Cancer Management and Research

Elevate Series

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ORIGINAL RESEARCH

A Comparison of Stereotactic Radiation Therapy in Elderly Patients with Central or Peripheral Stage I-II (T1-3 N0 M0) Non-Small Cell Lung Cancer

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Purpose: The objective of this study was to compare the clinical outcomes of stereotactic body radiation therapy (SBRT) in elderly patients aged 65 or older with clinical stage I–II non-small-cell lung cancer (NSCLC), specifically examining the differences between centrally located lung tumors and peripherally located lung tumors.

Methods: From April 2009 to January 2020, a total of 136 patients with 136 tumors (65 central, 71 peripheral; NSCLC) at an early stage (T1-3N0M0) were treated with SBRT at a single institution. Central/peripheral location was assessed retrospectively on planning CT scans. A propensity score matching analysis was utilized to compare the two groups. In addition, the prognosis and related toxicity were compared between the two study arms.

Results: A total of 33 central tumors and 33 peripheral tumors were matched and analyzed. The results showed no significant differences in overall survival (OS) and progression-free survival (PFS) between the two groups. The 2-year OS was 71.88% (95% CI, 57.87%-89.27%) in the central lung cancer group, while it was 93.94% (95% CI, 86.14%-100.00%) in the peripheral lung cancer group (P=0.462). The 2-year PFS was 43.75% in the central lung cancer group, while it was 78.79% in the peripheral lung cancer group (P=0.279). Further subgroup analysis indicated that the location of peripheral tumor have a positive impact on OS in patients with adenocarcinoma. The occurrence of local failure, regional failure, or distant failure was comparable between central and peripheral tumors. There was no statistically significant difference in toxicity between the central and the peripheral tumor groups.

Conclusion: The outcomes of SBRT for central tumors versus peripheral lung tumors in elderly patients with early-stage NSCLC were similar. SBRT demonstrated a similar level of safety in terms of toxicity for both central and peripheral lung tumors.

Keywords: Non-small cell lung cancer, stereotactic body radiation therapy, central lung cancer, elderly patients, propensity score matching

Introduction

Lung cancer is the leading cause of cancer-related mortality globally, with NSCLC comprising 85% of cases.[1] In addition to the phenomenon of an aging population, there has been a notable rise in the number of elderly individuals being diagnosed with lung cancer. NSCLC is often diagnosed in older patients, as 65% of patients are ≥65 years and 25% of patients are ≥75 years.[2] The classification of elderly patients varies between regions, the elderly are considered as > 75 years in Europe, whereas > 65 years in USA.[3,4]

For stage I and II NSCLC, surgery is a standard treatment for elderly patients, as it has shown a local failure rate of less than 20%.[5] However, for patients who are unwilling to undergo surgery due to associated risks or who are deemed medically unfit for surgery, an alternative option is curative radiotherapy (RT) using SBRT.[6,7] Several retrospective studies and prospective trials have demonstrated that the OS rates following SBRT in medically inoperable patients are comparable to, or even better than, those observed with pulmonary resection.[8–10] The utilization of stereotactic body

Received: 17 July 2024
Accepted: 26 October 2024
Published: 5 November 2024

radiation therapy (SBRT) as a viable alternative treatment modality for elderly patients has been experiencing a notable surge in recent times.[11,12]

At present, SBRT has been widely used in inoperable peripheral early-stage lung cancer, and has achieved gratifying outcomes, with a local control rate of >90%.[12,13] However, because central lung cancer is adjacent to vital organs such as the bronchi (trachea), large blood vessels, spinal cord, and heart, the toxicities of SBRT have become the main limiting factor. Therefore, a balance between efficacy and toxicity needs to be concerned. One study showed that the closer the tumor was to the bronchial tree, the higher the risk of non-cancer death from SBRT.[14] There are also studies supporting the use of SBRT to cure centrally located early-stage NSCLC.[15–17] In our previous work,[18] we conducted a retrospective analysis of patients aged ≥65 years with stage I–II centrally located NSCLC who underwent SBRT. The findings of this study indicated that SBRT is capable of effectively control local tumor progression with acceptable toxicity. However, our previous study lacked a control group, and to date, there have been few studies that compared the efficacy and safety of SBRT in elderly patients with centrally versus peripherally located NSCLC. Therefore, we have innovatively conducted the current study, employing a propensity score-matched pair approach for a less-biased comparison of central and peripheral lung tumor SBRT. This approach ensured that the study groups had similar baseline characteristics and received comparable treatment.

Methods

Patients

In this retrospective study, patients aged ≥65 years, who received SBRT for T1-3N0M0 clinically or pathologically confirmed NSCLC from April 2009 to October 2020 were eligible for inclusion. All patients underwent whole-body imaging, including computed tomography (CT), bone imaging, and or positron emission computed tomography (PET/CT) and brain magnetic resonance imaging (MRI). A biopsy is recommended for all patients. If the biopsy was considered medically unsafe or the patient refused the biopsy, it was necessary to combine the patient's clinical symptoms, PET/CT and tumor markers (without elevated neuron-specific enolase), and be diagnosed as NSCLC by at least three experts. Clinical stage I–II was performed using the Union for International Cancer Control TNM Classification of Malignant Tumors, 8th edition. Central lung cancer refers to a tumor that is situated in close proximity, within 2 cm, in all directions of any critical mediastinal structure, including the bronchial tree, heart, esophagus, spinal cord, brachial plexus, major vessels, phrenic nerve, and recurrent laryngeal nerve, as observed on a computed tomography (CT) scan. Otherwise, it was defined as peripheral lung cancer. Patients who had prior thoracic radiotherapy or underwent surgery were excluded. This study encompassed a cohort of 136 individuals who were selected as participants (Table 1).

Treatment

All patients were either medically inoperable or chose SBRT over surgery after considering the risks and benefits. In this study, all patients were treated with CyberKnife (Accuray Incorporated, Sunnyvale, CA, USA). 93 patients underwent CT-guided implantation of 1–3 gold fiducials within the lesion, using synchronous breathing tracking. 43 patients did not receive gold fiducials due to concomitant diseases, so XSight-lung tracking or XSight-spine tracking was used. Approximately 1 week after implantation, patients underwent simulation and immobilization with a vacuum pad. A four-dimensional CT scan (4DCT) was required for patients without implantation. The gross tumor volume (GTV) was contoured and expanded 0–8 mm in all directions to generate a planning target volume (PTV). The formulation of radiotherapy plan needs to consider tumor size, tumor location, performance status and age-adjusted Charlson Comorbidity Index (aCCI), etc. Dose limitation to organs at risk are based on the recommendations of the American Association of Physicists in Medicine Task Group 101 report, the RTOG 0813 study, and the experience of the MD Anderson Center.

