

Impact of maximum standardized uptake value of non-small cell lung cancer on detecting lymph node involvement in potential stereotactic body radiotherapy candidates

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Background: The retrospective study investigated the association between the maximum standardized uptake value (SUV_{max}) of primary tumor and lymph node involvement in potential stereotactic body radiotherapy (SBRT) candidates.

Methods: A total of 185 patients with clinical stage I NSCLC were enrolled in the current study. All patients underwent lobectomy with systematic lymph node dissection following preoperative FDG-PET/CT scanning. The association between clinicopathological variables and lymph node involvement was analyzed by univariate and multivariate analysis. Spearman's correlation test was used to evaluate the correlation between them. Receiver operating characteristic (ROC) analysis was performed to calculate the area under the curve.

Results: Among these patients, 22.1% had occult lymph node involvement, 15.1% were N1 and 7.0% were N2. Greater tumor size (P=0.007), elevated CEA (P=0.006), central location (P=0.002), higher SUV_{max} (P<0.001), solid nodule type (P=0.002), visceral pleural invasion (P=0.001) and presence of micropapillary and solid patterns (P=0.002) were significantly associated with lymph node involvement. In multivariate analysis, lymph node involvement was associated with central location (OR 5.784, 95% CI: 1.584–21.114, P=0.008), SUV_{max} (increase of 1 unite, OR 1.147, 95% CI: 1.035–1.272, P=0.009) and visceral pleural invasion (OR 3.044, 95% CI: 1.369–6.769, P=0.006). ROC area under the curve of SUV_{max} for lymph node involvement was 0.770 (95% CI: 0.698–0.841), the sensitivity and specificity were 85.4% and 63.2%, respectively. Spearman's correlation test showed that SUV_{max} of tumor mostly depended on tumor size and nodule type.

Conclusions: SUV_{max} of primary tumor was a predictor of lymph node involvement for potential SBRT candidates. Centrally located tumor and visceral pleural invasion were related to higher rate of nodal metastasis. Lobectomy and systemic lymph node dissection should be performed in these patients, instead of SBRT.

Keywords: Potential SBRT candidates; lymph node involvement; SUV_{max}

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Introduction

Lung cancer is the most frequently diagnosed cancer and the leading cause of cancer death worldwide (1). The increasing detected rate of early stage non-small cell lung cancer (NSCLC) is due to low-dose computer tomography screening during the past decade (2). For resectable NSCLC, anatomical lobectomy with systematic lymph node dissection is considered as the standard treatment (3). Stereotactic body radiotherapy (SBRT, also called stereotactic ablative therapy) is a new approach to treating early stage lung cancer, especially for elderly patients with poor cardiopulmonary function. Meanwhile, SBRT have shown a promising result for treating operable stage I NSCLC in several studies (4-6). However, local recurrence, which might attribute to the occult lymph node metastasis, is one of the most controversial issues (6-8). It is important to rule out lymph node involvement when selecting SBRT candidates.

¹⁸F-fluorodeoxyglucose positron emission tomography integrated with computed tomography (FDG-PET/CT) has been widely used in malignant tumor preoperative staging work-up, especially in lung cancer (9). FDG-PET/CT provided morphological information and FDG uptake to distinguish the benign and malignant lymph node. Increasing evidence supported the clinical value of FDG-PET/CT for mediastinal lymph node staging. FDG-PET/CT had been performed to exclude nodal positive NSCLC patients in cohort of SBRT studies, but lymph node involvement was found in 7.6–19.2% patients (6,10-12). Several studies had identified that the maximum standardized uptake value (SUV_{max}) of primary tumor was a significant risk factor of occult lymph node metastasis for clinical N0 NSCLC (10-14). However, the conclusion was not widely accepted (15,16).

The International Association for the Study of Lung Cancer (IASLC), the American Thoracic Society (ATS) and the European Respiratory Society (ERS) proposed a new historical classification of lung adenocarcinoma in 2011 (17). Haruhiko and his colleagues found that SUV_{max} of primary tumor reflected the malignant grade and associated with adenocarcinoma patterns (18). Meanwhile, micropapillary and solid patterns were considered as poor prognostic factors, and associated with occult lymph node metastasis (19,20).

