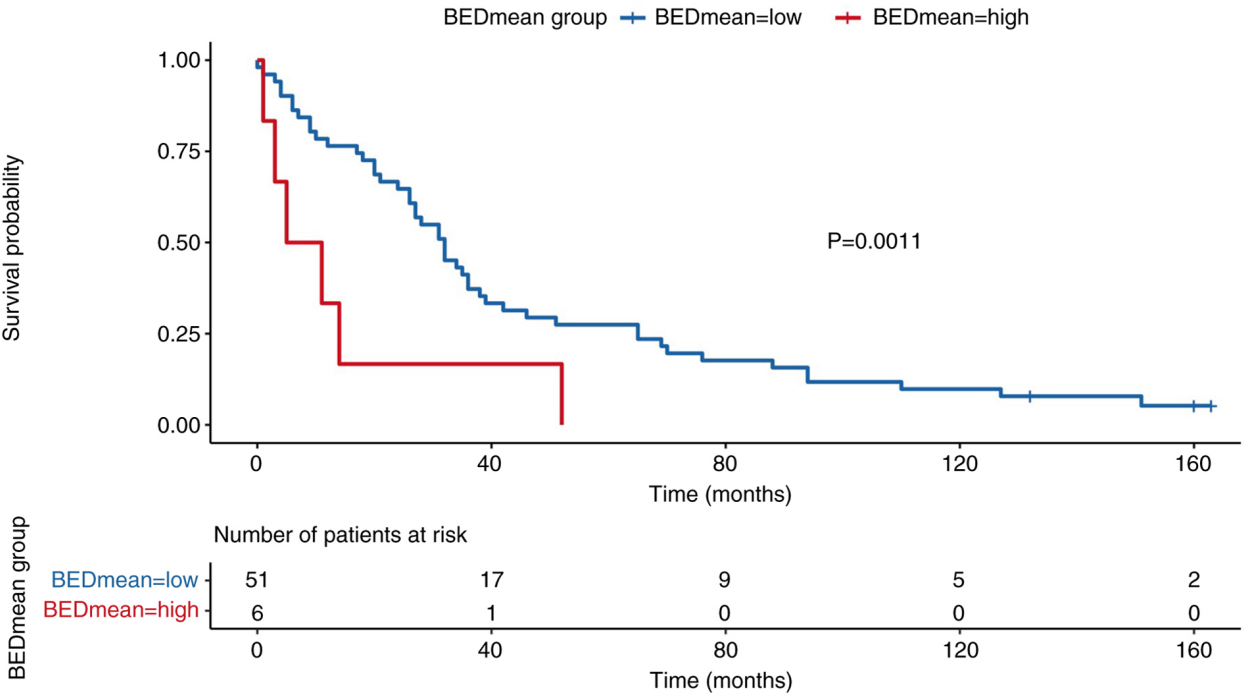


Figure 6. Kaplan-Maier curve of the survival outcome of all patients with lung cancer stratified by BEDmean groups. BED, biologically effective dose.