Follow-Up

The patients underwent clinical and imaging examinations at three-month intervals during the initial two-year period, followed by examinations every six months for the subsequent three years, and finally transitioning to annual examinations. The evaluation of toxicity was conducted based on the Common Terminology Criteria for Adverse Events Version

Table 1 Comparison of baseline variables between central lung cancer and peripheral lung groups in the original and matched data sets

Characteristic	Unmatched cohort			Propensity-score-matched cohort		
	Central lung cancer (n=65)	Peripheral lung cancer (n=71)	P	Central lung cancer (n=33)	Peripheral lung cancer (n=33)	P
Age (years)			0.478			1.000
≤ 80	51 (78.5%)	52 (73.2%)		26 (78.8%)	26 (78.8%)	
> 80	14 (21.5%)	19 (26.8%)		7 (21.2%)	7 (21.2%)	
Gender			0.215			0.708
Male	58 (89.2%)	58 (81.7%)		30 (90.9%)	28 (84.8%)	
Female	7 (10.8%)	13 (18.3%)		3 (9.1%)	5 (15.2%)	
T category※			0.001			0.509
T1	12 (18.5%)	34 (47.9%)		9 (27.3%)	10 (30.3%)	
T2	37 (56.9%)	28 (39.4%)		22 (66.7%)	18 (54.5%)	
T3	16 (24.6%)	9 (12.7%)		2 (6.1%)	5 (15.2%)	
Diagnostic mode			048			0.757
Clinical	13 (20.0%)	25 (35.2%)		6 (18.2%)	7 (21.2%)	
Histological/cytological	52 (80.0%)	46 (64.8%)		27 (81.8%)	26 (78.8%)	
Histology			0.096			0.858
Squamous	35 (53.8%)	27 (38.0%)		16 (48.5%)	17 (51.5%)	
Adenocarcinoma	17 (26.2%)	19 (26.8%)		11 (33.3%)	9 (27.3%)	
Missing	13 (20.0%)	25 (35.2%)		6 (18.2%)	7 (21.2%)	
Smoking history			0.557			0.792
No	27 (41.5%)	26 (36.6%)		10 (30.3%)	11 (33.3%)	
Yes	38 (58.5%)	45 (63.4%)		23 (69.7%)	22 (66.7%)	
Performance status			0.351			0.353
0-1	53 (81.5%)	62 (87.3%)		25 (75.8%)	28 (84.8%)	
2	12 (18.5%)	9 (12.7%)		8 (24.2%)	5 (15.2%)	
aCCI			0.846			0.592
≤5	23 (35.4%)	24 (33.8%)		9 (27.3%)	11 (33.3%)	
>5	42 (64.6%)	47 (66.2%)		24 (72.7%)	22 (66.7%)	
Tumor size (cm)			0.000			1.000
≤ 3.3	10 (15.4%)	35 (49.3%)		9 (27.3%)	9 (27.3%)	
> 3.3	55 (84.6%)	36 (50.7%)		24 (72.7%)	24 (72.7%)	
PTV (cc)			0.000			1.000
≤ 40.3	17 (26.2%)	55 (77.5%)		17 (51.5%)	17 (51.5%)	
> 40.3	48 (73.8%)	16 (22.5%)		16 (48.5%)	16 (48.5%)	
BED (Gy)			0.000			1.000
≤ 137.7	54 (83.1%)	35 (49.3%)		24 (72.7%)	24 (72.7%)	
> 137.7	11 (16.9%)	36 (50.7%)		9 (27.3%)	9 (27.3%)	
Tracking methods			0.209			0.838
Synchrony	45 (69.2%)	48 (67.6%)		26 (78.8%)	24 (72.7%)	
XSight-lung	3 (4.6%)	9 (12.7%)		2 (6.1%)	3 (9.1%)	
XSight-spine	17 (26.2%)	14 (19.7%)		5 (15.2%)	6 (18.2%)	

Notes: ※According to the American Joint Committee on Cancer and the Union for International Cancer Control stage system (8th edition).
Abbreviations: SBRT, stereotactic body radiotherapy.

5.0. Local failure (LF) was defined as regrowth of the lesion within the irradiated field. Regional failure (RF) was defined as the time from initiation of SBRT to the appearance of a new positive mediastinal or hilar node or ipsilateral lung tumor. Distant failure (DF) was the presence of metastases in the contralateral lung or outside the chest. OS was the period from the date of SBRT initiation to the date of death or last assessment of vital status. Progression-free survival (PFS) was defined as the interval from the initiation of SBRT to any disease failure.

Statistical Analysis

Categorical variables were assessed using either the Pearson chi-square test or Fisher's exact test. Numerical variables with a normal distribution were compared using the *t*-test. When a non-normal distribution was found, the nonparametric Wilcoxon test was used to mitigate the potential influence of confounding variables between the central lung cancer and peripheral lung cancer groups, a propensity score-matched (PSM) analysis was conducted for the treatment groups. The propensity score model incorporated several variables, namely T stage, gender, age, performance status, tumor size, aCCI, PTV, and BED. Then, patients with central or peripheral lesions were grouped into pairs based on their propensity scores using a one-to-one nearest neighbor calliper with a width of 0.1, which represents the maximum acceptable difference in propensity scores. A stabilized inverse probability of treatment weighting (IPTW) was calculated on the basis of the propensity score matching. To mitigate potential data sparsity, the weights were truncated at the 5th and 95th percentile. We calculated the standardized mean difference (SMD) to evaluate balance prior to and after matching and weighting. Smaller SMD values indicate a more favorable balance. The Log rank test was used to compare the Kaplan-Meier estimators calculated for each group. The Cox proportional hazards regression model was utilized to assess and compare the relative prognosis among different groups based on tumor location. We further performed an interaction analysis to explore whether the effect of tumor location varied in subgroups defined according to tumor size and performance status and prescribed dose. An HR less than 1.00 favored central lung cancer. The cumulative incidence of failure was estimated using competitive risk analysis, specifically Gray's test. Statistical analysis was done using SPSS version 24.0 and R version 4.2.2. All tests were displayed on both sides, with 95% CIs and relevant p values.

Results

Patient Characteristics

A total of 136 patients were selected for matching. 130 patients had primary NSCLC, 6 had locally recurrent NSCLC after systemic therapy. There were 65 (47.8%) patients with central lung cancer and 71 (52.2%) patients with peripheral lung cancer. Baseline patient characteristics are listed in Table 1. Patients with centrally located lung tumors had larger tumors (Tumor size > 3.3 cm, 84.6% vs 50.7%, P=0.000), more advanced T stage (T3, 24.6% vs 12.7%, P=0.001), and more frequently lower BED (BED ≤ 137.7 Gy, 83.1% vs 49.3%, P=0.000) than those with peripherally located lung tumors. Matching by PSM achieved adequate balance between the centrally and peripherally NSCLC groups for all covariates (Supplementary Table 1, supplementary Figure 1). This eliminated the influence of these differences between variables on subsequent analysis.

Treatment Features

The median time from diagnosis to SBRT was 36 (2–1834) days. Prior to PSM, the centrally located group had a median total prescribed dose of 52 Gy, ranging from 42 to 60 Gy, administered in 3 to 6 fractions. On the other hand, the peripherally located group had a median total prescribed dose of 60 Gy, ranging from 48 to 66 Gy, administered in 2 to 10 fractions. The biological effective dose (BED) ranged from 71.4 to 180.0 Gy, with a median BED10 of 124.8 Gy in the central lung cancer group, while BED ranged from 86.4 to 211.2 Gy, with a median BED10 of 150 Gy in the peripheral lung cancer group. The median volume of the PTV was 63.60 cm^3 (range of 7.80–282.40 cm^3) and 21.03 cm^3 (range of 1.03–120.67 cm^3) in the centrally and peripherally group, respectively. There were significant differences in the baseline characteristics of SBRT before PSM between the centrally and peripherally groups. To address these selection biases, a PSM analysis was conducted, resulting in the identification of 33 patients from each treatment group who had similar characteristics. These patients were then selected for further analysis (Table 1). The characteristics of the SBRT in the unmatched and matched cohort were shown in Supplementary Table 2, respectively.

