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Impact of ground-glass component on prognosis in early-stage lung cancer treated with stereotactic body radiotherapy via Helical Tomotherapy

Jintao Ma[1], Shaonan Fan[1], Wenhan Huang[1], Xiaohong Xu[1], Yong Hu[1] and Jian He[1*]

Abstract

Purpose This study aims to investigate the prognostic impact of ground-glass opacity (GGO)-component in early-stage lung cancer patients treated with stereotactic body radiotherapy (SBRT).

Methods From January 2013 to December 2022, 239 early-stage lung cancer patients (T1-2N0M0) underwent SBRT. They were categorized into two groups based on the presence of GGO-component: 65 patients in the subsolid group with a consolidation tumor ratio (CTR) between 0.25 and 1 and 174 patients in the solid group with a CTR of 1. Lung cancer-specific survival (LCSS) and progression-free survival (PFS) were analyzed using Cox regression models for both univariate and multivariate analyses to identify prognostic factors. Stabilized inverse probability of treatment weighting (IPTW) was employed for adjusting confounding factors. Recurrence incidence was assessed using competing risk analysis and compared using Gray's test.

Results In the multivariate analysis, female, peripheral location, and subsolid nodules were favorable prognostic factors for LCSS; peripheral location, subsolid nodules, and adjuvant therapy were favorable prognostic factors for PFS. Between the subsolid ($n=65$) and solid groups ($n=174$), the median LCSS were not reached ($p=0.003$), with 3-, 5-, and 9-year LCSS rates of 94.7% versus 80.3%, 90.9% versus 64.1%, 82.7% versus 53.5%, respectively. The median PFS were 72.5 months and 50.5 months ($p=0.030$), with 3-, 5-, and 9-year PFS rates of 75.4% versus 61.2%, 56.6% versus 44.9%, 48.6% versus 23.3%, respectively. After stabilized IPTW ($n=240$), the median LCSS were not reached ($p=0.024$), with 3-, 5-, and 9-year LCSS rates of 94.0% versus 82.4%, 92.2% versus 67.7%, 85.3% versus 58.2%, respectively. The median PFS were 60.2 months and 50.5 months ($p=0.096$), with 3-, 5-, and 9-year PFS rates of 73.8% versus 61.0%, 53.5% versus 46.2%, 46.8% versus 22.4%, respectively. The subsolid group had lower rates of locoregional recurrence (LRR) (10.4% vs. 25.9%, $p=0.035$) and distant metastasis (DM) (17.1% vs. 37.9%, $p=0.064$) compared to the solid group.

Conclusions The presence of GGO-component in the lesion is an independent prognostic factor for LCSS and PFS. Subsolid nodules treated with SBRT demonstrated better prognosis, with significantly lower rates of local-regional

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recurrence. We should highlight GGO-component as a practical indicator for risk stratification of SBRT patients to guide treatment decisions.

Keywords Early-stage lung cancer, Stereotactic body radiation therapy, GGO-component, Prognosis

Background

Lung cancer is the leading cause of cancer-related mortality worldwide. Around 20–25% of patients are diagnosed with early-stage disease [1]. The use of low-dose computed tomography (CT) for lung cancer screening has become increasingly prevalent, leading to a higher detection rate of pulmonary nodules and more patients being diagnosed at an early stage. However, several patients are unable to undergo surgical resection due to the location of the lesion or severe comorbidities. Stereotactic body radiotherapy (SBRT) has emerged as an alternative treatment, offering excellent LC rates comparable to surgery and superior overall survival (OS) compared to conventional radiotherapy [2–5]. Consequently, SBRT has become the recommended definitive treatment for medically inoperable early-stage NSCLC (ES-NSCLC) patients [6, 7].

However, several studies have identified that approximately 30% of patients may experience relapse after SBRT, primarily due to distant metastases (DM) [8]. The median OS after the first recurrence is approximately 14.8 months, with survival times for patients with distant lesions ranging from only 6 to 9 months [9]. Improving prognosis in ES-NSCLC patients undergoing SBRT remains a crucial clinical objective. A retrospective analysis revealed that for peripheral lesions, escalating the dose while ensuring organs at risk constraints reduced local recurrence ($p=0.011$) and further enhanced lung cancer-specific survival (LCSS) ($p=0.002$) [10]. Another retrospective study demonstrated that poor performance status (PS) and a high Charlson comorbidity index (CCI) were correlated with reduced OS. PS and tumor size were significant factors influencing LCSS [11].

Studies have shown that an increased proportion of solid component in surgically treated early lung cancer patients was associated with poorer PFS and OS [12–14]. A prospective study conducted by the Japan Clinical Oncology Group 0201 proposed defining non-invasive adenocarcinoma as adenocarcinoma≤2 cm with a consolidation tumor ratio (CTR) of ≤0.25 [15]. Xu's [16] research demonstrated that nodules with CTR > 0.25 are abou t 70% invasive adenocarcinomas, showing significantly increased recurrence rates. The ground-glass opacity (GGO)-component in the lesion refers to the increased density shadow that does not obscure the bronchial or vascular bundles, in contrast to the solid component. The impact of GGO-component in the lesion on the prognosis of patients undergoing SBRT has rarely been taken into account in the past. This study includes eligible early lung cancer patients treated with SBRT using Helical Tomotherapy (HT-SBRT) at our center, aiming to investigate the effect of GGO-component on patient prognosis and provide insights for clinical treatment decisions.

Methods

Data collection

We retrospectively analyzed early-stage lung cancer patients treated with HT-SBRT at Zhongshan Hospital, Fudan University, from January 2013 to December 2022. Inclusion criteria were as follows: (1) Patients diagnosed through pathology or clinical evaluation, (2) American Joint Committee on Cancer 8th edition staging of T1-2N0M0, (3) completion of definitive SBRT, and (4) follow-up duration>6 months. Exclusion criteria included incomplete medical records, uncontrolled other carcinomas, synchronous multiple primary lung cancers, and a survival time<3 months due to non-cancer-related deaths. Clinical staging involved chest and upper abdominal contrast-enhanced CT, brain magnetic resonance imaging (MRI) or CT, bone emission computed tomography (ECT), or fluorodeoxyglucose-positron emission tomography (FDG-PET). The study adhered to the principles of the Declaration of Helsinki (2013 revision) and was approved by the Ethics Committee of Zhongshan Hospital (B2024-103R).

A multidisciplinary team (MDT) is comprised of specialists in thoracic surgery, radiation oncology, and radiology. They conducted a thorough evaluation of patients based on clinical symptoms, physical examinations, laboratory test results, such as lung cancer tumor markers (CEA, SCC, NSE, Cyfra21-1, Pro-GRP), and imaging findings from CT or PET-CT scans. However, early-stage lung cancer often presented with mild clinical symptoms and negative tumor markers, which made the imaging characteristics of the lesions especially crucial.