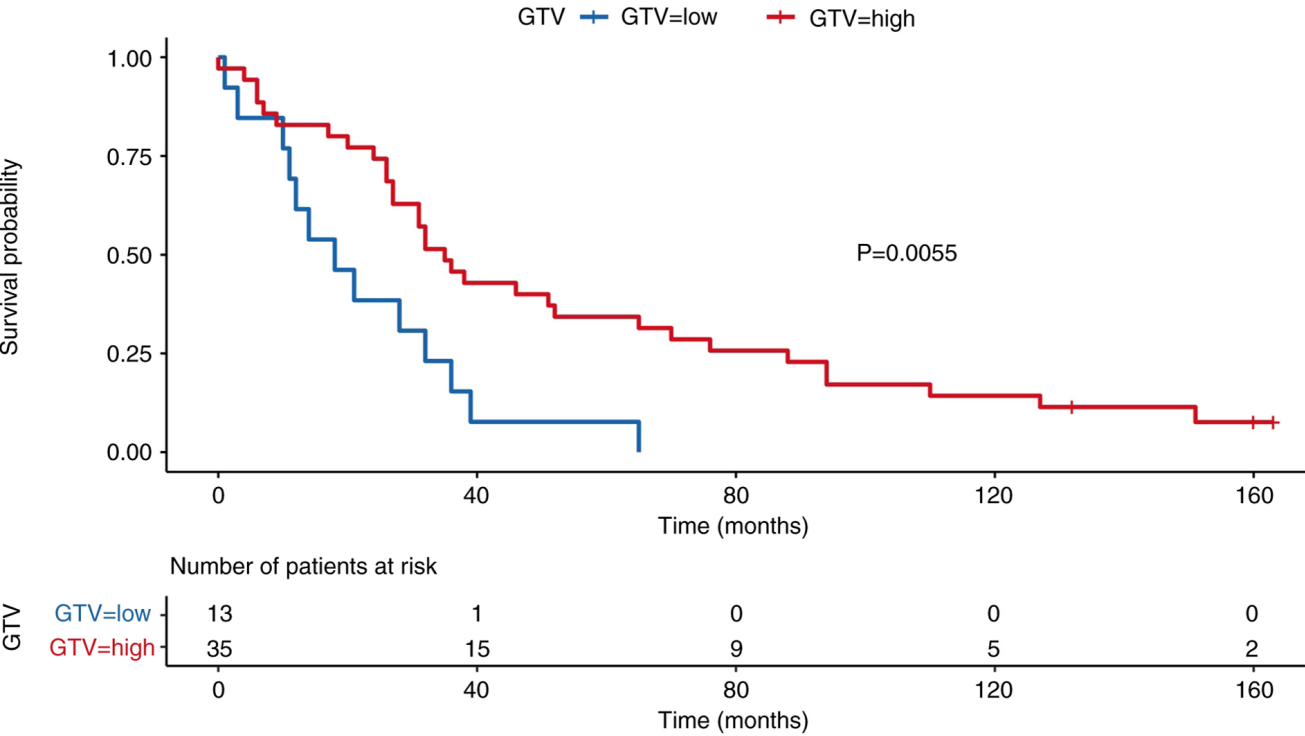


Figure 7. Kaplan-Maier curve of the survival outcome of all patients with lung cancer stratified by GTV. GTV, gross tumor volume.

1.01; 95% CI, 1.00-1.02, $P<0.001$). BEDmean also showed improved survival in the imputed model (HR, 0.99; 95% CI, 0.97-1.00; $P=0.14$), but this was not statistically significant. Taken together, the sensitivity analysis supported the robustness of the aforementioned findings, particularly regarding age and GTV, and further validation of the multivariate model despite missing data (Table IV).

Discussion

The primary aim of the present study was to analyze data on the long-term (10-year) OS of patients with NSCLC treated with SBRT in a real-world setting. To the best of our knowledge there have only been a few analyses that have provided 10-year follow-up data of patients treated with SBRT (34-37).

Table IV. Sensitivity analysis using multiple imputation.

Characteristic	Univariate Cox model (multiple imputation)			Multivariate stepwise model		
	HR	95% CI	P-value	HR	95% CI	P-value
Age, years						
<75	-	-		-	-	
≥75	0.50	0.29-0.88	0.016	0.49	0.29-0.85	0.012
Sex						
Female	-	-				
Male	1.03	0.58-1.83	>0.924			
CCI	1.05	0.87-1.25	0.671			
Karnofsky performance status	1.00	0.98-1.01	0.542			
BED _{mean} /Gy ₁₀	0.99	0.97-1.00	0.141			
GTV	1.01	1.00-1.02	0.007	1.01	1.00-1.02	<0.001

Sensitivity analysis of the Cox regression model using multiple imputation (m=5) to address potential bias due to missing data. HR with 95% CI and P-values are reported for both univariate models based on imputed datasets and the multivariate stepwise model. HR, hazard ratio; CI, confidence interval; CCI, Charlson comorbidity index; BED, biologically effective dose; GTV, gross tumor volume.

The working group ‘Extracranial Stereotactic Radiotherapy’ of the German Society for Radiation Oncology previously investigated the efficacy and safety of SBRT based on a retrospective multicentric analysis (38). Data of 582 NSCLC patients treated with SBRT at 13 institutions between 1998 and 2011 were retrospectively analyzed. The BED was the most significant factor associated with freedom from local progression (FFLP) and OS; 3-year FFLP and OS were 92.5 and 62.2%, respectively (38). In the present dataset, the 3-year OS was lower (35.09%) compared with the of the aforementioned working group study. However, the analysis by Guckenberger *et al* (38) exclusively included patients with stage I NSCLC. By contrast, the present cohort comprised 64% patients with stage I NSCLC. Additionally, the baseline KPS in the SBRT working group cohort was 80%, whereas in the present dataset, 59% of patients with NSCLC had a KPS of ≤70%. Therefore, the observed difference in 3-year OS may be attributed to the poorer clinical performance status of the present cohort and the inclusion of patients with NSCLC with more advanced UICC stages.

In contrast to previously published findings (39), BED_{mean} did not remain a significant predictor of OS in the multivariate analysis (P=0.2), despite being associated with survival in univariate Cox regression (HR, 0.99; 95% CI, 0.97-1.00; P=0.2) and showing a significant difference in Kaplan-Meier analysis (P=0.011). These inconsistent findings may reflect the complex interplay between dose, tumor volume and patient frailty (40,41). However, the current literature specifically addressing the use of SBRT in elderly patients, particularly with respect to survival outcomes, is scarce. This gap in the literature highlights the relevance of the present study and supports the need for further research in this underrepresented patient subgroup. Furthermore, the sensitivity analysis using multiple imputations demonstrated that the BED_{mean} only had a non-significant trend toward improved survival (HR, 0.99; 95% CI, 0.97-1.00;

P=0.14). This suggested that while BED remains a key dosimetry parameter, its prognostic impact on OS may be diminished in heterogeneous, comorbidity-burdened patient populations such as in the present study. In a Chinese retrospective multicenter analysis from 2023 analyzing a total of 145 early-stage NSCLC patients treated with SBRT, the 5-year local recurrence rate was 5.1% and progression-free survival (PFS) rates at 3- and 5-years were 69.2 and 60.5%, respectively. The corresponding OS rates were 78.1 and 70.1% (42).

