Stereotactic body radiotherapy for early-stage non-small cell lung cancer: Comprehensive analysis of outcomes and recurrence from a single-center experience

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Abstract. This study aimed to analyze prognostic factors in patients with early-stage non-small cell lung cancer (NSCLC) treated with stereotactic body radiotherapy (SBRT), focusing on symptomatic radiation pneumonitis (RP) and treatment failure patterns. This retrospective cohort study included 271 patients with early-stage NSCLC (276 lesions) treated with SBRT from May 2012 to January 2022. SBRT was administered according to standardized protocols with doses ranging from 28.5 to 80 Gy in 1 to 10 fractions. Tumor recurrence, RP, and failure patterns were assessed through imaging and clinical evaluations. Prognostic factors for overall survival (OS) and local control (LC) were identified using Kaplan-Meier survival analysis, Cox models, and logistic regression for RP risk. With a median follow-up of 30.8 months, the 1-, 2- and 3-year OS rates were 96.1, 91.8, and 86.5%, respectively, and LC rates were 98.8, 96.5, and 92.9%, respectively. The Eastern Cooperative Oncology Group performance status (P=0.002) and higher fractional dose (P=0.041) were significant predictors of OS. Larger tumor size (P<0.001) and higher solid-to-total tumor ratio (P=0.028) were associated with increased local recurrence risk. Symptomatic RP (7.2% of lesions) was associated with solid tumor size (P=0.050). Larger tumors with a higher solid component had more in-field recurrences, while marginal recurrences were often attributable to air space spread and pleural involvement. Higher fractional doses in SBRT benefit patients with early-stage NSCLC, especially those with larger tumors or significant solid components, suggesting that dose escalation or more biologically effective therapies could enhance outcomes and optimize SBRT protocols.

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Abbreviations: BED, biologically effective dose; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CT, computed tomography; ECOG-PS, Eastern Cooperative Oncology Group performance status; GTV, gross tumor volume; HR, hazard ratio; IQR, interquartile range; IRB, institutional review board; LC, local control; MLD, mean lung dose; NSCLC, non-small cell lung cancer; PTV, planning target volume; OR, odds ratio; OS, overall survival; PET-CT, positron emission tomography-computed tomography; RP, radiation pneumonitis; SBRT, stereotactic body radiation therapy; STAS, tumor spread through air spaces; VMAT, volumetric modulated arc therapy

Key words: local control, non-small cell lung cancer, prognostic factors, radiation pneumonitis, stereotactic body radiotherapy, survival analysis

Introduction

Non-small cell lung cancer (NSCLC), including adenocarcinoma, squamous cell carcinoma, and large cell carcinoma, accounts for about 85% of lung cancer cases and is a leading cause of cancer deaths worldwide due to its prevalence and aggressiveness (1). In 2022, lung cancer resulted in

approximately 2.48 million new cases and 1.8 million deaths globally, with NSCLC predominant, underscoring its major public health impact (2).

Although surgery remains the standard treatment modality for early-stage NSCLC, many patients are medically inoperable owing to advanced age, comorbidities, or poor lung function, necessitating alternative curative approaches. Stereotactic body radiotherapy (SBRT) has emerged as a safe and effective treatment modality for patients with early-stage NSCLC, as it offers a non-invasive alternative to surgery, particularly in patients who are medically inoperable or at high surgical risk. By delivering ablative radiation doses over a limited number of fractions with high precision, SBRT achieves excellent local control (LC) while minimizing toxicity to surrounding healthy tissues, making it a promising option, with its benefits supported by increasing clinical evidence (3).

Over the past two decades, advances in imaging, motion management, and treatment planning have established SBRT as a standard curative option for inoperable early-stage NSCLC, enabling precise high-dose delivery with minimal toxicity. However, despite these advancements, the role of SBRT relative to surgical intervention remains an area of ongoing investigation (4). Several clinical trials, including the STARS and ROSEL trials (5), have aimed to directly compare the outcomes of SBRT with those of lobectomy, the traditional standard of care for operable stage I NSCLC. These studies have shown comparable survival rates between SBRT and surgery, particularly in patients with operable tumors. However, the data are limited by small sample sizes and early trial closures. Large-scale randomized controlled trials, such as VALOR, STABLE-MATES, and POSTILV, are currently underway to address these limitations and provide more definitive evidence (6-8). Until these results become available, clinical practice often relies on existing guidelines and expert consensus.

The American Society for Radiation Oncology provides evidence-based guidelines recommending SBRT primarily for patients who are medically inoperable or at high surgical risk (9). These guidelines also caution against the use of SBRT in standard-risk operable patients outside of a clinical trial. Nevertheless, in clinical practice, the decision to use SBRT is often influenced by patient preference and the clinical judgment of the treating physician, resulting in variability in treatment decisions. This underscores the need for further research into prognostic factors that can more accurately identify patients who might benefit most from SBRT while also considering the potential risks of complications such as radiation pneumonitis (RP), which can significantly affect patient outcomes and quality of life.