Survival Analysis

Overall Survival and Cancer-Specific Death

The median follow-up time was 105.2 (93.7–116.7) months for all patients. In unmatched analysis, the median OS was 42.7 months (95% CI, 32.9–77.1 months) for central lung cancer group and 61.5 months (95% CI, 48.9-NA months) for

peripheral lung cancer group. The 2-year OS was 73.44% (95% CI, 63.38%-85.10%) in central lung cancer group, compared to 90.14% (95% CI, 83.47%- 97.35%) in peripheral lung cancer group. The peripherally group has a distinct advantage in terms of survival when compared to the centrally group (log-rank P=0.017; Figure 1A and Table 2). However, in the PSM cohort, the peripheral lung tumor was not associated with a significant OS benefit. The 2-year OS was 71.88% (95% CI, 57.87%-89.27%) in central lung cancer group, compared to 93.94% (95% CI, 86.14%-100.00%) in peripheral lung cancer group (log-rank P=0.462; Figure 1B and Table 2). IPTW analysis revealed similar results. The 2-year OS was 75.37% in central lung cancer group, compared to 92.47% in peripheral lung cancer group (log-rank P=0.279; Figure 1C and Table 2).

To investigate the potential benefits of specific variable signatures for patients with peripheral lung cancer, we conducted subgroup analyses on a matched cohort. We found some evidence of heterogeneity of OS by performance status (interaction P=0·002; Figure 2). The prognostic consistency analysis needed to be further explored. Patients with good performance status had a longer OS regardless of centrally (Log-rank P=0.004; Supplementary Figure 2A) or peripherally located tumors (Log-rank P=0.011; Supplementary Figure 2B). Notably, the peripheral lung cancer was beneficial for OS in patients with adenocarcinoma (stratified HR, 5.53; 95% CI, 1.18 to 25.78; P=0.353 for interaction; Figure 2).

The lung cancer-specific death curves before and after matching are shown in Figure 3. Prior to PSM, the cumulative incidences of cancer-specific death at 2 years were 20.31% (95% CI, 11.45–30.97%) and 8.45% (95% CI, 3.42–16.39%) for the centrally and the peripherally group, respectively (Table 2). The mortality rate for central lung cancer was significantly higher compared to peripheral lung cancer (SHR, 2; 95% CI, 1.23–3.28; P=0.006; Figure 3A). With PSM, the cumulative incidences of cancer-specific death at 2-year were 18.75% (95% CI, 7.45–33.99%) and 3.03% (95% CI, 0.22–13.59%) for the centrally and the peripherally group, respectively (Table 2). There was no significant difference in cancer-specific mortality rates between central lung cancer and peripheral lung cancer (SHR, 1.53; 95% CI, 0.802–2.91; P=0.2; Figure 3B).

Progression Free Survival

In the unmatched analysis, the median PFS was 24.4 months (95% CI, 17.8–47.6 months) for the centrally group and 49.6 months (95% CI, 38.1–75.6 months) for the peripherally group. In comparison to the centrally grouped individuals, those in the peripherally grouped individuals experienced a benefit in terms of PFS (log-rank P=0.003; Figure 4A). In the PSM analysis, the peripherally group did not show a survival advantage in terms of PFS compared to the centrally group (log-rank P=0.458; Figure 4B and Table 2). This is consistent with the result of the IPTW analysis (log-rank P=0.159; Figure 4C and Table 2).

On subgroup analyses in the matched cohort, central lung cancer had a beneficial effect on PFS in patients with poor performance status (stratified HR, 10.08; 95% CI, 1.19 to 85.58). There was a notable correlation observed between the location of the tumor and the performance status (interaction P=0·000; Figure 5). Exploratory analyses showed that

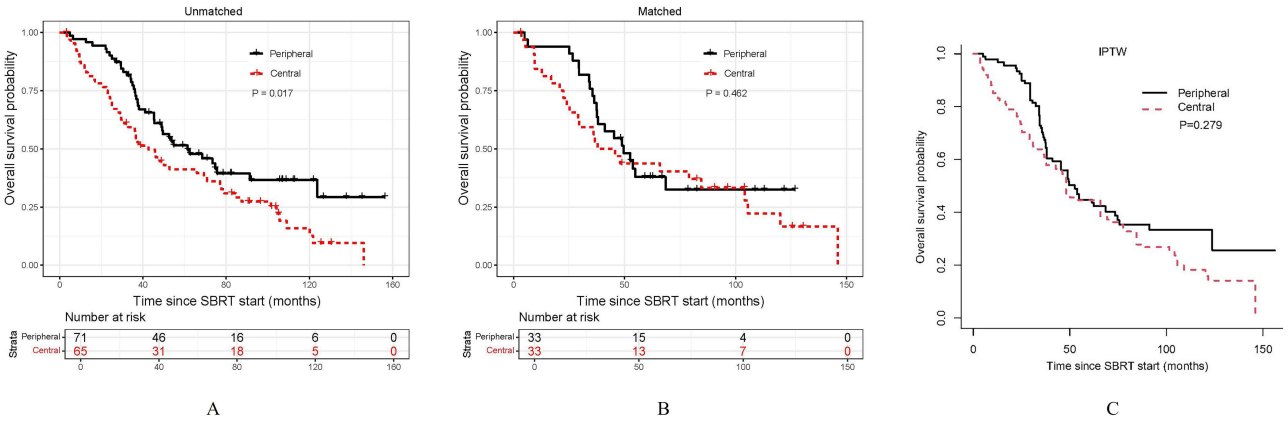

Figure 1 Kaplan-Meier curves for OS. (**A**) OS of the unmatched cohort; (**B**) OS of the propensity score matched group; (**C**) OS of the inverse probability of treatment weight-adjusted group.

Table 2 Summary of estimated treatment effect for main outcome measures in unmatched, propensity Matched and IPTW groups