In the present analysis, older age was associated with a survival benefit compared with younger patients in the univariate Cox regression (HR, 0.54; 95% CI, 0.31-0.92; P=0.025), although this association did not remain statistically significant in the multivariate model (HR, 0.55; 95% CI, 0.30-1.01; P=0.057). This finding may be explained by notable differences in baseline characteristics between the two age groups. In the younger cohort (<75 years), 71% of patients had a KPS of ≤70%, 48% were diagnosed with COPD stage IV and 64% had an age-adjusted CCI score of ≥6. By contrast, older patients (≥75 years) were more frequently characterized by higher performance status and less severe COPD staging. Given that SBRT is typically offered to patients deemed medically inoperable, it could be considered that younger patients in the present cohort were selected for SBRT only when significant comorbidities or poor functional status precluded surgical treatment. This selection bias may have contributed to the unexpected survival disadvantage in the younger subgroup.

Similar to the analysis by Guckenberger *et al* (38) real-world outcomes of SBRT treatment in inoperable patients with stage I NSCLC were reported from a Japanese cohort (42). In this retrospective study, 399 patients with a median age of 75 years were analyzed (43). The overall 3-year survival rate in this cohort was 77%, which was even higher compared with the 3-year survival rate reported by Guckenberger *et al* (38).

Most of these patients had optimal performance status scores ($n=237$ had an ECOG score of 0) and no pulmonary comorbidities ($n=255$ had no emphysema; $n=292$ had no pulmonary interstitial changes), which is in contrast to 31% of the patients in the present study who had COPD grade IV.

Kreinbrink *et al* (40) investigated the safety and efficacy of SBRT in patients ≥ 80 years with early-stage NSCLC, and it reported that the median survival was 29.1 months. In comparison, the overall median survival in the present analysis was slightly higher at 32 months (95% CI, 10-35 months). However, the shorter survival observed in their cohort could be attributed to a worse median Eastern Cooperative Oncology Group (ECOG) performance status of 2 (range, 0-3) and an increased median age of 83 years. By contrast, only 52% of patients in the present dataset was ≥ 75 years. Overall, Kreinbrink *et al* (40) reported high efficacy and low toxicity rates in a cohort of elderly, inoperable patients with NSCLC.

A large proportion of patients in the current study presented with high T-stages (T3-stage, 4.0%; T4-stage, 6%) and N+ status, which may be explained by several factors. In interpreting the present findings, it is important to acknowledge the potential variability in T- and N-staging within the cohort, particularly given the retrospective nature of the study and the heterogeneity of available documentation. In certain cases, multiple tumor lesions within the ipsilateral lung may have contributed to a higher T-stage classification. Additionally, centrally located tumors could have raised diagnostic uncertainty regarding the involvement of hilar lymph nodes. In such instances, the distinction between direct tumor invasion and true nodal metastasis may have been unclear, potentially leading to an N+ classification despite the absence of pathological confirmation. These considerations highlight the inherent limitations of retrospective staging assessments and underline the need for cautious interpretation of TN-stage-based survival outcomes in this context. Such diagnostic challenges, particularly in borderline cases, may have potentially influenced staging decisions.

Prior studies have shown the superiority of CCI compared with individual comorbid conditions in the prediction of survival (19,20,30). However, to the best of our knowledge, there are only few analyses available using CCI as predictor for survival in a cohort of patients treated with SBRT (44-46). Baker *et al* (46) investigated the role of CCI and the cumulative illness rating scale (CIRS) as prognostic factors for death within 6 months after SBRT; it was reported that CIRS and tumor diameter were more accurate predictors in terms of early-mortality in early-stage lung cancer after SBRT (46). A subsequent trial performed by Eriguchi *et al* (47) retrospectively analyzed operable stage I NSCLC treated with SBRT, staged as cT1-2N0M0. The median follow-up after SBRT was 40 months and in their multivariate regression analysis, age and CCI were found to be significantly associated with OS (47). By contrast, the present analysis did not find a significant association between CCI and OS. Patients with a CCI score of 4-5 had a hazard ratio of 1.36 (95% CI, 0.73-2.53) and those with a score >5 had a hazard ratio of 1.11 (95% CI, 0.53-2.30) compared to patients with a CCI <4 . Neither comparison reached statistical significance ($P=0.6$) and these findings were consistent across both univariate

and multivariate models. However, the median age of the cohort in the study by Eriguchi *et al* (47) was slightly older at 79 years (range, 55-88 years) compared with that of the present SBRT cohort at 74 years (range, 45-91 years). Furthermore, the median follow-up time of their study was notably shorter compared with that of the present analysis (40 vs. 149 months). In addition, different ethnic backgrounds (Asian vs. European patients) should be considered in the interpretation of the different outcomes between CCI and survival.