When follow-up thin-section CT showed certain changes in pulmonary nodules, they indicated a higher likelihood of malignancy: (1) an increase in diameter and a doubling time consistent with the growth patterns of malignant tumors; (2) the lesions were stable or enlarged, with the appearance of solid components; (3) the emergence of solid components or an increase in solid components; (4) the presence of vascular invasion; (5) the appearance of lobulation, spiculation, pleural retraction, or vascular convergence.

In the study, measurements were taken on thin-section CT lung windows with a slice thickness of

1 mm–0.625 mm (window width 1600 Hu, window level −600 Hu), with three measurements taken and averaged. All measurements were conducted on the original images before fusion and were completed within the same CT scan. CTR was defined as the ratio of the maximum diameter of the solid component to the maximum diameter of the tumor [15]. The presence of GGO-component in the lesion was defined relative to the solid component. A CTR between 0.25 and 1 indicated the presence of the GGO component, classifying the lesion as the subsolid group. A CTR of 1 indicated the absence of the GGO component, classifying the lesion as the solid group.

SBRT delivery

All eligible patients underwent SBRT using the Helical Tomotherapy Hi-Art Treatment System (Accuray, Madison, WI, USA). The treatment protocol comprised CT simulation, target delineation, treatment planning, and SBRT delivery. All patients were scanned in the supine position using a head and neck shoulder frame for stabilization and underwent respiration-correlated four-dimensional computed tomography (4D-CT) for simulation. The scanning encompassed the neck, chest, and upper abdomen to include tumor lesions and critical organs at risk (OARs), with a slice thickness of 3 mm.

Gross tumor volume (GTV) was defined as the visible tumor observed on lung window CT or FDG-PET scans. The 4D-CT scans were used to assess lesion motion due to respiratory cycles. Each lesion was delineated separately on the original CT scan and on CT scans at different respiratory phases, generating different GTVs. These GTVs were then fused using the fusion function to create the internal target volume (ITV). The planning target volume (PTV) was subsequently generated by expanding ITV by 3–5 mm to accommodate setup uncertainties. The expansion boundary primarily took into account the lesion's location and the size of the spicules. Typically, a 3 mm expansion was applied; however, for peripheral lesions located in the lower lobe of the lung or for lesions with longer spicules, a 5 mm expansion was recommended.

Prior to each treatment session, cone beam CT was employed to verify the precise positioning of the target volume. The median prescribed dose was 60 Gy (Gy) (range: 48–65 Gy), administered over a median of 10 fractions (F) (range: 5–15 F). Dose fractionation schemes were determined based on tumor location, size, and lung function. Peripheral lesions typically received 50 Gy in 5 F or 65 Gy in 10 F, whereas central lesions were treated with 50 Gy in 10 F or 60 Gy in 10 F. The classification of central lung cancer adhered to the criteria defined in the Radiation Therapy Oncology Group (RTOG) 0236 study [17].

Biologically effective dose (BED) calculations were derived using the linear quadratic formula with an α/β ratio of 10. Dose constraints for OARs adhered to the guidelines set forth by RTOG 0236 [17].

Follow-up

In principle, after curative SBRT, follow-up contrast-enhanced chest CT scans were conducted every 3–6 months for 3 years. Subsequently, contrast-enhanced chest CT scans were performed every 6 months for 2 years. Afterward, low-dose chest CT scans were conducted annually. Brain MRI or CT, bone ECT, and FDG-PET were also scanned if needed.

The endpoints are LCSS and PFS. LCSS is defined as the time from the start of SBRT to death due to lung cancer progression. PFS is defined as the time from the start of SBRT to disease progression, death from any cause, or loss to follow-up. Local recurrence is defined as the reappearance within or adjacent to the PTV, at least 6 months post-SBRT, showing continuous enlargement on CT scans, marginal swelling, or FDG-PET SUVmax≥5, resembling pre-treatment levels. Regional recurrence is defined as lymph node metastasis in ipsilateral hilar, mediastinal, or supraclavicular regions confirmed by imaging or pathology. DM is defined as new lesions appearing in other sites. The last follow-up was on June 13, 2024. Toxicity was assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) 5.0.

Statistical analysis

Cox proportional hazards regression was used for univariate and multivariate analyses to identify prognostic factors for LCSS and PFS. Variables with $p<0.05$ in univariate analysis were included in the multivariate model. OS, LCSS, and PFS were assessed using Kaplan-Meier analysis with log-rank tests. Median follow-up was estimated using the reverse Kaplan-Meier method. Categorical variables were compared using Chi-square tests or Fisher's exact test. The comparison of continuous variables was performed using the Mann-Whitney test. Stabilized inverse probability of treatment weighting (IPTW) was applied to adjust for confounding factors, including age, sex, ECOG, CCI, location, tumor size, BED_{10}, and adjuvant therapy. Additionally, cumulative incidence for locoregional recurrence (LRR), and DM was calculated using the competing risk approach and compared using Gray's test. Analyses were two-sided with significance set at $p<0.05$. Statistical analyses and plots were performed using SPSS 26.0 (IBM, Chicago, IL, USA) and R 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria), utilizing packages such as "survival", "survminer", "IPW-survival", "ggpubr", "ggplot2", "forestploter", "grid", and "cmprsk".

Results

Baseline characteristics

Figure 1 illustrates the study flow. A total of 239 patients were included, with 27.2% in the subsolid group and 72.8% in the solid group. Among subsolid patients, 75.4% had a CTR between 0.5 and 1. The median age of the entire cohort was 74 years, with 25.5% aged 80 years or older. Male patients constituted 70.7%, and over half of the patients (n=127, 53.1%) had concomitant respiratory diseases such as bronchiectasis, chronic obstructive pulmonary disease, bronchitis, interstitial lung disease (ILD). Stage I included 78.2% of patients, while 21.8% were in stage II. Peripheral lesions accounted for 79.9%. Adjuvant therapy post-SBRT was received by 8.8% of patients: 8 had systemic chemotherapy, 4 immunotherapy, and 9 targeted therapy. As shown in Table 1.

Table 2 illustrates the baseline characteristics of patients in the subsolid and solid groups. The solid group had a higher proportion of male patients and more patients with tumor size>3 cm. Following stabilized IPTW, baseline characteristics between the groups were balanced.