	Unmatched			Propensity Matched			IPTW		
	Central lung cancer	Peripheral lung cancer	P	Central lung cancer	Peripheral lung cancer	P	Central lung cancer	Peripheral lung cancer	P
OS rate			0.017			0.462			0.279
1-year (%) (95% CI)	84.38 (75.93-93.76)	97.18 (93.41-100.00)		84.38 (72.69-97.94)	93.94 (86.14-100.00)		84.19	97.90	
2-year (%) (95% CI)	73.44 (63.38-85.10)	90.14 (83.47-97.35)		71.88 (57.87-89.27)	93.94 (86.14-100.00)		75.37	92.47	
3-year (%) (95% CI)	59.33 (48.43-72.69)	75.77 (66.37-86.50)		59.38 (44.58-79.08)	72.73 (59.01-89.63)		63.87	70.23	
5-year (%) (95% CI)	41.26 (30.66-55.51)	51.47 (40.77-64.97)		43.75 (29.54-64.80)	38.01 (24.33-59.39)		44.60	44.68	
10-year (%) (95% CI)	15.89 (7.98-31.62)	36.68 (25.89-51.95)		22.21 (10.43-47.28)	32.58 (19.00-55.86)		18.25	33.27	
PFS rate									
1-year (%) (95% CI)	67.20 (56.63-79.75)	90.14 (83.47-97.35)	0.003	68.75 (54.43,86.84)	87.88 (77.42,99.75)	0.458	70.92	87.95	0.159
2-year (%) (95% CI)	50.01 (39.15-63.89)	80.28 (71.54-90.09)		43.75 (29.54,64.80)	78.79 (66.00,94.05)		50.91	79.19	
3-year (%) (95% CI)	39.07 (28.77-53.06)	64.58 (54.32-76.77)		40.63 (26.72,61.76)	57.58 (42.96,77.17)		43.34	59.09	
5-year (%) (95% CI)	30.70 (21.16-44.55)	43.97 (33.67-57.41)		37.24 (23.69,58.54)	29.37 (17.15,50.29)		32.54	37.39	
10-year (%) (95% CI)	12.93 (5.92-28.23)	32.50 (22.58-46.80)		18.28 (7.50,44.57)	26.11 (14.54,46.88)		16.15	26.20	
Local failure rate			0.52			0.81	-	-	-
1-year (%) (95% CI)	12.48 (5.79-21.87)	4.23 (1.11-10.82)		12.50 (3.85-26.52)	6.06 (1.04-17.86)		-	-	-
2-year (%) (95% CI)	18.73 (10.25-29.18)	9.86 (4.30-18.16)		25.00 (11.57-41.02)	12.12 (3.74-25.79)				
3-year (%) (95% CI)	21.86 (12.64-32.70)	16.95 (9.26-26.61)		25.00 (11.57-41.02)	21.21 (9.18-36.54)				
5-year (%) (95% CI)	26.89 (16.56-38.33)	23.04 (13.88-33.59)		28.39 (13.86-44.82)	33.80 (18.03-50.32)				
10-year (%) (95% CI)		23.04 (13.88-33.59)					-	-	-
Regional failure rate			0.95			0.83	-	-	-
1-year (%) (95% CI)	4.69 (1.22-11.93)	2.82 (0.53-8.82)		0.00 (0.00-0.00)	0.00 (0.00-0.00)		-	-	-
2-year (%) (95% CI)	7.81 (2.85-16.09)	4.23 (1.11-10.82)		3.13 (0.22-14.03)	0.00 (0.00-0.00)				
3-year (%) (95% CI)	7.81 (2.85-16.09)	8.48 (3.43-16.44)		3.13 (0.22-14.03)	3.03 (0.22-13.60)				
5-year (%) (95% CI)	9.47 (3.81-18.27)	12.91 (6.29-21.99)		3.13 (0.22-14.03)	9.45 (2.29-22.89)				
10-year (%) (95% CI)	12.93 (5.96-22.68)	14.62 (7.42-24.15)		9.86 (2.36-23.86)	13.27 (3.94-28.33)				
Distant failure rate			0.32			0.3			
1-year (%) (95% CI)	9.38 (3.78-18.07)	1.41 (0.12-6.78)		9.38 (2.32-22.56)	0.00 (0.00-0.00)				
2-year (%) (95% CI)	14.06 (6.86-23.78)	5.63 (1.81-12.74)		18.75 (7.43-34.02)	3.03 (0.22-13.60)				
3-year (%) (95% CI)	20.31 (11.44-30.98)	11.32 (5.25-19.97)		25.00 (11.55-41.06)	12.12 (3.73-25.81)		-	-	-
5-year (%) (95% CI)	21.93 (12.67-32.80)	14.24 (7.25-23.51)		25.00 (11.55-41.06)	12.12 (3.73-25.81)		-	-	-
10-year (%) (95% CI)	23.60 (13.95-34.70)	17.77 (9.65-27.90)		28.37 (13.84-44.81)	20.09 (7.62-36.78)				
Cancer specific death rate			0.006			0.2			
1-year (%) (95% CI)	12.50 (5.80-21.91)	1.41 (0.12-6.78)		9.38 (2.33-22.54)	3.03 (0.22-13.59)				
2-year (%) (95% CI)	20.31 (11.45-30.97)	8.45 (3.42-16.39)		18.75 (7.45-33.99)	3.03 (0.22-13.59)				
3-year (%) (95% CI)	29.69 (18.98-41.17)	18.50 (10.41-28.42)		31.25 (16.10-47.68)	18.18 (7.23-33.07)				
5-year (%) (95% CI)	46.05 (33.24-57.92)	33.46 (22.51-44.76)		46.88 (28.69-63.14)	42.96 (25.47-59.33)				
10-year (%) (95% CI)	63.73 (48.88-75.32)	37.23 (25.56-48.88)		62.86 (40.73-78.67)	48.39 (28.60-65.64)		-	-	-

Abbreviations: IPTW, inverse probability of treatment weight; SBRT, stereotactic body radiotherapy.

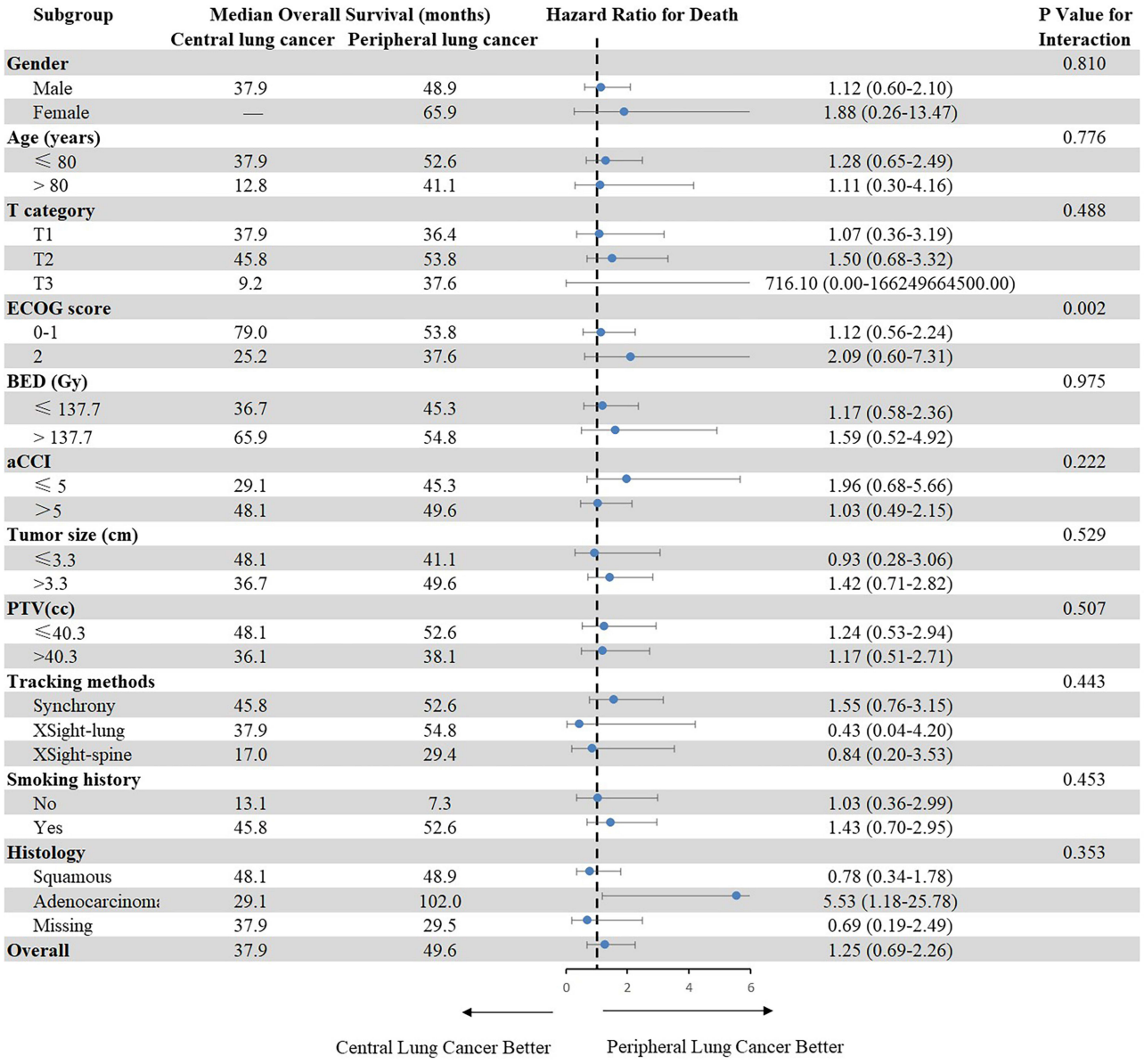

Figure 2 Forest plot of subgroup analyses of OS in matched population.

among patients with centrally located tumors, those with good performance status also had longer PFS than those with poor performance status (Log-rank P=0.002; Supplementary Figure 3).