Ganti *et al* (48) examined the prognostic role of CCI in terms of survival based on a large sample size ($n=617$) of patients with NSCLC and small cell lung cancer (SCLC). Multivariate regression models showed no correlation between survival and the age-adjusted CCI or CCI without age-adjustment. In contrast to the present findings, another study conducted on 2,221 patients with lung cancer treated with SBRT showed a significant association between OS and CCI as well as between lung cancer specific survival and CCI (49). The patient characteristics and follow-up time differed when compared with the present study; the median 5-year OS rate was 34 months for patients with pathological confirmation of their diagnosis compared with 26 months in the present study.

PET-CT based treatment planning have shown good clinical outcomes in inoperable adenocarcinoma, with higher PET-CT SUVmax values before SBRT being associated with increased risk of failure (50). When using PET-CT-based radiation planning, the GTV and clinical tumor volume could be significantly reduced and accuracy improved (51-53). Additionally, recent studies have established predictive models for treatment outcomes (PFS and distant metastasis-free survival) after SBRT based on radiomic features and PET-CT (54-57). Although PET-CT-based treatment planning has demonstrated clinical value in previous studies (52,54,58,59), it was not included in the present multivariate Cox regression model. Due to the limited overall sample size, the number of variables that could be entered into the model had to be restricted to avoid overfitting. As a result, only covariates with statistically significant associations in the univariate analysis ($P<0.05$) were selected for multivariate modeling. PET-CT did not meet this criterion and was therefore excluded from further analysis.

PET-CT was already established as a routine imaging modality during the treatment period and was used in a large proportion of the present cohort. The contribution of PET-CT to improved clinical outcomes may have been indirectly captured through a more accurate GTV definition, which was significantly associated with OS (52). PET-CT enables precise delineation of GTV, often resulting in reduced volumes and improved dose conformity (60). In the present dataset, GTV emerged as an independent predictor of OS in both univariate and multivariate analyses. Thus, the prognostic effect of PET-CT-based planning may have been reflected through its influence on GTV, even though it was not explicitly included as a covariate in the final model.

A key limitation of the present retrospective, single-center analysis lies in the inherent risk of selection bias and residual confounding due to the non-randomized nature of the cohort. Although missing data and potential bias was addressed through multiple imputations and complete-case sensitivity analyses, these methods rely on assumptions (for example, data

missing at random) that cannot be fully verified. Furthermore, the absence of randomization limits causal inference and associations observed in multivariate models should be interpreted as exploratory rather than confirmatory.

The monocentric design further restricts the generalizability of the present findings, as treatment protocols, patient selection and follow-up strategies may differ across institutions. The relatively small sample size limits statistical power, particularly for subgroup analyses, and increases the risk of type II errors. Although GTV and age emerged as significant prognostic factors in both primary and imputed models, these findings warrant validation in larger, multicenter cohorts. Additionally, the retrospective nature of data collection led to incomplete documentation of certain clinical variables and inconsistent reporting of toxicity or recurrence, precluding analysis of endpoints such as local control or PFS. Due to this, OS remained the only robust endpoint available for analysis. Finally, the lack of standardized imaging protocols and follow-up intervals may have introduced variability in outcome assessment. Despite the application of rigorous statistical methods, these methodological limitations underscore the need for prospective, multicenter studies with standardized data collection to improved understand the long-term outcomes of SBRT in early-stage NSCLC.

A potential concern in long-term survival analyses of elderly or comorbid patients is the risk of loss to follow-up or competing events unrelated to cancer, such as non-cancer-related deaths. In the present cohort, follow-up was actively conducted via association with the local citizen registration office, which allowed for robust and reliable ascertainment of vital status for all patients. Therefore, no patients were lost to follow-up and OS could be determined with high confidence. However, due to the retrospective design and limited availability of cause-of-death information and cancer-specific survival could not be evaluated. As such, the reported OS includes both cancer-related and non-cancer-related deaths. This limitation is particularly relevant in an elderly cohort with substantial comorbidities, where non-cancer mortality may compete with oncologic outcomes. While the CCI was included in the analysis to account for overall comorbidity burden, it was not significantly associated with survival in the present models. The influence of competing risks, especially in older patients or those with severe COPD, should be considered when interpreting the OS results. Future prospective studies with detailed documentation of cause of death and competing events are warranted to separate cancer-specific outcomes from broader survival metrics in SBRT-treated patients with NSCLC.