This study aimed to analyze prognostic factors in patients who have undergone SBRT for early-stage NSCLC, with a detailed evaluation of dosimetric parameters and clinical factors associated with the development of RP. We also conducted an in-depth analysis of failure patterns. By elucidating these factors, the study seeks to provide comprehensive insights into the determinants of survival outcomes, the risk of treatment-related toxicities, and local recurrence patterns, including true in-field and marginal recurrences, in patients with early-stage NSCLC treated with SBRT. These insights will contribute to optimizing SBRT planning, thereby enhancing the effectiveness and safety of treatment strategies for early-stage NSCLC.

Materials and methods

Study population. This retrospective cohort study evaluated patients aged ≥19 years diagnosed with early-stage NSCLC and treated with curative-intent radiotherapy between May 2012 and January 2022 at Yonsei Cancer Center, Severance Hospital, Yonsei University Health System. Data were accessed between January 2023 and September 2024. The exclusion criteria were as follows: advanced-stage lung cancer, metastatic lung cancer, recurrent lung cancer, prior radiotherapy to the lungs or thoracic region, a history of other malignancies that could significantly affect prognosis, inability to perform dosimetric parameter analysis, or lack of follow-up for radiotherapy-related toxicities. Early-stage NSCLC was defined as clinical T1aN0 (stage IA1) to T2aN0 (stage IB) disease. The feasibility of biopsy is often limited in inoperable patients with compromised pulmonary function or other high-risk conditions. In this study, biopsy was accordingly omitted when the patient had severe pulmonary disease, high surgical or bleeding risk, or technically challenging tumor locations (Fig. S1). Additionally, some biopsy attempts yielded insufficient tissue samples despite strong clinical and radiologic evidence of malignancy. For these patients who did not undergo biopsy, treatment decisions were guided by comprehensive imaging [e.g., computed tomography (CT), positron emission tomography-computed tomography (PET-CT)] and longitudinal follow-up to minimize diagnostic uncertainty.

Ethics statement. This study was approved by the Institutional Review Board (IRB) of Severance Hospital (IRB No. 4-2022-1463) and was conducted in accordance with the principles of the Declaration of Helsinki; the need for written consent was waived due to the retrospective nature of the study.

Treatment. All patients received SBRT following a standardized protocol. Regardless of the specific SBRT modality, each patient underwent thorough motion assessment with four-dimensional CT (4D-CT) during treatment planning, ensuring that tumor motion throughout the respiratory cycle was accurately captured. Additionally, daily modality-specific image guidance (e.g., cone-beam CT, megavoltage CT) was performed before each treatment fraction to account for any potential tumor shift and maintain adequate target coverage, including for lower-lobe lesions. To ensure patient stability, simulation CT was performed using immobilization devices, including whole-body vacuum systems or stereotactic body frames. Respiratory motion was primarily managed with an abdominal compression device, and for patients with diaphragmatic movement exceeding 1 cm vertically, additional respiratory management techniques (e.g., shallow breathing) were applied based on individual tolerance. The gross tumor volume (GTV) was delineated across all phases of 4D-CT, and the planning target volume (PTV) was generated by expanding the internal GTV (iGTV) by 5-10 mm. For CyberKnife (Accuray, Inc., Sunnyvale, CA) treatments,

PTV margins were minimized to 2-3 mm given the real-time tracking capabilities.

The core principle of SBRT is to deliver an ablative dose to a confined lung volume, using precise target delineation, careful motion management, and strict dose constraints, regardless of the specific technique. Following these principles preserves treatment consistency and supports optimal outcomes across various SBRT platforms. Consequently, we retained all SBRT modalities in our study to provide a more comprehensive view of real-world clinical practice. Particularly, we included patients who underwent SBRT using multiple techniques [volumetric modulated arc therapy (VMAT), three-dimensional conformal radiation therapy, tomotherapy, and CyberKnife] rather than restricting the analysis to patients who underwent a uniform SBRT modality. The radiation dose varied according to tumor characteristics, with treatments delivered in 1 to 10 fractions, totaling 28.5-80 Gy. The aim was to ensure comprehensive coverage of the PTV with at least 80% of the prescribed dose. Treatment plans were developed using advanced planning systems customized for each specific treatment modality, ensuring strict adherence to dose constraints for surrounding healthy tissues as recommended by the American Association of Physicists in Medicine Task Group 101. Quality assurance measures, including 4D cone-beam CT or megavoltage CT, were employed during each treatment session to confirm precise dose delivery.