As shown in Table 3, approximately 71.5% of patients received a dose fractionation regimen of either 50 Gy in 5 F or 60 Gy in 10 F, with no significant statistical difference between the subsolid and solid groups. Furthermore, there were no significant statistical differences in the ITV and PTV between the two groups.

Clinical outcomes

In the univariate analysis of LCSS, sex, tumor location, and nodule type were significant prognostic factors. Multivariate analysis identified female, peripheral location, and subsolid nodules as independent favorable prognostic factors for LCSS. In the univariate analysis of PFS, age, ECOG, tumor location, nodule type, and adjuvant therapy showed prognostic significance. Multivariate analysis revealed that peripheral location, subsolid nodules, and adjuvant therapy were independent favorable prognostic factors for PFS. As shown in Fig. 2.

The median follow-up time for the entire cohort was 58.1 months (range 3.9-129.1 months). In the subtypes, the median follow-up time was 52.9 months (range 4.7-110.5 months) for the subsolid group, and 60.4 months

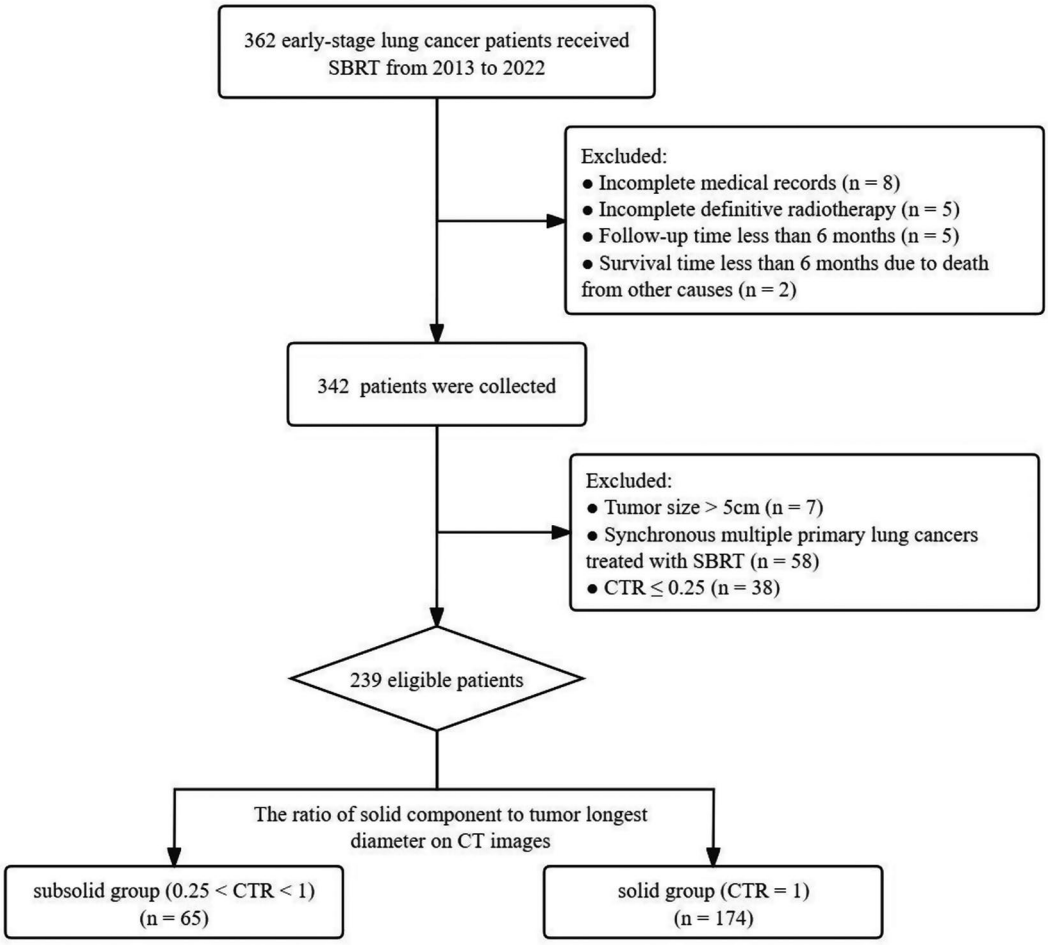

Fig. 1 Patient inclusion flow chat

Table 1 The baseline demographic and clinical characteristics of 239 patients

Characteristics	Number (%)
Age (year) (median, IQR)	74 (68–80)
Sex	
Male	169 (70.7)
Female	70 (29.3)
ECOG PS	
0	50 (20.9)
1	118 (49.4)
2	71 (29.7)
Smoking history	
No	120 (50.2)
Yes	119 (49.8)
CCI	
0	51 (21.3)
1	68 (28.5)
2	66 (27.6)
3	33 (13.8)
4	14 (5.9)
5	3 (1.3)
6	4 (1.7)
Respiratory system disease	
No	112 (46.9)
Yes	127 (53.1)
ILD	
No	216 (90.4)
Yes	23 (9.6)
Prior lung cancer	
No	207 (86.6)
Yes	32 (13.4)
T stage (AJCC 8th)	
T1a	18 (7.5)
T1b	88 (36.8)
T1c	88 (36.8)
T2a	37 (15.5)
T2b	8 (3.3)
Location	
Peripheral	191 (79.9)
Central	48 (20.1)
Tumor size (mm) (median, IQR)	24.0 (17.7–30.0)
FDG-PET Staging done	159 (66.5)
FDG-PET SUVmax (median, IQR)	8.2 (3.1–13.9)
Nodule type	
Subsolid, 0.25 < CTR ≤ 0.5	16 (6.7)
Subsolid, 0.5 < CTR < 1	49 (20.5)
Solid	174 (72.8)
Solid component diameter (median, range)	21.6 (6.0–50.0)
GGO-component diameter (median, range)	0.0 (0.0–25.2)
Histological diagnosis	
No	130 (54.4)
Yes	109 (45.6)
Histology	
Adenocarcinoma	63 (57.8)
Squamous cell	42 (38.5)
NSCLC, others	4 (3.7)
Radiation site	
RUL	79 (33.1)
RML	19 (7.9)
RLL	43 (18.0)
LUL	55 (23.0)
LLL	43 (18.0)
Adjuvant therapy	
No	218 (91.2)
Yes	21 (8.8)

IQR=interquartile range, ECOG PS=Eastern Cooperative Oncology Group performance status, CCI=Charlson comorbidity index, ILD=interstitial lung disease, FDG-PET=Fluorodeoxyglucose-positron emission tomography, SUVmax=maximal standardized uptake value, CTR=consolidation tumor ratio, GGO=ground-glass opacity, NSCLC=non-small cell lung cancer, RUL=right upper lobe, RML=right middle lobe, RLL=right lower lobe, LUL=left upper lobe, LLL=left lower lobe

(range 3.9-129.1 months) for the solid group. By the last follow-up, 91 patients had died, with 53 deaths attributed to tumor progression, and 81 patients experiencing disease progression. The median OS for all patients was 72.5 months, with 3-, 5-, and 9-year OS rates of 76.1%, 58.9%, and 36.9%, respectively (Fig. 3A). The median LCSS was not reached, with 3-, 5-, and 9-year LCSS rates of 84.0%, 70.8%, 60.3%, respectively (Fig. 3B). The median PFS was 57.4 months, with 3-, 5-, and 9-year PFS rates of 65.0%, 47.9%, 29.8%, respectively (Fig. 3C).