In the present multivariate Cox regression analysis, GTV emerged as an independent predictor of OS, with larger tumor volumes being significantly associated with worse outcomes. This finding is consistent with previously published evidence, reinforcing the prognostic relevance of tumor volume in SBRT-treated patients with NSCLC. Kessel *et al* (61) analyzed 219 patients with lung metastases and confirmed that smaller GTV and PTV were significantly associated with improved OS using a univariate analysis. In addition to the favorable oncologic outcomes, low rates of physician- and patient-reported high-grade toxicity even after long-term follow-up, were reported. This underlines the importance of minimizing irradiated volume not only to reduce toxicity

but also to potentially improve survival. The integration of patient-reported outcomes further emphasized the impact of respiratory symptoms such as severe dyspnea on patients' quality of life and highlights the clinical relevance of sparing functional lung tissue, especially in patients with compromised pulmonary function (61). These results underscore the importance of volumetric parameters such as GTV and PTV in SBRT planning and outcomes. The present results contributed to this evidence by demonstrating that even in a real-world cohort with heterogeneous stages and performance statuses, tumor volume remained a robust and independent prognostic factor for survival. Future analysis should also focus on the long-term outcomes of medically operable early-stage patients with lung cancer treated with surgery compared with SBRT. Due to the lack of prospective, randomized trials comparing both treatments, advanced statistical methods such as propensity score matching are needed to evaluate these treatment outcomes.

The present study provided long-term survival data for early-stage patients with NSCLC treated with SBRT. Although OS rates remained limited, patients aged ≥ 75 years demonstrated better outcomes, likely reflecting more selective inclusion of older patients with lower tumor burden and favorable clinical characteristics. Tumor volume was independently associated with OS, highlighting its prognostic relevance in this setting. By contrast, BEDmean and performance status were not significant predictors. These findings emphasize the importance of tumor characteristics over chronological age when considering SBRT for early-stage NSCLC.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

JAM performed the data analysis. SG, CK, CP and DV contributed to the refinement of the analysis. All authors read and approved the final manuscript. JAM and DV confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of the Medical Faculty of Martin Luther University Halle-Wittenberg [Halle (Saale), Germany; approval no. 2025-006]. As patient data was obtained from the University Hospital Halle, it should be noted that the University Hospital Halle serves as the academic teaching hospital and clinical center of the Medical Faculty of Martin Luther University Halle-Wittenberg.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work the author(s) used ChatGPT, a language model developed by OpenAI Inc., in order to improve writing style and check grammar and spelling. After using this tool, the authors reviewed and edited the content as needed and took full responsibility for the content of the publication.