Assessment of tumor recurrence and radiation pneumonitis. Tumor recurrence and RP were systematically evaluated during routine follow-up visits. Imaging studies, including chest CT, were performed at 1, 3, and 6 months post-treatment, with additional imaging performed as clinically indicated. Tumor response was assessed using the Response Evaluation Criteria in Solid Tumors version 1.1, ensuring consistent measurement of tumor burden over time. The evaluation of tumor recurrence extended beyond the thoracic region and included comprehensive imaging techniques such as brain magnetic resonance imaging, chest CT, abdominal-pelvic CT, and PET-CT to assess both local and distant disease progression. Local failure was defined as tumor regrowth with its center overlapping the PTV, characterized by a ≥20% increase in size or the emergence of new lesions. Marginal failure was defined as tumor progression with its center located outside but within 1 cm of the PTV. RP was diagnosed based on clinical symptoms and radiologic findings within 6 months following SBRT, with the severity of RP graded using the Common Terminology Criteria for Adverse Events version 5.0, with only symptomatic cases defined as grade 2 or higher included in the analysis. Recurrence patterns were analyzed by two independent board-certified radiation oncologists, with over 5 and 25 years of experience, respectively. In cases of disagreement, a subsequent review was conducted to reach a consensus.

Statistical analysis. Continuous variables are presented as medians with corresponding interquartile ranges (IQRs). The Kaplan-Meier method was used to estimate overall survival (OS) and LC rates. Univariable and multivariable Cox proportional hazards models were utilized to identify significant prognostic factors associated with OS and LC. Logistic regression analysis was conducted to evaluate factors contributing to the development of symptomatic RP. Given that Cox proportional hazards and logistic regression models do not require normal distributions of the data, formal normality checks were not performed. A P-value of less than 0.05 was considered statistically significant for all analyses. All statistical analyses were performed using R software, version 4.3.3.

Results

Patient characteristics. This study included 271 patients with early-stage NSCLC treated with SBRT across 276 lesions. Detailed patient, tumor, and treatment characteristics are presented in Table I. The median age of the patients was 78 years (IQR, 73-82), with a predominance of men (69%). Most patients were diagnosed with stage I disease (77.6%), while the remaining 22.4% were diagnosed with stage II disease. A significant portion of the cohort had a history of smoking (61.3%), and 24.7% had been diagnosed with chronic obstructive pulmonary disease (COPD). Notably, 49.3% of the patients were treated without pathological confirmation of malignancy.

The Eastern Cooperative Oncology Group performance status (ECOG-PS) was predominantly 0-1 (89.3%). The primary reasons for undergoing SBRT were inoperability due to medical comorbidities (77.5%) and patient refusal of surgery (22.5%). The reasons for inoperability were advanced age (51.0%), poor general condition (13.8%), severe COPD (13.8%), severe interstitial lung disease (3.8%), and other comorbidities (17.6%). Tumor characteristics included a median size of 2.1 cm (IQR, 1.6-2.9 cm) on CT. The median GTV was 3.0 cm^3 (IQR, 1.5-5.8 cm^3), with an internal target volume of 10.8 cm^3 (IQR, 5.5-21.4 cm^3) and a PTV of 24.7 cm^3 (IQR, 16.1-43.2 cm^3). The solid portion of the tumors had a median diameter of 1.4 cm (IQR, 0.1-2.2 cm). Volumetric modulated arc therapy was used in 90.9% of cases. The most common SBRT regimen was 60 Gy delivered in 4 fractions (31.1%), followed by 50 Gy in 5 fractions (25.6%) and 45 Gy in 3 fractions (13.5%).

Survival outcomes. The median follow-up period was 30.8 months (IQR, 21.6-41.1). The 1, 2, and 3-year OS rates were 96.1, 91.8, and 86.5%, respectively. Correspondingly, the LC rates were 98.8% at 1 year, 96.5% at 2 years, and 92.9% at 3 years (Fig. S2).

In the univariable analysis, an ECOG-PS of 2-3 was significantly associated with worse OS [hazard ratio (HR): 2.85, 95% confidence interval (CI): 1.34-6.07, P=0.007]. This association was even more pronounced in the multivariable analysis (HR 5.75, 95% CI 1.86-17.79, P=0.002). Pathological subtype was also a significant predictor of OS in the univariable model, with squamous and other non-adenocarcinoma histologies associated with a higher mortality risk compared to unconfirmed pathology (HR 3.09, 95% CI 1.40-6.83, P=0.005). However, this association was not significant after adjustment in the multivariable model (HR 2.77, 95% CI 1.02-7.52, P=0.461). A higher fractional dose was associated with better survival in the multivariable analysis (HR 0.88, 95% CI 0.77-0.99, P=0.041), although it was not significant in the univariable analysis (HR 0.95, 95% CI 0.88-1.02, P=0.151) (Table II). The multivariable OS model showed a C-index of 0.686.

Table I. Patient and treatment characteristics.