Patterns of Failure

Before the implementation of PSM, there was no significant difference in the rate of local failure between central lung cancer and peripheral lung cancer (SHR, 1.25; 95% CI, 0.635–2.46; P=0.52; Figure 6A). The cumulative incidences of local failure at 1-year in the central group and the peripheral group were 12.48% and 4.23%, respectively (Table 2). With PSM, local failure occurred in 9 (27.3%), and 11 (33.3%) patients for the centrally and the peripherally group, respectively, with no statistical difference (SHR, 0.9; 95% CI, 0.37–2.16; P=0.81; Figure 6B).

As for regional failure, there was no statistical difference between the central lung cancer group and the peripheral lung cancer group before and after matching (Table 2, Figure 6C and D).

In the unmatched groups, when using competing risk analysis, the cumulative incidence of distant failure at 1 year was 9.38% (95% CI, 3.78–18.07%) for the centrally group and 1.41% (0.12–6.78%) for the peripherally group. The DF

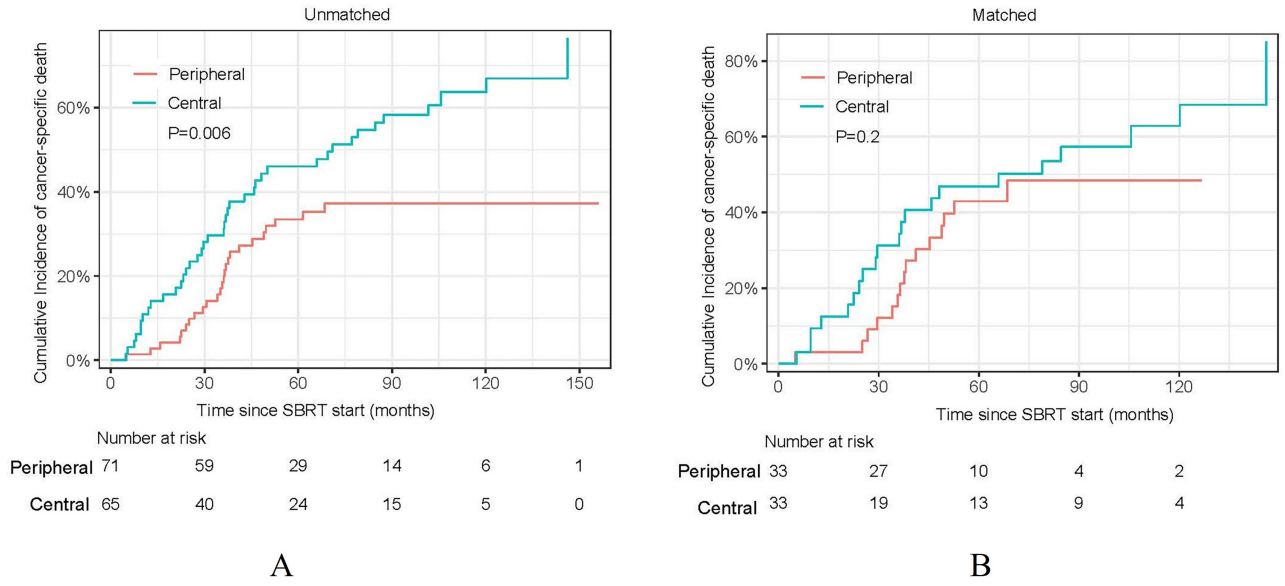

Figure 3 The cumulative incidence curve of cancer specific death after SBRT. (**A**) The unmatched cohort; (**B**) The propensity score matched group.

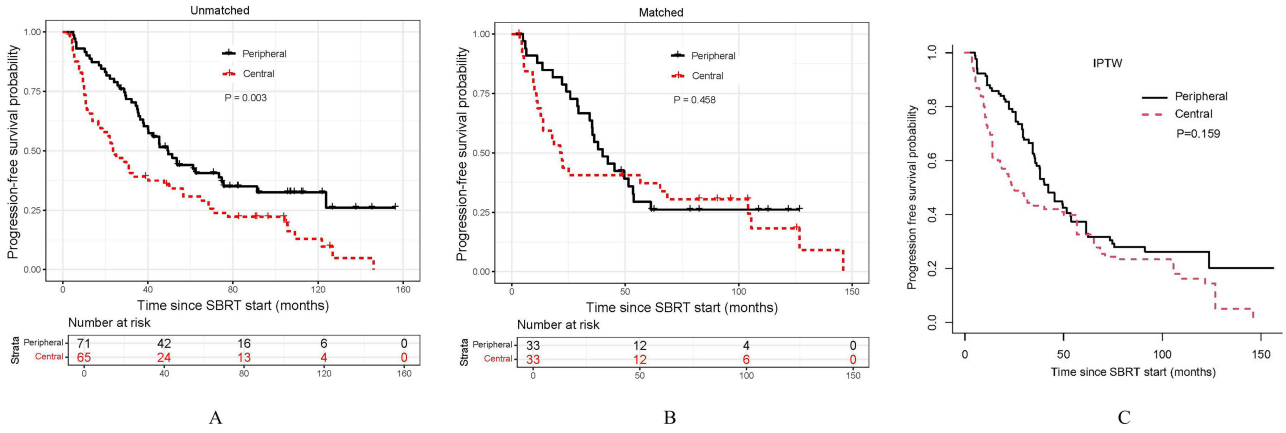

Figure 4 Kaplan-Meier curves for PFS. (**A**) PFS of the unmatched cohort; (**B**) shows PFS of the propensity score matched group; (**C**) shows PFS of the inverse probability of treatment weight-adjusted group.

rate of central lung cancer was not significantly different from that of peripheral lung cancer (SHR, 1.47; 95% CI, 0.69–3.12; P=0.32; Figure 6E and Table 2). This is consistent with the result of the propensity-score-matched analysis. The cumulative incidence of DF was 9.38% (95% CI, 2.32–22.56) for the centrally group and 0.00% for the peripherally group at 1 year (SHR, 1.7; 95% CI, 0.62–4.65; P=0.3; Figure 6F and Table 2).

Treatment Toxicity

The overall toxic effects of SBRT were mild. Common toxicities were grade 1 and 2 of transient fatigue, cough, and anorexia. There were no grade 4–5 toxic effects attributable to SBRT. Before PSM, in the acute hematological toxicity, rates of anemia were statistically different: 43.1% versus 26.8% (Grade 1–2) and 9.2% versus 2.8% (Grade 3) for central versus peripheral tumors, respectively (P=0.027, table 3). In acute non-hematological toxicity, cough (Grade 1–2, 30.8% vs 11.3%), hoarseness (Grade 1–2, 10.8% vs 0%), fatigue (Grade 1–2, 26.2% vs 9.9%) and radiation pneumonitis (Grade 1–2, 30.8% vs 4.2%) were more likely to occur in the central group than in the peripheral group, with statistical differences (Table 3).