References

- Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A and Bray F: Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 71: 209-249, 2021.
- Islami F, Torre LA and Jemal A: Global trends of lung cancer mortality and smoking prevalence. *Transl Lung Cancer Res* 4: 327-338, 2015.
- Koch M, Gräfenstein L, Karnosky J, Schulz C and Koller M: Psychosocial burden and quality of life of lung cancer patients: Results of the EORTC QLQ-C30/QLQ-LC29 questionnaire and hornheide screening instrument. *Cancer Manag Res* 13: 6191-6197, 2021.
- Lu T, Yang X, Huang Y, Zhao M, Li M, Ma K, Yin J, Zhan C and Wang Q: Trends in the incidence, treatment, and survival of patients with lung cancer in the last four decades. *Cancer Manag Res* 11: 943-953, 2019.
- Besse B, Adjei A, Baas P, Meldgaard P, Nicolson M, Paz-Ares L, Reck M, Smit EF, Syrigos K, Stahel R, *et al*: 2nd ESMO consensus conference on lung cancer: Non-small-cell lung cancer first-line/second and further lines of treatment in advanced disease. *Ann Oncol* 25: 1475-1484, 2014.
- Tan WL, Jain A, Takano A, Newell EW, Iyer NG, Lim WT, Tan EH, Zhai W, Hillmer AM, Tam WL and Tan DSW: Novel therapeutic targets on the horizon for lung cancer. *Lancet Oncol* 17: e347-e362, 2016.
- Palma D, Visser O, Lagerwaard FJ, Belderbos J, Slotman BJ and Senan S: Impact of introducing stereotactic lung radiotherapy for elderly patients with stage I non-small-cell lung cancer: A population-based time-trend analysis. *J Clin Oncol* 28: 5153-5159, 2010.
- Palma DA and Senan S: Improving outcomes for high-risk patients with early-stage non-small-cell lung cancer: Insights from population-based data and the role of stereotactic ablative radiotherapy. *Clin Lung Cancer* 14: 1-5, 2013.
- Potters L, Kavanagh B, Galvin JM, Hevezi JM, Janjan NA, Larson DA, Mehta MP, Ryu S, Steinberg M, Timmerman R, *et al*: American society for therapeutic radiology and oncology (ASTRO) and American college of radiology (ACR) practice guideline for the performance of stereotactic body radiation therapy. *Int J Radiat Oncol Biol Phys* 76: 326-332, 2010.
- Timmerman R, Paulus R, Galvin J, Michalski J, Straube W, Bradley J, Fakiris A, Bezjak A, Videtic G, Johnstone D, *et al*: Stereotactic body radiation therapy for inoperable early stage lung cancer. *JAMA* 303: 1070-1076, 2010.
- Senthi S, Haasbeek CJA, Slotman BJ and Senan S: Outcomes of stereotactic ablative radiotherapy for central lung tumours: A systematic review. *Radiother Oncol* 106: 276-282, 2013.
- Ball D, Mai GT, Vinod S, Babington S, Ruben J, Kron T, Chesson B, Herschtal A, Vanevski M, Rezo A, *et al*: Stereotactic ablative radiotherapy versus standard radiotherapy in stage 1 non-small-cell lung cancer (TROG 09.02 CHISEL): A phase 3, open-label, randomised controlled trial. *Lancet Oncol* 20: 494-503, 2019.
- Chang JY, Senan S, Paul MA, Mehran RJ, Louie AV, Balter P, Groen HJM, McRae SE, Widder J, Feng L, *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* 16: 630-637, 2015.
- Chang JY, Mehran RJ, Feng L, Verma V, Liao Z, Welsh JW, Lin SH, O'Reilly MS, Jeter MD, Balter PA, *et al*: Stereotactic ablative radiotherapy for operable stage I non-small-cell lung cancer (revised STARS): Long-term results of a single-arm, prospective trial with prespecified comparison to surgery. *Lancet Oncol* 22: 1448-1457, 2021.
- Altorki N, Wang X, Damman B, Mentlick J, Landreneau R, Wigle D, Jones DR, Conti M, Ashrafi AS, Liberman M, *et al*: Lobectomy, segmentectomy, or wedge resection for peripheral clinical T1aN0 non-small cell lung cancer: A post hoc analysis of CALGB 140503 (Alliance). *J Thorac Cardiovasc Surg* 167: 338-347.e1, 2024.
- Raz DJ, Zell JA, Ou S-HI, Gandara DR, Anton-Culver H and Jablons DM: Natural history of stage I non-small cell lung cancer: Implications for early detection. *Chest* 132: 193-199, 2007.
- Baine MJ, Verma V, Schonewolf CA, Lin C and Simone CB II: Histology significantly affects recurrence and survival following SBRT for early stage non-small cell lung cancer. *Lung Cancer* 118: 20-26, 2018.
- Zhang J, Yang F, Li B, Li H, Liu J, Huang W, Wang D, Yi Y and Wang J: Which is the optimal biologically effective dose of stereotactic body radiotherapy for Stage I non-small-cell lung cancer? A meta-analysis. *Int J Radiat Oncol Biol Phys* 81: e305-e316, 2011.
- Birim O, Kappetein AP and Bogers AJJC: Charlson comorbidity index as a predictor of long-term outcome after surgery for non-small cell lung cancer. *Eur J Cardiothorac Surg* 28: 759-762, 2005.
- Birim O, Maat APWM, Kappetein AP, van Meerbeeck JP, Damhuis RAM and Bogers AJJC: Validation of the Charlson comorbidity index in patients with operated primary non-small cell lung cancer. *Eur J Cardiothorac Surg* 23: 30-34, 2003.
- Charlson ME, Pompei P, Ales KL and MacKenzie CR: A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. *J Chronic Dis* 40: 373-383, 1987.
- Edge SB and Compton CC: The American joint committee on cancer: The 7th edition of the AJCC cancer staging manual and the future of TNM. *Ann Surg Oncol* 17: 1471-1474, 2010.
- Brierley JD, Gospodarowicz MK and Wittekind C (eds.): *TNM Classification of Malignant Tumours*, 8th Edition. Wiley-Blackwell, Hoboken, NJ, USA, pp 129-136, 2016.
- Cerfolio RJ, Ojha B, Bryant AS, Raghuvver V, Mountz JM and Bartolucci AA: The accuracy of integrated PET-CT compared with dedicated PET alone for the staging of patients with non-small cell lung cancer. *Ann Thorac Surg* 78: 1017-1023, 2004.
- Clarke K, Taremi M, Dahele M, Freeman M, Fung S, Franks K, Bezjak A, Brade A, Cho J, Hope A and Sun A: Stereotactic body radiotherapy (SBRT) for non-small cell lung cancer (NSCLC): Is FDG-PET a predictor of outcome? *Radiother Oncol* 104: 62-66, 2012.
- Freeman M, Ennis M and Jerzak KJ: Karnofsky performance status (KPS) ≤ 60 is strongly associated with shorter brain-specific progression-free survival among patients with metastatic breast cancer with brain metastases. *Front Oncol* 12: 867462, 2022.
- Buccheri G, Ferrigno D and Tamburini M: Karnofsky and ECOG performance status scoring in lung cancer: A prospective, longitudinal study of 536 patients from a single institution. *Eur J Cancer* 32A: 1135-1141, 1996.
- Agustí A, Celli BR, Criner GJ, Halpin D, Anzueto A, Barnes P, Bourbeau J, Han MK, Martinez FJ, Montes de Oca M, *et al*: Global initiative for chronic obstructive lung disease 2023 report: GOLD executive summary. *Am J Respir Crit Care Med* 207: 819-837, 2023.
- Mirza S, Clay RD, Koslow MA and Scanlon PD: COPD guidelines: A review of the 2018 GOLD report. *Mayo Clin Proc* 93: 1488-1502, 2018.
- Charlson ME, Carrozzino D, Guidi J and Patierno C: Charlson comorbidity index: A critical review of clinimetric properties. *Psychother Psychosom* 91: 8-35, 2022.
- Fowler JF: The linear-quadratic formula and progress in fractionated radiotherapy. *Br J Radiol* 62: 679-694, 1989.
- Klement RJ, Sonke JJ, Allgauer M, Andratschke N, Appold S, Belderbos J, Belka C, Blanck O, Diekmann K, Eich HT, *et al*: Correlating dose variables with local tumor control in stereotactic body radiation therapy for early-stage non-small cell lung cancer: A modeling study on 1500 individual treatments. *Int J Radiat Oncol Biol Phys* 107: 579-586, 2020.