Therefore, in this study, we aim to retrospectively investigate the association between clinicalpathological variables, especially the SUV_{max} of primary tumor, and lymph node involvement in potential SBRT candidates with

clinical stage I NSCLC (cT1-2aN0M0).

Methods

We retrospectively reviewed the records of 537 NSCLC patients who underwent radical surgical resection from May 2010 to December 2015 at the department of Thoracic Surgery II, Peking University Cancer Hospital. All patients received contrast-enhanced chest CT scan, FDG-PET/CT and brain magnetic resonance imaging for preoperative staging work-up. A total of 185 patients with clinical stage I NSCLC were enrolled in the current study. Inclusion criteria were as follows: tumor less than 4 cm, identified clinical N0 based on CT and FDG-PET/CT imaging, underwent lobectomy with systematic lymph node dissection.

Lymph nodes with a short-axis ≥ 1 cm on CT or SUV_{max} ≥ 2.5 on FDG-PET/CT were considered as nodal involvement. We defined systematic lymph node dissection according to the American College of Surgeons Oncology Group (ACOSOG) Z0030 criteria, which required removing lymphatic tissue from stations 2R, 4R, 7, and 10R for right-sided tumors and from stations 5, 6, 7, and 10L for left-sided tumors. The remaining of N1 nodes (11-14) were removed as part of the resection specimen.

Patient clinicalpathological characteristics were collected from the medical records. All chest CT images and FDG-PET/CT reports were reviewed for tumor size, tumor location, nodule type, clinical stage and SUV_{max}. Tumor was considered peripheral if located within the outer two-thirds of the lung on CT scan. Nodule types were classified into ground-glass opacity (GGO) group and solid group. Tumors with GGO ratio more than 50% were divided into GGO group. Determination of clinical stage was based on the 8th TNM classification of the International Union Against Cancer and the American Joint Committee on Cancer (UICC/AJCC). Pathological reports were reviewed for tumor histology, adenocarcinoma patterns, visceral pleural invasion and lymph node involvement. The new IASLC/ATS/ERS classification of adenocarcinoma was used to identify the adenocarcinoma patterns. Micropapillary and solid patterns were recorded if the percentage of histological component exceeded 5%. The retrospective study was approved by Institutional Review Board at Beijing Cancer Hospital (2015KT04). The requirement of patient consent was obtained in this retrospective study.

Student's *t*-test was used to analyze for comparing continuous variables, Pearson's chi-squared test or Fisher's

Table 1 Patient characteristics

Characteristics	Distribution (%)
Age	58.54±8.94
Gender	
Male	84 (45.4)
Female	101 (54.6)
Smoking history	
Yes	63 (34.1)
No	122 (65.9)
Tumor size (cm)	2.37±0.72
Clinical T stage	
T1a	1 (0.5)
T1b	39 (21.1)
T1c	42 (22.7)
T2a	103 (55.7)
Serum CEA (ng/mL)	
≤5	153 (82.7)
>5	32 (17.3)
Tumor SUV _{max}	5.21±3.97
Tumor location	
Central	13 (7.0)
Peripheral	172 (93.0)
Nodule type	
GGO	36 (19.5)
Solid	149 (80.5)
Histology	
Squamous cell carcinoma	10 (5.4)
Adenocarcinoma	175 (94.6)
Micropapillary and solid patterns	
Present	39 (21.1)
Absent	136 (78.9)
Visceral pleural invasion	
Present	68 (36.8)
Absent	117 (63.2)
Number of dissection lymph node	18 [7–48]
Pathological N stage	
N0	144 (77.9)
N1	28 (15.1)
N2	13 (7.0)

exact test was performed to assess the categorical variables. Receiver operating characteristic (ROC) analysis was performed to calculate the area under the ROC curve (AUC). Medcalc was used to compare ROC curves and calculated P value. Binary logistic regression was used to identify the risk factors for occult nodal metastasis. Spearman's correlation test was used to calculate the correlations between clinicalpathological variables. All tests were two-sided. P values of less than 0.05 were considered to indicate statistical significant difference. The Statistical Package for the Social Sciences version 20.0 software package (SPSS, Chicago, IL, USA) was used for statistical analysis.