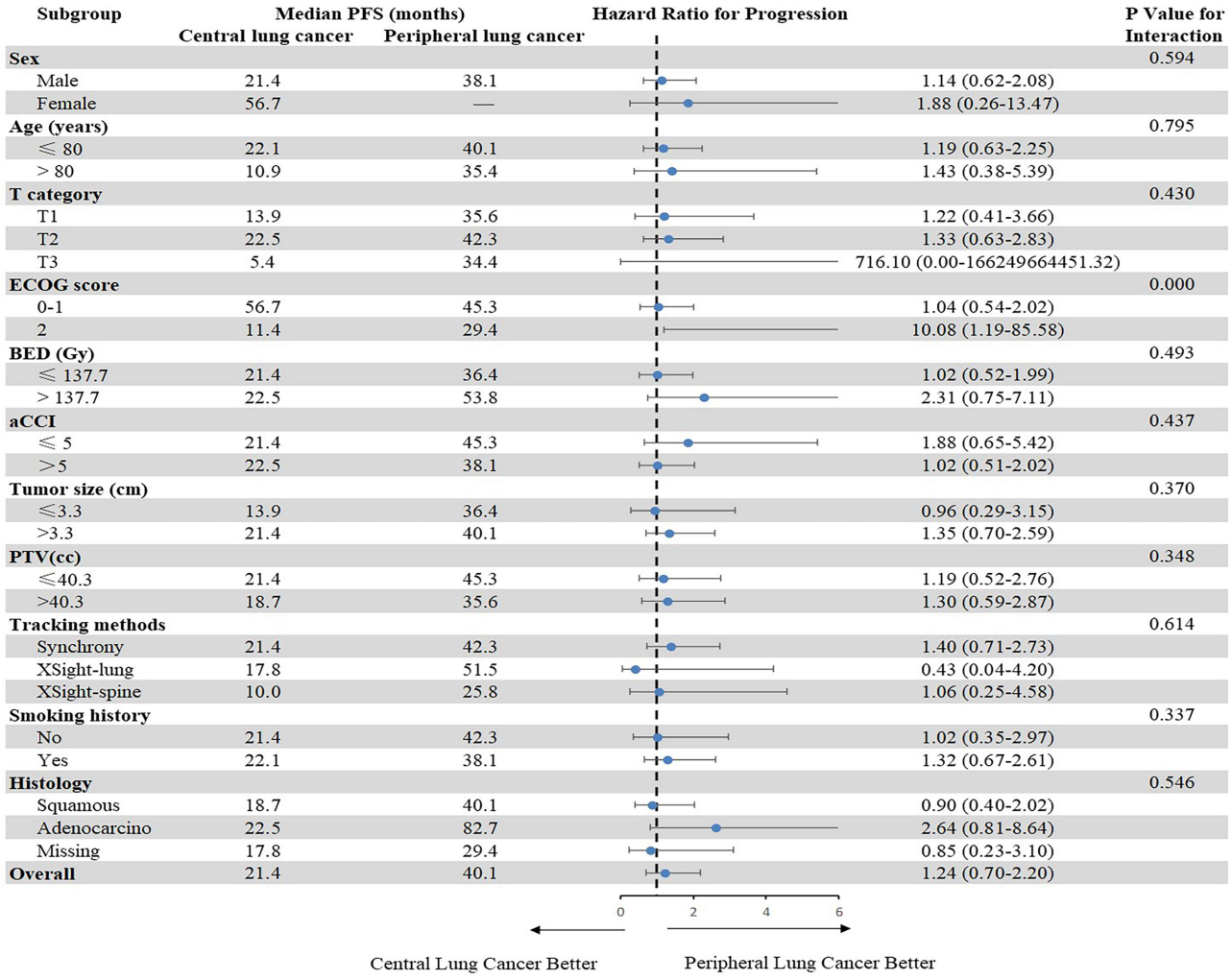

Figure 5 Forest plot of PFS subgroup analyses in matched study population.
Abbreviations: PFS, progression-free survival; SBRT, stereotactic body radiotherapy.

After PSM, grade 3 toxicity was observed in 6 cases in the centrally group and 7 cases in the peripherally group, respectively. The majority of these reactions were resolved with symptomatic treatment. No deaths were attributed to SBRT. Overall, there was no significant difference in toxicity between the central and peripheral lung cancer groups. The comparison of toxicity between the centrally group and the peripherally group were summarized in table 3.

Discussion

The future is expected to see a rise in the occurrence of NSCLC among elderly individuals. When making treatment decisions for this group, factors such as the patient's life expectancy, existing health conditions, potential benefits and risks of treatment, and the patient's own preferences should be taken into account.[19] The management of early-stage NSCLC is recommended to be approached in a multidisciplinary manner, with physicians and patients making decisions together, according to international guidelines.[20,21] The current guidelines endorse the use of SBRT in patients who are at a high risk for surgery, such as those with a predicted FEV1 less than 50%, predicted carbon monoxide diffusing capacity less than 50%, or a combination of factors like age, impaired lung function, pulmonary hypertension, and poor left ventricular function. In addition, it is recognized that age alone is an inadequate criterion for defining elderly patient status. As such, various prognostic scores, notably the G8 screening tool and CCI, have been developed to more accurately identify patients who truly require specialized consideration.[22–24] Cuccia et al[24] found that the G8 screening tool could predict the risk of late toxicity after lung SBRT in elderly patients with lung cancer, which helps to better evaluate older patients prior to lung SBRT.