Characteristics	N (%)	Median (IQR)
Age, years		78.0 (73.0-82.0)
Sex		
Male	187 (69)	
Female	84 (31)	
Smoking		
No	105 (38.7)	
Yes	166 (61.3)	
COPD		
No	204 (75.3)	
Yes	67 (24.7)	
ECOG-PS		
0	49 (18.1)	
1	193 (71.2)	
2	23 (8.5)	
3	6 (2.2)	
Tumor size, cm		2.2 (1.8-2.9)
Solid size, cm		1.4 (0.0-2.1)
Location		
RUL	84 (30.4)	
RML	20 (7.3)	
RLL	77 (27.9)	
LUL	65 (23.6)	
LLL	30 (10.9)	
Stage		
T1aN0 (IA1)	6 (2.2)	
T1bN0 (IA2)	120 (43.5)	
T1cN0 (IA3)	88 (31.9)	
T2aN0 (IB)	62 (22.5)	
Pathology		
Not confirmed	136 (49.3)	
Adenocarcinoma	96 (34.8)	
Squamous cell carcinoma	39 (14.1)	
Others	5 (1.8)	
Reason for RT		
Inoperable	210 (77.5)	
Refusal	61 (22.5)	
RT modality		
3D	14 (5.1)	
VMAT	251 (90.9)	
Tomotherapy	1 (0.4)	
Cyberknife	10 (3.6)	
Total dose (BED, a/b=10), Gy		112.5 (100.0-150.0)
Total fraction		4.0 (4.0-5.0)
Fractional dose, Gy		12.5 (10.0-15.0)
PTV volume, mm^3		24.7 (16.1-43.2)

IQR, interquartile range; COPD, chronic obstructive pulmonary disease; ECOG-PS, Eastern Cooperative Oncology Group performance status; RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe; RT, radiotherapy; 3D, three-dimensional conformal radiotherapy; VMAT, volumetric modulated arc therapy; PTV, planning target volume; BED, biologically effective dose.

In total, 15 patients (5.4%) developed local recurrence, of whom 9 patients were confirmed to have true local recurrence. The univariable analysis identified larger tumor size (HR: 2.13, 95% CI: 1.17-3.89, P=0.014), solid tumor size (HR: 3.01, 95% CI: 1.61-5.61, P=0.001), and solid-to-total tumor ratio (HR: 7.96, 95% CI: 1.04-61.13, P=0.046) as significant predictors of local recurrence. Multivariable analysis confirmed tumor size (HR: 5.43, 95% CI: 2.19-13.44, P<0.001) and the solid-to-total tumor ratio (HR: 11.86, 95% CI: 1.31-107.70, P=0.028) as independent predictors, although solid tumor size itself was not significant in the multivariable model. COPD was not a significant factor in the univariable analysis (HR: 2.36, 95% CI: 0.82-6.81, P=0.111) but approached borderline significance in the multivariable analysis (HR: 3.49, 95% CI: 0.96-12.76, P=0.058) (Table III). The multivariable LC model had a C-index of 0.797.

Incidence and influencing factors of symptomatic radiation pneumonitis. Symptomatic RP was observed in 20 lesions, accounting for 7.2% of the treated lesions. While solid tumor size was a borderline significant factor for the development of symptomatic RP in univariable analysis (OR 1.53, 95% CI 0.93-2.60, P=0.099), it achieved statistical significance in the multivariable analysis (OR 2.00, 95% CI 1.05-4.27, P=0.050). Although the total fractional dose was not significant in the univariable analysis, it approached borderline significance in the multivariable analysis, suggesting a decreased risk of RP with lower doses (OR 0.49, 95% CI 0.20-0.97, P=0.090). No other dosimetric factors were significantly associated with RP (Table IV).

Local recurrence including true in-field and marginal failures. Table V provides an analysis of 15 local recurrences, with 9 classified as true in-field failures and 6 as marginal, occurring adjacent to the primary lesion. The nine true in-field recurrences were associated with a slightly lower median biological effective dose (BED) of 105.6 Gy (IQR, 85.5-119.0 Gy) compared to the overall cohort. In contrast, the marginal recurrences exhibited a median BED of 131.3 Gy (IQR, 95.4-150.0 Gy), consistent with that noted for the overall population. True in-field recurrences were characterized by a larger tumor burden, with a median CT-measured tumor diameter of 3.3 cm (IQR, 2.3-3.6 cm), a median PTV of 44.8 cm^3 (IQR, 25.8-60.3 cm^3), and a median solid tumor portion of 2.6 cm (IQR, 2.3-3.3 cm). Marginal recurrences did not differ significantly from the overall cohort in terms of tumor diameter (median, 2.6 cm; IQR, 2.0-2.8 cm) and PTV (median, 26.5 cm^3; IQR, 14.2-50.1 cm^3), although a trend toward a larger solid tumor portion was observed (median, 2.4 cm; IQR, 2.0-2.7 cm). Airway-associated recurrence was suspected in four cases, with one occurring in the true in-field group and three in the marginal group (Fig. S3). Additionally, one case of true in-field recurrence was suspected to involve pleural spread (Fig. S4).