Between subsolid group (n=65) and solid group (n=174), the median OS were 85.4 months and 68.4 months (p=0.085), with 3-, 5-, and 9-year OS rates of 83.1% versus 73.6%, 68.6% versus 55.5%, 47.0% versus 33.7%, respectively; the median LCSS were not reached (p=0.003), with 3-, 5-, and 9-year LCSS rates of 94.7% versus 80.3%, 90.9% versus 64.1%, 82.7% versus 53.5%, respectively (Fig. 4A); the median PFS were 72.5 months and 50.5 months (p=0.030), with 3-, 5-, and 9-year PFS rates of 75.4% versus 61.2%, 56.6% versus 44.9%, 48.6% versus 23.3%, respectively (Fig. 4B).

In the matched population after stabilized IPTW (n=240), the median OS was 75.1 months, with 3-, 5-, and 9-year OS rates of 77.5%, 60.2%, and 38.5%, respectively. The median LCSS was not reached, with 3-, 5-, and 9-year LCSS rates of 85.3%, 73.5%, 64.7%, respectively. The median PFS was 57.4 months, with 3-, 5-, and 9-year PFS rates of 64.3%, 48.2%, 28.4%, respectively.

Between subsolid group (n=66) and solid group (n=174) after stabilized IPTW, the median OS were 85.4 months and 68.7months (p=0.301), with 3-, 5-, and 9-year OS rates of 82.7% versus 75.7%, 64.4% versus 58.6%, 48.0% versus 35.4%, respectively; the median LCSS were not reached (p=0.024), with 3-, 5-, and 9-year LCSS rates of 94.0% versus 82.4%, 92.2% versus 67.7%, 85.3% versus 58.2%, respectively (Fig. 4C); the median

Table 2 Comparison of baseline characteristics between subsolid and solid patients

Characteristics	Unmatched				Stabilized IPTW			
	Subsolid group	Solid group	*P* value	SMD	Subsolid group	Solid group	*P* value	SMD
Age (year)			0.885	0.042			0.764	0.050
< 75	33 (50.8)	92 (52.9)			36.2 (55.2)	91.7 (52.7)		
≥ 75	32 (49.2)	82 (47.1)			29.4 (44.8)	82.3 (47.3)		
Sex			< 0.001	0.746			0.946	0.010
Female	35 (53.8)	35 (20.1)			18.9 (28.9)	51.0 (29.3)		
Male	30 (46.2)	139 (79.9)			46.6 (71.1)	123.0 (70.7)		
ECOG			0.797	0.061			0.985	0.003
≤ 1	47 (72.3)	121 (69.5)			46.1 (70.3)	122.5 (70.4)		
> 1	18 (27.7)	53 (30.5)			19.5 (29.7)	51.5 (29.6)		
CCI			0.229	0.197			0.87	0.028
≤ 1	37 (56.9)	82 (47.1)			33.7 (51.4)	87.1 (50.1)		
> 1	28 (43.1)	92 (52.9)			31.8 (48.6)	86.9 (49.9)		
Location			0.197	0.224			0.635	0.091
Peripheral	56 (86.2)	135 (77.6)			49.6 (75.7)	138.3 (79.5)		
Central	9 (13.8)	39 (22.4)			15.9 (24.3)	35.6 (20.5)		
Tumor size (mm)			0.102	0.278			0.669	0.081
≤ 30	56 (86.2)	131 (75.3)			53.6 (81.8)	136.7 (78.6)		
> 30	9 (13.8)	43 (24.7)			11.9 (18.2)	37.2 (21.4)		
BED_{10}(Gy)			0.235	0.194			0.957	0.009
≥ 100	32 (49.2)	69 (39.7)			27.2 (41.5)	73.0 (41.9)		
< 100	33 (50.8)	105 (60.3)			38.3 (58.5)	101.0 (58.1)		
Adjuvant therapy			0.534	0.134			0.808	0.049
Yes	4 (6.2)	17 (9.8)			6.7 (10.2)	15.3 (8.8)		
No	61 (93.8)	157 (90.2)			58.8 (89.8)	158.6 (91.2)		

SMD = standard mean difference, IPTW = inverse probability of treatment weighting, ECOG PS = Eastern Cooperative Oncology Group performance status, CCI = Charlson comorbidity index, BED_{10} = Biologically effective dose using α/β ratio of 10 Gy, Gy = Gray

Table 3 Dosimetric parameters

Characteristics	All patients	Subsolid group	Solid group	*P* value
Dose fractionation schemes				
60 Gy/15F	5 (2.1%)	1 (1.5%)	4 (2.3%)	1.000
50 Gy/10F	21 (8.8%)	2 (3.1%)	19 (10.9%)	0.057
60 Gy/10F	112 (46.9%)	30 (46.2%)	82 (47.1%)	0.893
65 Gy/10F	16 (6.7%)	2 (3.1%)	14 (8.0%)	0.282
50 Gy/5F	59 (24.7%)	19 (29.2%)	40 (23.0%)	0.319
60 Gy/6F	26 (10.9%)	11 (16.9%)	15 (8.6%)	0.067
Total dose (median, range)	60.0 (48.0–65.0)	60.0 (48.0–65.0)	60.0 (48.0–65.0)	0.859
Fraction dose (median, range)	6.0 (4.0–10.0)	6.2 (4.5–10.0)	6.0 (4.0–10.0)	0.031
BED_{10}(Gy) (median, range)	96.0 (75.0–120.0)	96.0 (75.0–120.0)	96.0 (75.0–120.0)	0.066
ITV (cm^3) (median, range)	18.1 (0.4–154.6)	15.6 (0.9–154.6)	18.2 (0.4–110.6)	0.216
PTV (cm^3) (median, range)	28.1(2.1–191.8)	28.1(2.1–191.8)	28.0 (2.6–118.3)	0.282

PFS were 60.2 months and 50.5 months (p=0.096), with 3-, 5-, and 9-year PFS rates of 73.8% versus 61.0%, 53.5% versus 46.2%, 46.8% versus 22.4%, respectively (Fig. 4D).