33. Zhang Z: Variable selection with stepwise and best subset approaches. *Ann Transl Med* 4: 136, 2016.
34. Henschke CI, Yip R, Sun Q, Li P, Kaufman A, Samstein R, Connery C, Kohman L, Lee P, Tannous H, *et al*: Prospective cohort study to compare long-term lung cancer-specific and all-cause survival of clinical early stage (T1a-b; ≤ 20 mm) NSCLC treated by stereotactic body radiation therapy and surgery. *J Thorac Oncol* 19: 476-490, 2024.
35. Fan S, Zhang Q, Chen J, Chen G, Zhu J, Li T, Xiao H, Du S, Zeng Z and He J: Comparison of long-term outcomes of stereotactic body radiotherapy (SBRT) via Helical tomotherapy for early-stage lung cancer with or without pathological proof. *Radiat Oncol* 18: 49, 2023.
36. Speicher PJ and D'Amico TA: Weighing the relative importance of short-term versus long-term outcomes when comparing surgery versus stereotactic body radiation therapy (SBRT) for early-stage non-small cell lung cancer. *J Thorac Dis* 10 (Suppl 17): S2022-S2024, 2018.
37. Arnett ALH, Mou B, Owen D, Park SS, Nelson K, Hallemeier CL, Sio T, Garces YI, Olivier KR and Merrell KW: Long-term clinical outcomes and safety profile of SBRT for centrally located NSCLC. *Adv Radiat Oncol* 4: 422-428, 2019.
38. Guckenberger M, Allgäuer M, Appold S, Dieckmann K, Ernst I, Ganswindt U, Holy R, Nestle U, Nevinny-Stickel M, Semrau S, *et al*: Safety and efficacy of stereotactic body radiotherapy for stage I non-small-cell lung cancer in routine clinical practice: A patterns-of-care and outcome analysis. *J Thorac Oncol* 8: 1050-1058, 2013.
39. Jimenez-Jimenez E, Marti-Laosa MM, Nieto-Guerrero JM, Perez ME, Gómez M, Lozano E and Sabater S: Biologically effective dose (BED) value lower than 120 Gy improve outcomes in lung SBRT. *Clin Transl Oncol* 26: 1203-1208, 2024.
40. Kreinbrink P, Blumenfeld P, Tolekidis G, Sen N, Sher D and Marwaha G: Lung stereotactic body radiation therapy (SBRT) for early-stage non-small cell lung cancer in the very elderly (≥ 80 years old): Extremely safe and effective. *J Geriatr Oncol* 8: 351-355, 2017.
41. Pop DD, Hopîrtean C, Coşer F, Dan F, Zah T, Fekete Z, Chiş A, Tufăscu G, Udrea A and Mihai A: Implementation of advanced radiotherapy techniques: Stereotactic body radiotherapy (SBRT) for oligometastatic patients with lung metastasis-a single institution experience. *Med Pharm Rep* 95: 410-417, 2022.
42. Guo Y, Zhu Y, Zhang R, Yang S, Kepka L, Viani GA, Milano MT, Sio TT, Sun X, Wu H, *et al*: Five-year follow-up after stereotactic body radiotherapy for medically inoperable early-stage non-small cell lung cancer: A multicenter study. *Transl Lung Cancer Res* 12: 1293-1302, 2023.
43. Onishi H, Shioyama Y, Matsumoto Y, Matsuo Y, Miyakawa A, Yamashita H, Matsushita H, Aoki M, Nihei K, Kimura T, *et al*: Real-world results of stereotactic body radiotherapy for 399 medically operable patients with stage I histology-proven non-small cell lung cancer. *Cancers (Basel)* 15: 4382, 2023.
44. Snider M, Salama JK and Boyer M: Survival and recurrence rates following SBRT or surgery in medically operable stage I NSCLC. *Lung Cancer* 197: 107962, 2024.
45. Wong OY, Yau V, Kang J, Glick D, Lindsay P, Le LW, Sun A, Bezjak A, Cho BCJ, Hope A and Giuliani M: Survival impact of cardiac dose following lung stereotactic body radiotherapy. *Clin Lung Cancer* 19: e241-e246, 2018.
46. Baker S, Sharma A, Peric R, Heemsbergen WD and Nuytens JJ: Prediction of early mortality following stereotactic body radiotherapy for peripheral early-stage lung cancer. *Acta Oncol* 58: 237-242, 2019.
47. Eriguchi T, Takeda A, Sanuki N, Tsurugai Y, Aoki Y, Oku Y, Hara Y, Akiba T and Shigematsu N: Stereotactic body radiotherapy for operable early-stage non-small cell lung cancer. *Lung Cancer* 109: 62-67, 2017.