Discussion

This study analyzed 271 patients with 276 lesions, reaffirming SBRT as an effective treatment for early-stage NSCLC, particularly in medically inoperable patients. Previous

Table II. Univariable and multivariable analysis of factors associated with overall survival.

	Univariable		Multivariable	
Variable	HR (95% CI)	P-value	HR (95% CI)	P-value
Age, years	1.02 (0.97-1.07)	0.502		
Sex				
Male	1.00 (Ref.)	(Ref.)		
Female	0.68 (0.33-1.41)	0.301		
Smoking				
No	1.00 (Ref.)	(Ref.)		
Yes	1.42 (0.73-2.78)	0.307		
ECOG-PS				
0-1	1.00 (Ref.)	(Ref.)	1.00 (Ref.)	(Ref.)
2-4	2.85 (1.34-6.07)	0.007	5.75 (1.86-17.79)	0.002
COPD				
No	1.00 (Ref.)	(Ref.)		
Yes	1.11 (0.54-2.29)	0.783		
Tumor location				
Upper/middle lobe	1.00 (Ref.)	(Ref.)		
Lower lobe	0.89 (0.45-1.75)	0.741		
Tumor size, cm	1.10 (0.76-1.60)	0.609		
Solid size, cm	0.73 (0.47-1.14)	0.171		
Solid/total ratio	0.49 (0.17-1.38)	0.178		
Pathology				
Not confirmed	1.00 (Ref.)	(Ref.)	1.00 (Ref.)	(Ref.)
Adenocarcinoma	1.19 (0.55-2.54)	0.661	0.68 (0.21-2.23)	0.525
Squamous and others	3.09 (1.40-6.83)	0.005	2.77 (1.02-7.52)	0.461
Total dose (BED, a/b=10), Gy	1.00 (0.99-1.01)	0.541		
Total fraction	1.13 (1.00-1.28)	0.059		
Fractional dose, Gy	0.95 (0.88-1.02)	0.151	0.88 (0.77-0.99)	0.041

HR, hazard ratio; CI, confidence interval; Ref., reference category; ECOG-PS, Eastern Cooperative Oncology Group performance status; COPD, chronic obstructive pulmonary disease; BED, biologically effective dose.

studies indicate that different SBRT techniques yield similar outcomes when key principles such as precise target delineation, motion management, and strict dose constraints are upheld (10,11). Accordingly, we included all SBRT modalities to reflect real-world clinical practice and enhance the generalizability of our findings. Our findings confirm high OS and LC rates and provide a detailed evaluation of key prognostic factors. Notably, the 3-year OS (86.5%) and LC (92.9%) rates are in line with those of recent multi-institutional SBRT studies (12-14) and approach outcomes seen in selected surgical cohorts (7,15). These findings contribute to a growing body of evidence suggesting that SBRT can serve as a feasible alternative to lobectomy for appropriately selected patients, particularly those at high surgical risk or with significant comorbidities. Additionally, our comprehensive analysis of recurrence patterns, including their relationship with tumor spread through air spaces (STAS), anatomical site characteristics, and tumor size in relation to BED, highlights the need for individualized dose optimization. Moreover, this study also examined symptomatic RP, offering valuable insights for optimizing clinical practice, including improved toxicity management and refined patient selection criteria. The detailed analysis of true in-field and marginal recurrences expands upon prior SBRT reports by elucidating how specific tumor characteristics (e.g., high solid-to-total tumor ratio) may be an indication for a more aggressive dose-fractionation approach.

Recent evidence highlights the importance of delivering a sufficiently high BED in SBRT for early-stage NSCLC. High dose-per fraction SBRT not only induces extensive DNA double-strand breaks in hypoxic radioresistant regions, but may also produce additional effects, including vascular endothelial cell damage and immunogenic cell death, beyond the linear-quadratic model. Consequently, larger or solid-dominant tumors, which typically harbor more hypoxic areas, generally require higher BED to achieve durable LC. This approach is supported by several studies. Onishi *et al* (16) reported significantly improved LC and survival rates with a BED_{10} >100 Gy. Moreno *et al* (17) also demonstrated superior 5-year

Table III. Univariable and multivariable analysis of factors associated with local control.