Failure pattern

By the last follow-up, a total of 81 patients (33.9%) experienced disease progression, with 22 patients (9.2%) developing local recurrence, 22 patients (9.2%) developing regional recurrence, and 54 patients (22.6%) developing DM. The recurrence details between the subsolid and solid subgroups are shown in Table 4. After controlling for competing risk events, the cumulative incidence of LRR was 21.6%, with rates at 3-, 5-, and 8-years of 15.2%, 18.2%, and 21.6%, respectively; the cumulative incidence of DM was 32.7%, with rates at 3-, 5-, and 8-years of 19.4%, 26.0%, and 32.7%, respectively.

In the subsolid and solid groups, the cumulative incidence of LRR was 10.4% and 25.9% (p=0.035), with rates at 3-, 5-, and 8-years of 7.8% versus 17.9%, 10.4% versus 21.0%, and 10.4% versus 25.9%, respectively (Fig. 5A). The incidence of DM in the two groups was 17.1% and 37.9% (p=0.064), with rates at 3-, 5-, and 8-years of 11.7% versus 22.1%, 17.1% versus 29.1%, and 17.1% versus 37.9%, respectively (Fig. 5B).

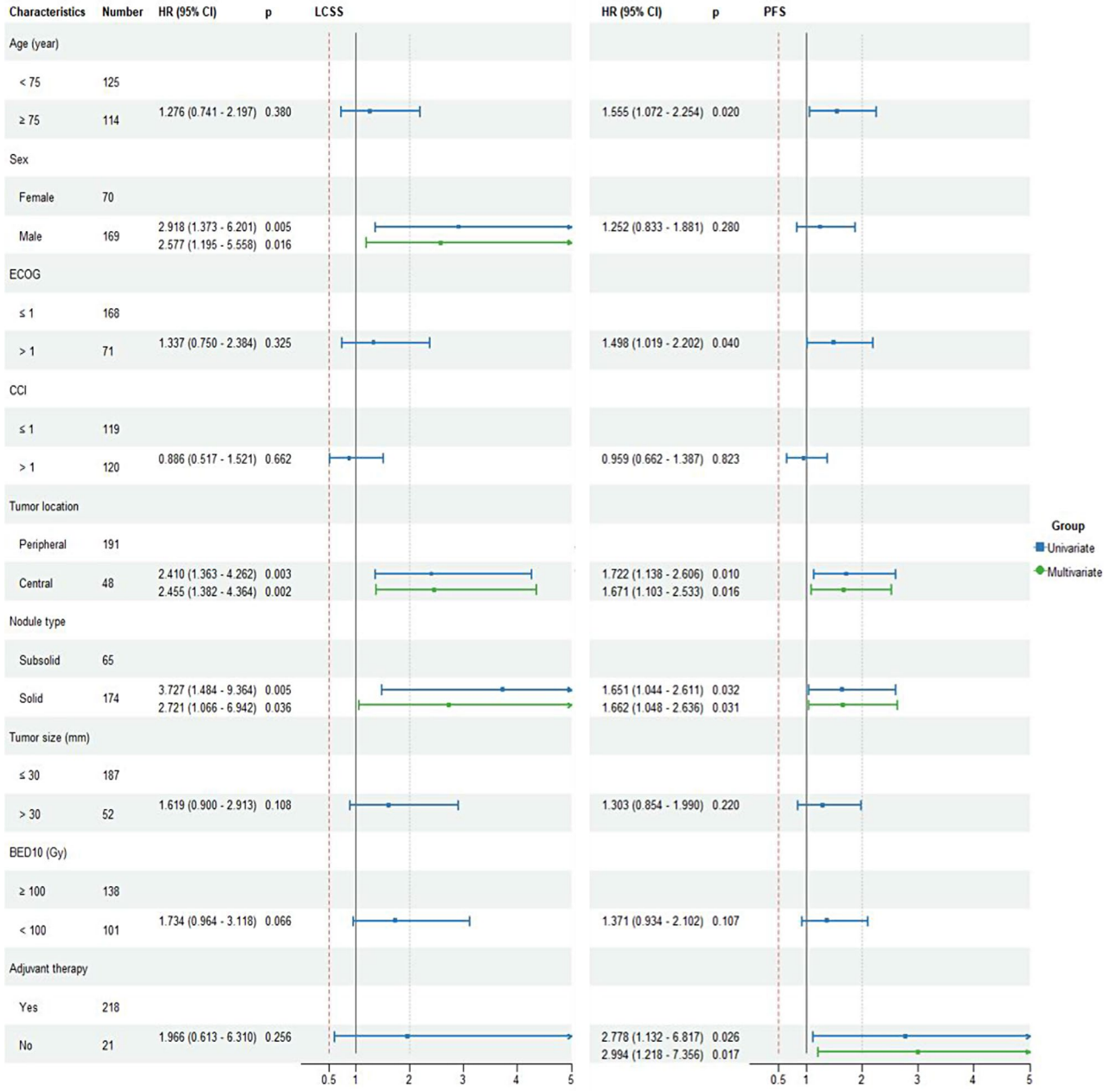

Fig. 2 Univariate and multivariate Cox regression analyses for LCSS and PFS

Toxicity

No severe (CTCAE grade 4–5) toxicity was reported in the study. In total, 41 patients (17.2%) experienced grade 1 acute radiation pneumonitis (RP), 17 patients (7.1%) experienced grade 2 acute RP, and 8 patients (3.3%) experienced grade 3 acute RP. The recurrence patterns between the subsolid and solid groups are detailed in Table 5.