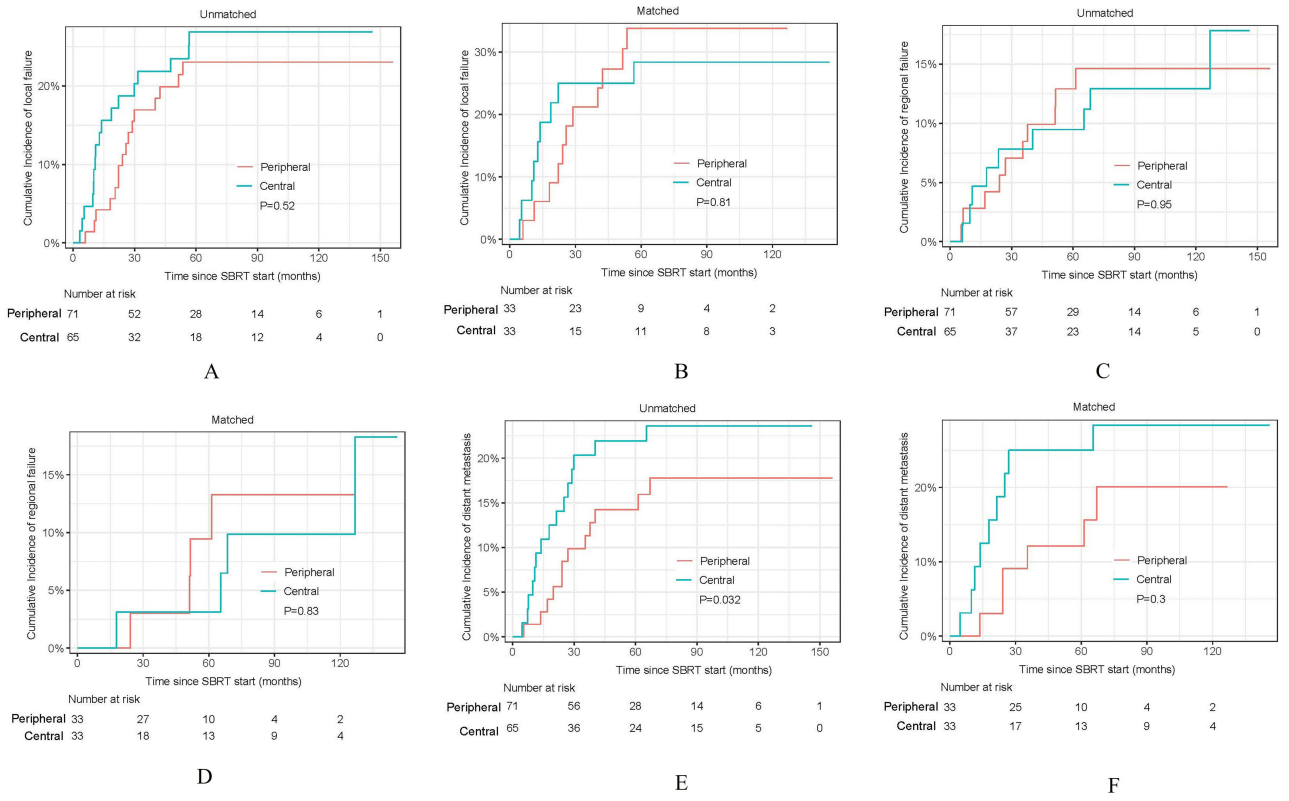

Figure 6 Cumulative incidence curves for the probability of each competing event. (**A**) cumulative incidence of local failure in the unmatched group; (**B**) cumulative incidence of local failure in the matched group; (**C**) cumulative incidence of regional failure in the unmatched group; (**D**) cumulative incidence of regional failure in the matched group; (**E**) cumulative incidence of distant failure in the unmatched group; (**F**) cumulative incidence of distant failure in the matched group.

In this study, we present our findings from comparing the outcomes of OS, PFS, LF, RF, DF, and toxicity in elderly patients with early-stage NSCLC treated with SBRT, focusing on the differences between central and peripheral tumors. Prior to PSM, central tumors have worse OS and PFS compared with peripheral lesions. In addition, anemia, cough,

Table 3 Toxicities between peripheral and central lung cancer groups

Toxicity	Unmatched					Propensity Matched				
	Central lung cancer (N = 65)		Peripheral lung cancer (N = 71)		P	Central lung cancer (N = 33)		Peripheral lung cancer (N = 33)		P
	Grade 1-2	Grade 3	Grade 1-2	Grade 3		Grade 1-2	Grade 3	Grade 1-2	Grade 3	
Acute										
Hematological										
Neutropenia	12 (18.5%)	1 (1.5%)	10 (14.1%)	1 (1.4%)	0.747	8 (24.2%)	1 (3.0%)	5 (15.2%)	1 (3.0%)	0.764
Leukopenia	14 (21.5%)	2 (3.1%)	9 (12.7%)	1 (1.4%)	0.326	8 (24.2%)	1 (3.0%)	6 (18.2%)	0 (0%)	0.558
Anemia	27 (43.1%)	6 (9.2%)	19 (26.8%)	2 (2.8%)	0.027	13 (39.4%)	3 (9.1%)	9 (27.3%)	1 (3.0%)	0.329
Thrombocytopenia	5 (7.7%)	0 (0%)	5 (7.0%)	0 (0%)	1.000	4 (12.1%)	0 (0%)	2 (6.1%)	0 (0%)	0.672
Non-hematological										
Cough	20 (30.8%)	0 (0%)	8 (11.3%)	0 (0%)	0.005	5 (15.2%)	0 (0%)	7 (21.2%)	0 (0%)	0.523
Hemoptysis	9 (13.8%)	0 (0%)	4 (5.6%)	0 (0%)	0.104	3 (9.1%)	0 (0%)	4 (12.1%)	0 (0%)	1.000
Hoarseness	7 (10.8%)	0 (0%)	0 (0%)	0 (0%)	0.005	3 (9.1%)	0 (0%)	0 (0%)	0 (0%)	0.238
Dyspnea	5 (7.7%)	0 (0%)	3 (4.2%)	0 (0%)	0.479	2 (6.1%)	0 (0%)	3 (9.1%)	0 (0%)	1.000
Chest pain	5 (7.7%)	0 (0%)	2 (2.8%)	0 (0%)	0.258	0 (0%)	0 (0%)	1 (3.0%)	0 (0%)	1.000
Dysphagia	6 (9.2%)	0 (0%)	2 (2.8%)	0 (0%)	0.152	2 (6.1%)	0 (0%)	2 (6.1%)	0 (0%)	1.000

(*Continued*)

Table 3 (Continued).

Toxicity	Unmatched					Propensity Matched				
	Central lung cancer (N = 65)		Peripheral lung cancer (N = 71)		P	Central lung cancer (N = 33)		Peripheral lung cancer (N = 33)		P
	Grade 1-2	Grade 3	Grade 1-2	Grade 3		Grade 1-2	Grade 3	Grade 1-2	Grade 3	
Fever	1 (1.5%)	0 (0%)	3 (4.2%)	0 (0%)	0.621	1 (3.0%)	0 (0%)	3 (9.1%)	0 (0%)	0.613
Fatigue	17 (26.2%)	1 (1.5%)	7 (9.9%)	1 (1.4%)	0.019	8 (24.2%)	1 (3.0%)	3 (9.1%)	1 (3.0%)	0.256
Anorexia	13 (20%)	1 (1.5%)	6 (8.5%)	0 (0%)	0.064	4 (12.1%)	0 (0%)	3 (9.1%)	0 (0%)	1.000
Radiation pneumonitis	20 (30.8%)	0 (0%)	3 (4.2%)	4 (5.6%)	0.000	3 (9.1%)	0 (0%)	1 (3.0%)	4 (12.1%)	0.127
Esophagotracheal fistula	0 (0%)	0 (0%)	0 (0%)	0 (0%)	—	0 (0%)	0 (0%)	0 (0%)	0 (0%)	—
Cardiac	0 (0%)	0 (0%)	0 (0%)	0 (0%)	—	0 (0%)	0 (0%)	0 (0%)	0 (0%)	—
Late										
Cough	8 (12.3%)	0 (0%)	5 (7.0%)	0 (0%)	0.297	5 (15.2%)	0 (0%)	4 (12.1%)	0 (0%)	1.000
Hemoptysis	2 (3.1%)	0 (0%)	0 (0%)	0 (0%)	0.227	2 (6.1%)	0 (0%)	0 (0%)	0 (0%)	0.492
Dyspnea	5 (7.7%)	0 (0%)	3 (4.2%)	0 (0%)	0.479	3 (9.1%)	0 (0%)	3 (9.1%)	0 (0%)	1.000
Chest pain	1 (1.5%)	0 (0%)	2 (2.8%)	0 (0%)	1.000	1 (3.0%)	0 (0%)	1 (3.0%)	0 (0%)	1.000
Radiation pneumonitis	3 (4.6%)	0 (0%)	3 (4.2%)	0 (0%)	1.000	2 (6.1%)	0 (0%)	3 (9.1%)	0 (0%)	1.000

hoarseness, fatigue and radiation pneumonitis were more likely to occur in the central group than in the peripheral group, with statistical differences. The adenocarcinoma tends to be peripheral type, and squamous cell carcinoma tends to be central type, but there was no statistical difference. After PSM was performed, the 2 groups were similarly matched, with no significant difference in baseline patient and tumor factors. Our findings indicated that the survival outcomes of central and peripheral lung tumors were comparable when treated with SBRT. In addition, we observed a low occurrence of severe toxicities associated with treatment, and there was no notable distinction between central and peripheral lung tumors. However, subgroup analysis showed that the peripheral group had a longer OS for patients with adenocarcinoma. This is probably due to that there exist significant differences between squamous cell carcinoma and adenocarcinoma. Compared with adenocarcinoma, squamous cell carcinoma may show more malignant characteristics in some aspects.[25,26]