	Univariable		Multivariable	
Variable	HR (95% CI)	P-value	HR (95% CI)	P-value
Age, years	0.97 (0.91-1.04)	0.438		
Sex				
Male	1.00 (Ref.)	(Ref.)		
Female	0.68 (0.22-2.13)	0.504		
Smoking				
No	1.00 (Ref.)	(Ref.)		
Yes	2.26 (0.71-7.17)	0.166		
COPD				
No	1.00 (Ref.)	(Ref.)	1 (Ref.)	(Ref.)
Yes	2.36 (0.82-6.81)	0.111	3.49 (0.96-12.76)	0.058
Tumor location				
Upper/middle lobe	1.00 (Ref.)	(Ref.)		
Lower lobe	0.91 (0.31-2.73)	0.873		
Tumor size, cm	2.13 (1.17-3.89)	0.014	5.43 (2.19-13.44)	<0.001
Solid size, cm	3.01 (1.61-5.61)	0.001		
Solid/total ratio	7.96 (1.04-61.13)	0.046	11.86 (1.31-107.7)	0.028
Pathology				
Not confirmed	1.00 (Ref.)	(Ref.)		
Adenocarcinoma	2.46 (0.72-8.43)	0.151		
Squamous and others	3.01 (0.67-13.50)	0.149		
Total dose (BED, a/b=10), Gy	0.98 (0.97-1.00)	0.078		
Total fraction	1.07 (0.85-1.35)	0.544		
Fractional dose, Gy	0.91 (0.80-1.04)	0.160		

HR, hazard ratio; CI, confidence interval; Ref., reference category; COPD, chronic obstructive pulmonary disease; BED, biologically effective dose.

survival when the BED_{10} was at least 130 Gy. For peripheral lesions, ultra-hypofractionation (e.g., 1-3 fractions) can be safely performed (18), as evidenced by the RTOG 0915 trial results, in which toxicity was lower with the 34 Gy in 1 fraction protocol than with the 48 Gy in 4 fractions protocol (19). In contrast, centrally located tumors or hilar tumors in close proximity to critical structures often require longer regimens of at least eight fractions. In the Nordic HILUS trial, 34 and 15% of the patients developed grade 3-5 and grade 5 toxicities, respectively (20,21). These studies show that multiple SBRT regimens can be employed to achieve a BED_{10} of at least 100 Gy; these include 54 Gy in 3 fractions (18 Gy per fraction, BED_{10} ≈151 Gy), 48 Gy in 4 fractions (12 Gy per fraction, BED_{10} ≈106 Gy), and 60 Gy in 8 fractions (7.5 Gy per fraction, BED_{10} ≈105 Gy). These findings, including improved local control with higher BED but increased toxicity risks for centrally located tumors, highlight the importance of further investigating optimal SBRT strategies tailored to tumor anatomy, morphology, and composition, which our study aimed to address as an active area of research.

In our cohort, higher fractional doses were associated with improved OS, and tumors with a high solid-to-total tumor ratio showed a higher risk of local recurrence. In addition, local relapse correlated with a larger tumor size and lower BED, highlighting the need to individualize fractionation protocols according to tumor characteristics, including size, location, and oxygenation status (17,22). Advanced imaging modalities (e.g., PET-based hypoxia mapping) may further refine dose escalation, and therapies with high relative biological effectiveness (e.g., carbon-ion therapy) are promising alternative modalities to x-ray radiotherapy for resistant tumors (23,24). Moreover, a recent meta-analysis suggested that achieving a BED of >100 Gy yielded LC rates comparable to those of surgical resection in select patients (25). This highlights the potential of SBRT outcomes to match surgical outcomes when dose prescriptions are appropriately optimized. Future research should focus on refining individualized dose-fractionation strategies and exploring high linear energy transfer radiation to optimize the treatment outcomes of early-stage NSCLC.

The incidence of symptomatic RP in our study was 7.2%, notably lower than the 9-28% reported in other SBRT studies (26,27). This reduced incidence may be partly due to the more favorable dosimetric parameters observed in our cohort. Specifically, our patients had lower dosimetric values, with a mean lung dose (MLD) of 5.2 Gy, V5 of 23.1%, V10 of 14.6%, and V20 of 5.8%, compared to the MLDs of

Table IV. Univariable and multivariable analysis of factors associated with symptomatic radiation pneumonitis.