Discussion

The study enrolled 239 patients with early-stage lung cancer treated with HT-SBRT to explore the impact of GGO-components in lesions on prognosis. To the best of our knowledge, it represents the first report on survival outcomes based on different lesion densities, with long-term follow-up data provided. Multivariable regression analysis revealed that compared to patients with solid nodules, those with subsolid nodules had a 63.2% lower risk of tumor-specific mortality and a 39.8% lower risk of disease progression. Using stabilized IPTW to match clinical characteristics without loss of sample size, the

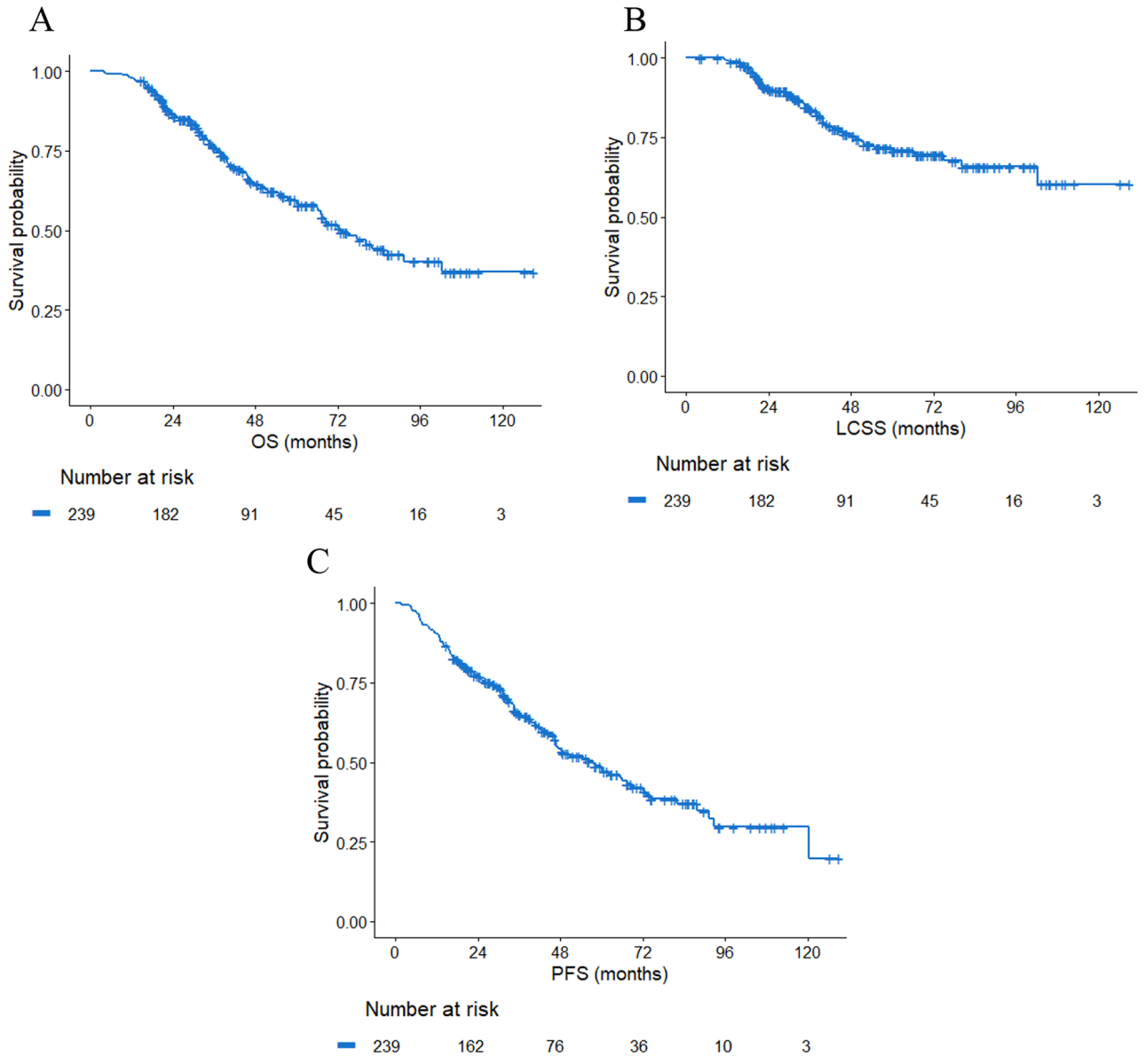

Fig. 3 OS (**A**), LCSS (**B**) and PFS (**C**) in all patients

subsolid group demonstrated significantly better LCSS and a trend towards improved PFS compared to the solid group. Regarding disease recurrence, solid nodules demonstrated a significantly higher cumulative rate of LRR and a discernible trend towards increased DM compared to the subsolid tumors. This indicates that among patients undergoing SBRT, solid tumors exhibit greater invasiveness, higher recurrence rates, and poorer prognosis, consistent with findings from studies on ES-NSCLC treated with surgery [12, 16, 18, 19]. Therefore, in clinical practice, stratifying early lung cancer patients treated with SBRT based on lesion density may guide individualized treatment. A recent phase II prospective clinical trial has demonstrated that stereotactic ablative radiotherapy combined with immunotherapy (I-SABR) improves the 4-year event-free survival (EFS) rate in ES-NSCLC patients, with tolerable toxicity [20]. The I-SABR treatment modality is emerging as an additional therapeutic recommendation for ES-NSCLC patients, with lesion density potentially aiding in the selection of suitable patient populations.

In this study, 57.7% of patients had a BED_{10} of less than 100 Gy, suggesting that inadequate dosing may contribute to an increased LR rate. As presented in Table 3, among this cohort, 112 patients received a dose fractionation regimen of 60 Gy in 10 F, while the remaining 26 patients were treated with either 50 Gy in 10 F or 60 Gy in 15 F. Notably, a higher proportion of patients in the