There are few comparative studies focusing on SBRT in older adults between central and peripheral lung cancer. Therefore, we compared the results of different studies on SBRT in peripheral or central lung cancer. Recent reports on central lung cancer have indicated that SBRT has demonstrated favorable OS rates. A retrospective study summarized 31 consecutive patients with early-stage NSCLC located centrally who underwent SBRT treatment. The prescribed radiation dose ranged from 100 to 119 Gy, delivered in 4 to 10 fractions. The reported 3-year and 5-year OS rates were 85.3% and 68.4%, respectively.[27] NRG Oncology/RTOG 0813 Phase I/II Study reviewed 120 patients with centrally located T1-2 N0M0 NSCLC who were treated with SBRT. The radiation dose was delivered at 10–12 Gy per fraction, given over five fractions. The 2-year OS rates were reported as 67.9% and 72.7% for the cohorts receiving 11.5 and 12.0 Gy per fraction, respectively.[17] Roach et al conducted a prospective phase I/II trial for patients with centrally located early-stage NSCLC undergoing SBRT. The 2-year OS rate reported in this trial was 43%.[28] In prior to PSM, our study achieved similar overall survival, with 2-, 3-, and 5-year OS rates of 73.44%, 59.33%, and 41.26%, respectively, in elderly patients with central lung cancer. The observed survival rate of peripheral lung cancer was notably lower than the OS rate, and this difference was statistically significant. This was attributed to the correlation between patients with centrally located lung tumors and larger tumor sizes, more advanced T stage, and a higher likelihood of having a lower BED compared to patients with peripherally located lung tumors. We employed PSM to achieve balance in the distribution of measured prognostic factors among the different study arms. Both cohorts were similar in terms of age, gender, T category, performance status, aCCI, tumor size, PTV, BED, and tracking methods. The findings of this study demonstrated that the overall survival rates at 3 and 5 years for the central group were similar to those reported for the peripheral group. These results align with the conclusions drawn in previous studies. In the study of Mangona et al,[29] they compared SBRT for central tumors versus peripheral lung tumors in 196 consecutive patients followed prospectively at a single institution received moderate-dose SBRT (48–60 Gy in 4–5 fractions) using 4-dimensional planning, online image-guided radiation

therapy, and institutional dose constraints. With 79 central and 79 peripheral tumors matched, 2-year OS rate were similar for central (71.7%) versus peripheral (69.1%) tumors.

SBRT in early-stage NSCLC is a well-tolerated and efficient treatment with high rates of local control when applied to peripherally located lesions. In a retrospective study conducted by Tateishi et al (12), individuals diagnosed with peripheral early-stage NSCLC were identified. These patients underwent treatment with SBRT consisting of 50 to 60 Gy administered in 5 fractions. 433 patients were categorized into high BED (BEDmax greater than 200 Gy) and low BED groups (BEDmax of 200 Gy or less), respectively. This study revealed a notable disparity in the local recurrence rate between the high BED group and the low BED group (5-year rate, 1.3% and 7.2%). In a prospective non-randomized study focusing on early-stage peripheral localized NSCLC, 2-year local control rates were 100% with CyberKnife.[30] The findings of our investigation revealed that elderly patients diagnosed with peripheral lung cancer experienced local failure rates of 12% and 33% at the 2-year and 5-year, respectively. The local control rate in our study was worse than previous studies probably because elderly patients are weaker and have more medical diseases. However, we found that the local failure in peripheral early-stage NSCLC was similar with central located NSCLC. Our 1-, 2- and 3-year cumulative incidences of LF in central group were 12.5%, 25% and 25%, respectively. This is comparable to other studies. According to the study conducted by Sun et al in 2020, the rates of local disease recurrence were observed to be 11.7% at 3 years and 21.5% at 5 years. The study by Zhao et al[31] presents a retrospective analysis of 98 patients with central and ultracentral lung cancers who underwent SBRT at a dosage of 60 Gy administered in 8 fractions. The findings revealed local control rates of 97.8%, 93.7%, and 84.5% at 1, 2, and 3 years, respectively. The NRG Oncology/RTOG 0813 trial demonstrated that the cohorts receiving radiation doses of 11.5 Gy/fx and 12.0 Gy/fx achieved local control rates of 89.4% and 87.9% respectively, over a period of two years.[17] Another systematic review summarized 315 early-stage NSCLC patients with 563 central lung lesions for SABR (stereotactic ablative radiotherapy). Local control rates were higher than 85% when the prescribed BED exceeded 100 Gy.[32] Similarly, Roach et al found that a dose-fractionation regimen of 55 Gy administered in 5 fractions resulted in a local control rate of 85% over a 2-year period.

In order to achieve optimal control of tumors, it is necessary to administer high ablative doses. However, when performing SBRT on tumors that are located in close proximity to critical structures such as major bronchi, esophagus, large vessels, and brachial plexus, there is a potential for increased risk of damage to these organs at risk (OAR). In a systematic review, the results of SBRT for central lung tumors showed an overall treatment-related mortality rate of 2.7%, with less than 9% of patients experiencing grade 3 or 4 toxicities.[32] The study conducted by RTOG 0813 demonstrated that a maximum tolerated dose of 12.0 Gy/fx was found to be correlated with a dose-limiting toxicity rate of 7.2%.[17] The studies conducted by Haasbeek et al[33] and Zhao et al[31] focused on evaluating the toxicity profile of patients with central lung cancer who underwent SBRT with a dose of 60 Gy administered in 8 fractions. The findings indicated that no grade 4–5 toxicities occurred in the patients included in the study. Most of the patients experienced acute toxic events categorized as CTCAE grade 1–2. These events typically refer to mild to moderate symptoms that may require minimal intervention or conservative management. The study mentioned that these symptoms were transient and resolved over time. Mangona et al[29] found that moderate-dose SBRT yield a similarly safe toxicity profile for both central and peripheral lung tumors. The two-year cumulative rates of grade 2 pain, musculoskeletal, pulmonary, and skin adverse events were found to be 14%, 5%, 6%, and 10% in the central group, compared to 19%, 10%, 10%, and 3% in the peripheral group, respectively. In our comparative analysis, both central and peripheral treatments exhibited a comparable incidence of severe adverse events. We demonstrated that elderly patients with centrally or peripherally located lung lesions were well tolerated by SBRT.

There are some limitations of this study. First, there may have been hidden biases because of the fact that the treatment groups were treated at different time periods. This can lead to stage migration, selection bias, improvements in diagnostic and treatment methods, such as the use of cone beam CT and the introduction of molecularly targeted drugs and immune checkpoint inhibitors. PSM was conducted to minimize this background bias. Although the cohorts were accurately matched, it is important to note that this study is retrospective in nature. In addition, there may be unidentified or unrecorded factors that have influenced the selection of patients. Although a single-center study has its limitations in terms of generalizability, it also has the advantage of consistency in treatment methodology. This allows for easier

comparison of outcomes. However, to obtain a comprehensive understanding of the outcomes for central and peripheral lung tumors, it is imperative to conduct large-scale randomized trials.

Conclusions

In conclusion, our study showed that SBRT can be considered a viable treatment option for elderly patients who are not suitable candidates for surgery, regardless of the tumor's location. Although the survival outcomes and toxicities of central and peripheral lung tumors were comparable when treated with SBRT, the peripheral cancer had a better OS for patients with adenocarcinoma. Therefore, further studies are needed to examine how tumor location and histological subtype influence the efficacy of SBRT.

Data Sharing Statement

The data used to support the findings of this study are available from the corresponding author upon request.

Ethical Statement

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was performed in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of Jinling hospital (No. 2023NZKY-034-02), which waived the informed consent requirement due to the retrospective design of the study. The patient data were anonymized.

Acknowledgments

Xiaoqin Ji and Xuebing Shi share first authorship.

Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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