	Univariable		Multivariable	
Variable	Odds (95% CI)	P-value	Odds (95% CI)	P-value
Age, years	1.03 (0.96-1.10)	0.456		
Sex				
Male	1.00 (Ref.)	(Ref.)		
Female	0.52 (0.15-1.47)	0.257		
Smoking				
No	1.00 (Ref.)	(Ref.)	1 (Ref.)	(Ref.)
Yes	2.02 (0.76-6.36)	0.186	1.71 (0.48-7.27)	0.430
COPD				
No	1.00 (Ref.)	(Ref.)		
Yes	0.77 (0.21-2.18)	0.644		
Tumor location				
Upper/middle lobe	1.00 (Ref.)	(Ref.)		
Lower lobe	1.64 (0.65-4.13)	0.288		
Tumor size, cm	1.24 (0.71-2.14)	0.445		
Solid size, cm	1.53 (0.93-2.60)	0.099	2.00 (1.05-4.27)	0.050
Solid/total ratio	2.46 (0.640-12.16)	0.219		
Pathology				
Not confirmed	1.00 (Ref.)	(Ref.)	1 (Ref.)	(Ref.)
Adenocarcinoma	0.41 (0.11-1.21)	0.131	0.24 (0.04-1.03)	0.076
Squamous and others	0.69 (1.53-2.28)	0.581	0.23 (0.03-1.25)	0.127
Total dose (BED, a/b=10), Gy	0.99 (0.98-1.01)	0.455		
Total fraction	0.75 (0.47-1.01)	0.126	0.49 (0.20-0.97)	0.090
Fractional dose, Gy	1.03 (0.92-1.16)	0.622		
PTV volume, mm^3	1.00 (0.98-1.02)	0.853		
Ipsilateral lung V5, %	1.03 (0.99-1.07)	0.121	1.05 (0.90-1.21)	0.518
Ipsilateral lung V10, %	1.03 (0.99-1.08)	0.137	0.98 (0.81-1.19)	0.838
Ipsilateral lung V15, %	1.04 (0.98-1.10)	0.204		
Ipsilateral lung V20, %	1.05 (0.97-1.13)	0.211		
Ipsilateral lung V30, %	1.07 (0.94-1.20)	0.254		
Ipsilateral lung V40, %	1.07 (0.86-1.27)	0.47		
Ipsilateral lung V50, %	1.01 (0.70-1.34)	0.959		
Ipsilateral lung mean dose, Gy	0.95 (0.78-1.12)	0.563		

CI, confidence interval; Ref., reference category; COPD, chronic obstructive pulmonary disease; BED, biologically effective dose; PTV, planning target volume.

9.1-11.0 Gy, V5 of 35.0-37.0%, V10 of 27.1-28.5%, and V20 of 16.6-16.9% reported in previous studies (28,29). The lower lung doses may have effectively minimized the occurrence of RP events, potentially explaining why traditional dosimetric factors, such as MLD and lung V5-V50, did not emerge as significant predictors in our analysis. Similar conclusions have been drawn in recent prospective reports (30), emphasizing the role of strict dose constraints to mitigate pulmonary toxicity.

Our detailed analysis of local recurrence patterns provides valuable insights for SBRT planning in early-stage NSCLC. True in-field recurrences were associated with a lower median BED and larger tumor size, particularly those with a greater solid tumor component. These findings suggest that standard SBRT dose schemes may be inadequate for controlling larger tumors, reinforcing the potential need for dose escalation or the incorporation of therapies with higher biological effectiveness, such as carbon ion therapy, as emphasized earlier. The occurrence of marginal recurrences, particularly those involving suspected airway-associated recurrences and pleural spread (31-34), emphasizes the necessity for meticulous treatment planning. Tumors located near airways or adjacent anatomical structures prone to facilitating tumor spread require special consideration to minimize the risk of recurrence. This includes addressing uncertainties related to tumor motion and ensuring adequate coverage of anatomical structures where recurrence is more likely, even when sufficient doses are administered to the primary tumor.

Table V. Detailed analysis of local recurrence cases.

Age, years	Sex	Pathology	Stage	Location	Tumor size, cm	Solid size, cm	PTV volume, mm^3	Dose scheme	BED, Gy	Recurrence pattern	Time-to-recurrence, months	Salvage treatment
82	Male	Adenoca	T1cN0	LUL	2.3	2.3	25.8	18 Gy * 3 fx	151.2	True in-field	83.5	Systemic therapy
85	Male	SqCCa	T2aN0	RLL	3.6	0.0	64.8	7 Gy * 10 fx	119	True in-field	37.5	Salvage re-RT
72	Female	Adenoca	T1cN0	RML	3.3	3.3	17.8	15 Gy * 4 fx	150	True in-field, suspicious pleural spread	28.5	None
83	Female	Adenoca	T1cN0	RUL	2.5	2.6	44.8	12.5 Gy * 4 fx	112.5	True in-field	27.6	Systemic therapy
75	Male	Not confirmed	T2aN0	RLL	4.0	3.6	44.9	9 Gy * 5 fx	85.5	True in-field	24.2	Systemic therapy
72	Male	Not confirmed	T2aN0	LUL	3.3	3.3	60.3	9 Gy * 5 fx	85.5	True in-field	11.7	Salvage re-RT
52	Female	Not confirmed	T1bN0	RUL	2.1	2.1	21.3	9 Gy * 5 fx	85.5	True in-field	34.0	Systemic therapy
73	Male	SqCCa	T2aN0	RLL	4.4	4.3	99.8	7 Gy * 5 fx	59.5	True in-field, suspicious airway-associated recurrence	9.4	Systemic therapy
68	Male	SqCCa	T1bN0	LUL	1.8	2.5	31.5	12 Gy * 4 fx	105.6	True in-field	24.4	Systemic therapy
82	Female	Adenoca	T2aN0	LUL	3.4	2.8	71.2	4.5 Gy * 10 fx	65.25	Marginal	25.3	Systemic therapy
80	Male	Adenoca	T1cN0	RUL	2.5	2.4	4.9	18 Gy * 3 fx	151.2	Marginal, suspicious airway-associated recurrence	40.5	Salvage re-RT
78	Male	Adenoca	T1bN0	RLL	1.5	1.2	10.3	15 Gy * 4 fx	150	Marginal, suspicious airway-associated recurrence	21.7	None
76	Male	SqCCa	T1bN0	RLL	1.8	1.8	26.0	13 Gy * 3 fx	89.7	Marginal, suspicious airway-associated recurrence	28.9	None
83	Male	Adenoca	T1bN0	RUL	2.8	2.8	26.9	12.5 Gy * 4 fx	112.5	Marginal	18.6	Systemic therapy
88	Male	Adenoca	T1cN0	RUL	2.7	2.4	57.8	15 Gy * 4 fx	150	Marginal	33.3	Systemic therapy