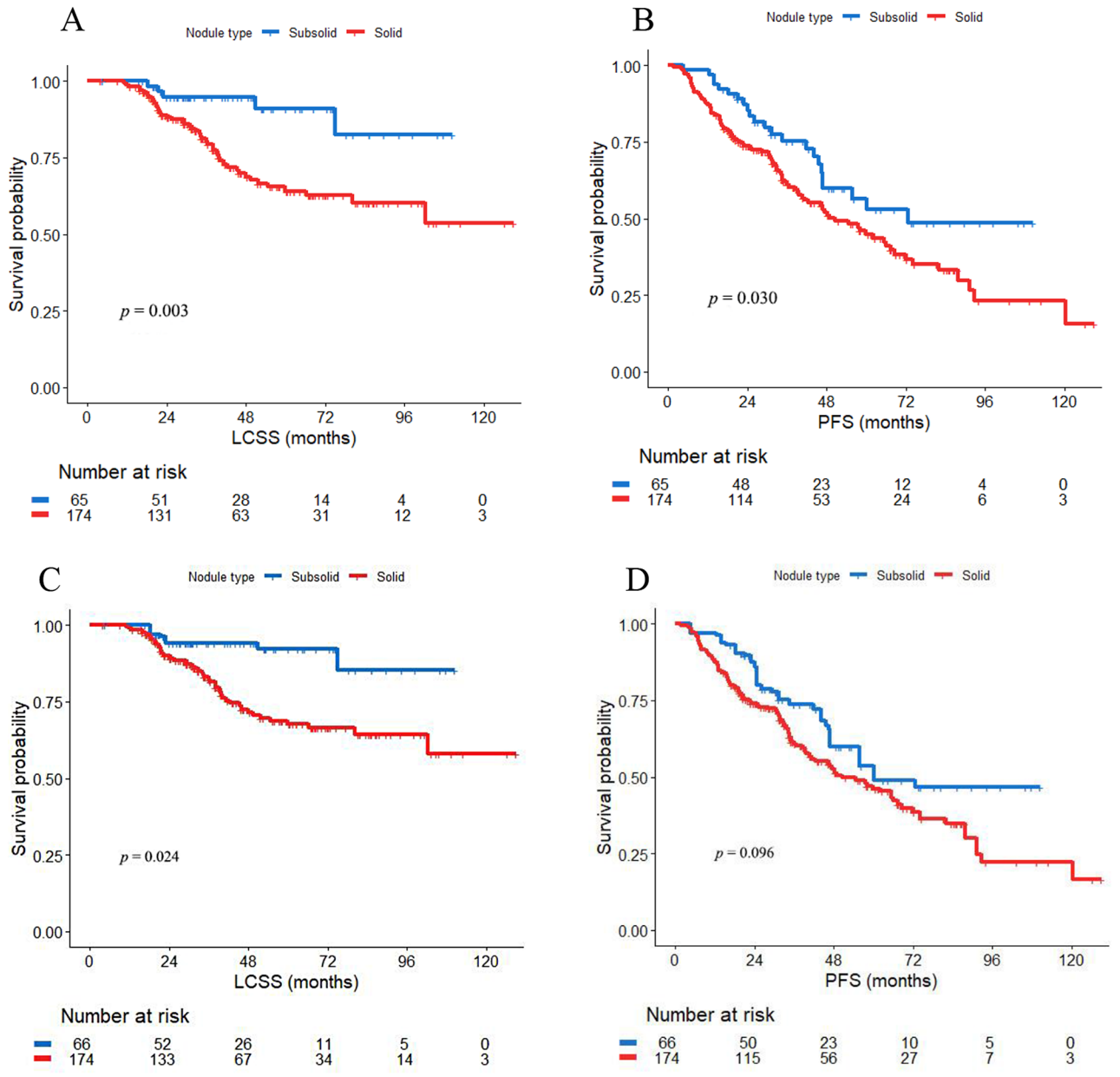

Fig. 4 LCSS and PFS between the subsolid and solid groups before and after stabilized IPTW. (**A**) LCSS between the two groups before stabilized IPTW. (B) PFS between the two groups before stabilized IPTW. (**C**) LCSS between the two groups after stabilized IPTW. (**D**) PFS between the two groups after stabilized IPTW

Table 4 The failure pattern of the patients

Failure pattern	All patients		Subsolid group		Solid group		*P* value
	N	%	*N*	%	*N*	%	
LR	22	9.2	2	3.1	20	11.5	0.045
RR	22	9.2	3	4.6	19	10.9	0.134
LRR	39	16.3	5	7.7	34	19.5	0.027
DM	54	22.6	9	13.8	45	25.9	0.048

LR=Local recurrence, RR=Regional recurrence, LRR=Locoregional recurrence, DM=Distant metastasis

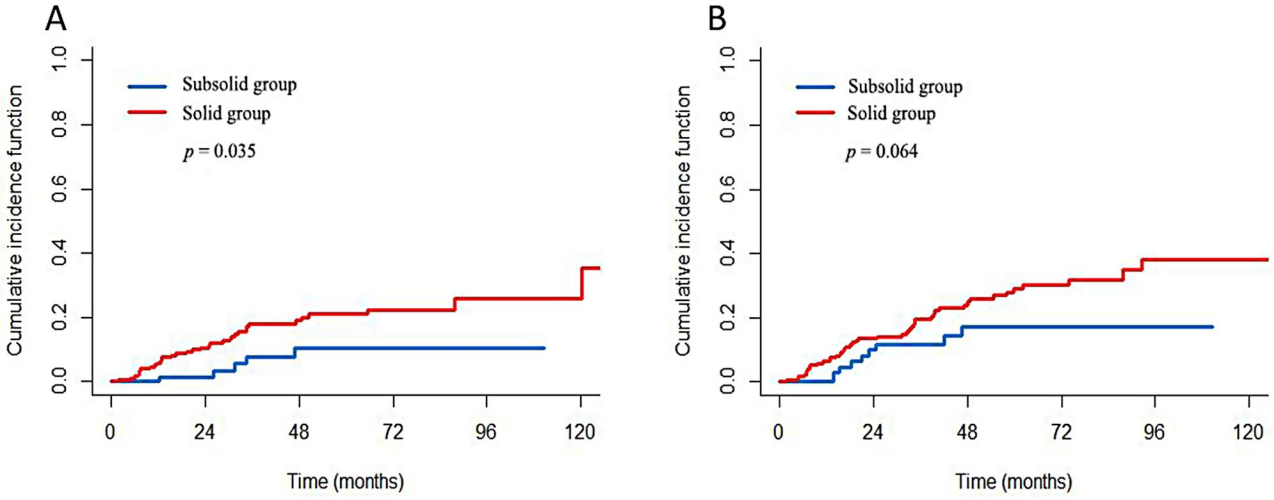

Fig. 5 Cumulative incidence of LRR (**A**) and DM (**B**) between subsolid and solid groups

Table 5 Radiation pneumonitis (RP) in the patient cohort

RP	All patients (*N*/%)	Subsolid group (*N*/%)	Solid group (*N*/%)	*P* value
Grade 1	41 (17.2)	13 (20.0)	29 (16.7)	0.547
Grade 2	17 (7.1)	7 (10.8)	10 (5.7)	0.255
Grade 3	8 (3.3)	1 (1.5)	7 (4.0)	0.687

solid group received the 50 Gy in 10 F regimen. Although this failed to reach statistical significance, it may have contributed to an increased local recurrence rate in the solid group.

Subsolid nodules are lesions characterized by the presence of both solid and GGO components. GGO are typically considered a non-invasive feature, and patients with a higher proportion of GGO components in lesions often have better prognosis, as evidenced in ES-NSCLC patients undergoing surgery in both retrospective and prospective studies [12–14]. A recent retrospective study analyzed the efficacy of SBRT in treating predominantly GGO lesions (CTR≤0.5). Pure GGO accounted for 43 cases (43.4%). During the follow-up period, the LC rate was 100%, and 3-, 5-year OS rates were 91.6%, 82.8%. The survival rates for subsolid nodules appeared to be lower, but did not reach statistical significance ($p=0.227$) [21]. Another study observed that among predominantly GGO lung nodules treated with SBRT, the 5-year OS rate was 78.0%, with a DM rate of merely 0.8% and no observed local or regional failures [22]. In our study, patients with subsolid nodules had 3-year and 5-year OS rates of 83.1% and 68.6%, respectively. However, considering the older age of the patients and the presence of multiple comorbidities leading to non-cancer-related deaths, we further observed LCSS rates of 94.7% and 90.0%. A study comparing part-solid nodules to pure-solid nodules in ES-NSCLC treated with surgery found that part-solid nodules had a significantly higher 5-year OS rate (95.3% versus 82.7%, $p<0.001$) [13], consistent with our research findings.