48. Ganti AK, Siedlik E, Marr AS, Loberiza FR Jr and Kessinger A: Predictive ability of Charlson comorbidity index on outcomes from lung cancer. *Am J Clin Oncol* 34: 593-596, 2011.
49. Wilkie JR, Lipson R, Johnson MC, Williams C, Moghanaki D, Elliott D, Owen D, Atluri N, Jolly S and Chapman CH: Use and outcomes of SBRT for early stage NSCLC without pathologic confirmation in the veterans health care administration. *Adv Radiat Oncol* 6: 100707, 2021.
50. Moraes FY, Abreu CECV, Siqueira GSM, Haddad CK, Degrande FAM, Hopman WM, Neves-Junior WFP, Gadia R and Carvalho HA: Applying PET-CT for predicting the efficacy of SBRT to inoperable early-stage lung adenocarcinoma: A Brazilian case-series. *Lancet Reg Health Am* 11: 100241, 2022.
51. Mahasittiwat P, Yuan S, Xie C, Ritter T, Cao Y, Ten Haken RK and Kong FMS: Metabolic tumor volume on PET reduced more than gross tumor volume on CT during radiotherapy in patients with non-small cell lung cancer treated with 3DCRT or SBRT. *J Radiat Oncol* 2: 191-202, 2013.
52. Chirindel A, Adebahr S, Schuster D, Schimek-Jasch T, Schanne DH, Nemer U, Mix M, Meyer P, Grosu AL, Brunner T and Nestle U: Impact of 4D-(18)FDG-PET/CT imaging on target volume delineation in SBRT patients with central versus peripheral lung tumors. Multi-reader comparative study. *Radiation Oncol* 115: 335-341, 2015.
53. Hoopes DJ, Tann M, Fletcher JW, Forquer JA, Lin PF, Lo SS, Timmerman RD and McGarry RC: FDG-PET and stereotactic body radiotherapy (SBRT) for stage I non-small-cell lung cancer. *Lung Cancer* 56: 229-234, 2007.
54. Chen K, Hou L, Chen M, Li S, Shi Y, Raynor WY and Yang H: Predicting the efficacy of SBRT for lung cancer with ^{18}F -FDG PET/CT radiogenomics. *Life (Basel)* 13: 884, 2023.
55. Thor M, Fitzgerald K, Apte A, Oh JH, Iyer A, Odiase O, Nadeem S, Yorke ED, Chaff J, Wu AJ, *et al*: Exploring published and novel pre-treatment CT and PET radiomics to stratify risk of progression among early-stage non-small cell lung cancer patients treated with stereotactic radiation. *Radiation Oncol* 190: 109983, 2024.
56. Yu X, He L, Wang Y, Dong Y, Song Y, Yuan Z, Yan Z and Wang W: A deep learning approach for automatic tumor delineation in stereotactic radiotherapy for non-small cell lung cancer using diagnostic PET-CT and planning CT. *Front Oncol* 13: 1235461, 2023.
57. Yu L, Zhang Z, Yi H, Wang J, Li J, Wang X, Bai H, Ge H, Zheng X, Ni J, *et al*: A PET/CT radiomics model for predicting distant metastasis in early-stage non-small cell lung cancer patients treated with stereotactic body radiotherapy: A multicentric study. *Radiat Oncol* 19: 10, 2024.
58. Tyrant M, Charrier N, Darreon J, Madroszyk A, Tallet A and Salem N: Early PET-CT after stereotactic radiotherapy for stage I non-small cell lung carcinoma is predictive of local control. *In Vivo* 32: 121-124, 2018.
59. Borm KJ, Oechsner M, Schiller K, Peeken JC, Dapper H, Münch S, Kroll L, Combs SE and Duma MN: Prognostische Faktoren bei der stereotaktischen Strahlentherapie von Lungenmetastasen. *Strahlenther Onkol* 194: 886-893, 2018.
60. Retif P, Verrecchia-Ramos E, Saleh M, Djibo Sidikou A, Letellier R, Al Salah A, Pfletschinger E, Taesch F, Ben-Mahmoud S and Michel X: On the use of 4D-PET/CT for the safe SBRT re-irradiation of central lung recurrence within radiation-induced fibrosis: A clinical case. *J Clin Med* 14: 4015, 2025.
61. Kessel KA, Grosser RCE, Kraus KM, Hoffmann H, Oechsner M and Combs SE: Stereotactic body radiotherapy (SBRT) in patients with lung metastases-prognostic factors and long-term survival using patient self-reported outcome (PRO). *BMC Cancer* 20: 442, 2020.



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