Adenoca, adenocarcinoma; SqCCa, squamous cell carcinoma; LUL, left upper lobe; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe; BED, biologically effective dose; PTV, planning target volume; fx, fractions; re-RT, re-radiotherapy.

This study has several limitations that should be considered when interpreting the findings. The retrospective design may have introduced potential biases related to patient selection and treatment variability. Another key limitation was that nearly half of the patients lacked pathological confirmation of malignancy. However, all patients were rigorously evaluated by a multidisciplinary tumor board using imaging and clinical assessments to ensure a high likelihood of malignancy before proceeding with SBRT. Although this may have introduced challenges in assessing tumor biology and treatment response, it reflects real-world clinical conditions where biopsy is often not feasible in medically inoperable patients. Furthermore, the absence of pathological confirmation raises the possibility that some patients may have had malignancy-mimicking conditions, including certain benign or infectious diseases (35). This could have influenced treatment outcomes. Previous studies suggested that patients without pathological confirmation may demonstrate more favorable prognoses. However, our multidisciplinary team, which included radiologists, ensured a rigorous clinical diagnosis through comprehensive radiologic assessment. Moreover, the median follow-up period of 30.8 months is only adequate for evaluating short- to mid-term outcomes, and it may not fully capture long-term survival or late-onset complications. Given that some patients were followed up for >3 years, the 3-year survival rate should be interpreted cautiously. Longer follow-up is necessary to validate the findings, particularly for late toxicities and long-term disease control. Future studies with extended observation periods will be crucial in providing a more comprehensive evaluation of SBRT outcomes over time. Furthermore, the outcomes of ongoing randomized trials (e.g., the VALOR, STABLE-MATES, and POSTILV trials) investigating whether SBRT can definitively match surgical resection in operable populations will further clarify the role of SBRT and provide more definitive guidance in early-stage NSCLC management (36). Finally, the statistical evaluation of LC and RP, wherein the number of events was small relative to the numerous covariates, raises concerns about the robustness of the findings, warranting cautious interpretation.

In conclusion, this study highlights the importance of individualized dose optimization in SBRT for early-stage NSCLC, particularly in managing tumor burden and recurrence. Our findings reinforce the benefits of higher fractional doses for larger tumors or those with a significant solid component, directly impacting LC and OS. Additionally, this study offers clinically relevant insights into recurrence patterns, underscoring the significance of higher BED in relation to tumor size and the proportion of the solid component, STAS-associated spread patterns, and anatomical site considerations for treatment planning. Collectively, the results align with emerging evidence that SBRT, when carefully planned, can yield survival outcomes similar to those of surgery in properly selected patients. This finding further supports its role as a standard treatment modality for early-stage NSCLC. Dose escalation strategies or high relative biological effectiveness therapies, such as carbon ion therapy, may be especially beneficial for radioresistant tumors. Integrating these findings into clinical practice can enhance patient selection, optimize treatment regimens, and improve long-term SBRT outcomes. Future research should further refine these strategies to enable more personalized treatment plans based on individual tumor characteristics.

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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

JC and EYK contributed to the conception and design of the study. Data collection was performed by SP, JWP, EHL, YJS, CYL, BJP, HIY and SHL. Formal analysis was conducted by SP, CGL and RC. SP and JWP wrote the original draft of the manuscript. The manuscript was reviewed and edited by SP, CGL, EYK and JC. EYK and JC supervised the study. SP, JWP and JC confirm the authenticity of all raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

This study was approved by the Institutional Review Board (IRB) of Severance Hospital (IRB no. 4-2022-1463), was conducted in accordance with the principles of the Declaration of Helsinki, and written consent was waived due to the retrospective nature of the study.

Patient consent for publication

Not applicable.

Competing interest

The authors declare that they have no competing interests.

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