SBRT treatment for central lung cancer demonstrates a higher risk of toxicity. To protect adjacent normal tissues, compromises in dosage are typically necessary, which may explain why central tumors treated with SBRT in the study had poorer outcomes compared to peripheral tumors. However, a study found no significant differences in OS (median OS: 34.8 months versus 36.1 months; 2-year OS rate: 71.6% versus 71.0%, $p=0.30$) and local control rates (88.6% versus 87.1%, $p=1.00$) between central and peripheral lesions [23]. The prognosis for central lesions was consistent with ours (median OS: 45.8 months, 2-year OS rate: 71.7%), whereas our study demonstrated markedly better outcomes for peripheral lesions (median OS: 81.8 months, 2-year OS rate: 90.1%). For inoperable peripheral tumors, the RTOG 0236 phase II trial demonstrated a median OS of 32.6 months and a 2-year OS rate of 54.7% with 54 Gy given in 3 F [17]. However, our study included some potentially operable patients, which may contribute to the relatively favorable prognosis observed in peripheral lung cancer patients. In the RTOG0618 study, 26 ES-NSCLC patients eligible for surgery underwent SBRT, showing a median PFS of 55.2 months with a 4-year PFS rate of 57%, and a median OS of 55.2 months with a 4-year OS rate of 56% [24]. In our study, peripheral lesions were mainly treated with 50 Gy/5 F or 65 Gy/10 F, demonstrating a 4-year OS rate of 68.2% and a 4-year PFS rate of 58.5%.

In the multivariate analysis of LCSS, female patients showed significantly better prognosis compared to males, consistent with findings from other studies [25, 26]. A large prospective study demonstrated that female lung cancer patients had markedly longer survival time. However, after adjusting for known prognostic factors such as lifestyle and treatment-related factors, the risk of death

among males decreased by over 80%. This suggests that much of the survival difference related to gender in lung cancer may be attributed to these factors [27]. In this study, these factors may include smoking history, poorer lung function, and more comorbidities among male patients.

Adjuvant systemic therapy (ST) has been recommended to improve prognosis for high-risk patients after surgery [6]. However, the role of ST following SBRT remains unclear. Research from public databases has demonstrated that SBRT + ST improves survival rates in patients with tumor sizes ≥ 4 cm compared to SBRT alone [28]. A multi-institutional analysis using propensity score matching revealed that the SBRT + ST exhibited significantly reduced rates of regional and distant failures and improved PFS. However, OS did not show a significant improvement [29]. Multivariate analysis in our study identified adjuvant therapy as an independent prognostic factor for PFS, but it did not significantly impact LCSS, suggesting that adjuvant ST may potentially prolong PFS for high-risk patients. Recently, a study by Chang demonstrated that the I-SABR significantly improved 4-year EFS in patients with ES-NSCLC or isolated lung parenchymal recurrence [20]. In the future, large phase III prospective clinical trials are needed to confirm.

The study has several limitations. First, as a single-center retrospective study, data collection is based on historical records, potentially leading to information and selection biases. Second, the sample size of subsolid nodules was small, and further analysis regarding different CTR ratios was not conducted. Third, approximately 54.4% of patients lacked pathological diagnosis. Despite based on pre-treatment imaging and lab results, the MDT concluded malignancy after discussion. Finally, although this study demonstrates that solid components are prognostic factors for LCSS and PFS, when delineating the target area, we contour the entire tumor visible on CT lung window. Therefore, the total tumor size remains crucial for selecting the dose segmentation pattern. Finally, while this study demonstrated that solid components were prognostic factors for LCSS and PFS, during target delineation, we contour the entire tumor visible on the CT lung window. Thus, the total tumor size remains critical for selecting the dose segmentation pattern.

Conclusions

In conclusion, the GGO-component in lesions is an independent prognostic factor affecting LCSS and PFS. Compared to solid nodules, subsolid nodules treated with SBRT demonstrated better prognosis, with significantly lower rates of LRR and a trend towards reduced DM. We should emphasize lesion density as a practical indicator for risk stratification of SBRT patients to guide treatment decisions. Since the study is a retrospective single-center study, further prospective research is required to validate these findings.

Abbreviations

BED_{10}	Biologically effective dose using α/β ratio of 10 Gy
CCI	Charlson comorbidity index
CT	Computed tomography
CTR	Consolidation tumor ratio
CTCAE	Common Terminology Criteria for Adverse Events
DM	Distant metastasis
ECOG	Eastern Cooperative Oncology Group
ECT	Bone emission computed tomography
EFS	Event-free survival
ES-NSCLC	Early-stage non-small cell lung cancer
4D-CT	Four-dimensional CT
FDG-PET	Fluorodeoxyglucose-positron emission tomography
Gy	Gray
GGO	Ground-glass opacity
GTV	Gross tumor volume
HR	Hazard ratio
HT	Helical tomotherapy
ILD	Interstitial lung disease
IPTW	Inverse probability of treatment weighting
I-SABR	Stereotactic ablative radiotherapy combined with immunotherapy
ITV	Internal target volume
LC	Local control
LCSS	Lung cancer-specific survival
LRR	Locoregional recurrence
MDT	Multidisciplinary team
MRI	Magnetic resonance imaging
NSCLC	Non-small cell lung carcinoma
OARs	Organs at risk
OS	Overall survival
PFS	Progression-free survival
PTV	Planning target volume
RP	Radiation pneumonitis
RTOG	Radiation Therapy Oncology Group
SBRT	Stereotactic body radiotherapy
ST	Systemic therapy
SUVmax	Maximal standardized uptake value

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Not applicable.

Author contributions

J.H conceived the study concept and design. J.T.M contributed to data collection, analysis, and manuscript drafting. S.N.F, W.H.H, X.H.X, and Y.H contributed to data collection and patient follow-up. All authors reviewed the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Human Ethics and Consent to Participate

The protocol was approved by the Ethics Committee of Zhongshan Hospital (B2024-103R), and the requirement of informed consent was waived by the Institutional Review Board since this was a retrospective analysis.

Consent for publication

Not applicable.

Competing interests

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Publisher's note

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