Results

Patient characteristics

Among all patients, 84 were male and 101 were female. The mean age was 58.54, with a range from 32 to 79. One hundred and seventy-two tumors were peripheral location. Only 19.5% of tumors were divided into GGO group. For tumor histology, 175 cases were confirmed with lung adenocarcinoma, others were squamous cell carcinoma. For the historical subtypes of adenocarcinoma, a total of 39 cases were identified with micropapillary and solid component exceeded 5%. Patients with pathological visceral pleural invasion accounted for 36.8%. The median number of lymph node dissection was 18 (range, 7–48). 90.2% patients had station 13 lymph nodes, 38.9% patients had station 14 lymph nodes. Forty one patients had occult lymph node metastasis, 28 were N1 and 13 were N2. Twenty-six patients confirmed lymph node metastasis in station 13 or 14. Patient characteristics were listed in *Table 1*.

Univariate analysis of risk factors for lymph node involvement

The association between clinicalpathological variables and lymph node involvement was investigated (*Table 2*). No significant differences were found in demographic data, including age, gender and smoking history. The mean tumor size was larger in those with lymph node involvement (2.30 *vs.* 2.64 cm, P=0.007). Clinical T stage had no association with nodal metastasis (P=0.112). Among the 32 patients with preoperative serum CEA >5 ng/mL, 13 were confirmed node-positive, while 28 of the remaining 153 patients with normal serum CEA had pathological lymph node involvement

Table 2 Univariate analysis of risk factors for lymph node involvement

Variable	Pathological N0 (n=144)	Pathological N1-2 (n=41)	P value
Age	58.67±8.79	58.10±9.53	0.720
Gender			0.566
Male	67	17	
Female	77	24	
Smoking history			0.464
Yes	51	12	
No	93	29	
Tumor size (cm)	2.30±0.71	2.64±0.69	0.007
Clinical T stage			0.112
T1a	1	0	
T1b	35	4	
T1c	31	11	
T2a	77	26	
Serum CEA (ng/mL)			0.006
≤5	125	28	
>5	19	13	
Tumor SUV _{max}	4.48±3.73	7.79±3.73	<0.001
Tumor location			0.002
Central	5	8	
Peripheral	139	33	
Nodule type			0.002
GGO	35	1	
Solid	109	40	
Histology			0.463
Squamous	9	1	
Adenocarcinoma	135	40	
Micropapillary and solid patterns			0.002
Present	23	16	
Absent	112	24	
Visceral pleural invasion			0.001
Present	44	24	
Absent	100	17	

SUV_{max}, the maximum standardized uptake value; GGO, ground-glass opacity.

(P=0.006). There was a significant difference in SUV_{max} of primary tumor between pathological N0 and N1-2 (4.48 vs. 7.79, P<0.001). For central location tumors, 61.5% were identified with lymph node metastasis, while 19.2% had pathological N1-2 in peripheral location (P=0.002). Among the 36 patients of GGO group, only one was confirmed with nodal metastasis, comparing to 40 of 149 in solid nodule (P=0.002). There was no association in tumor histology (P=0.463). Patients with visceral pleural invasion tended to have a higher rate of lymph node metastasis (P=0.001). For lung adenocarcinoma patients, the presence of micropapillary and solid patterns was association with occult lymph node involvement (P=0.002).

Multivariate analysis of risk factors for lymph node involvement

Tumor size and SUV_{max} was analyzed as continuous variables. The role of tumor SUV_{max} in predicting lymph node involvement was compared between Model 1 and Model 2 (Table 3). In multivariate analysis, SUV_{max} of primary tumor was not analyzed in Model 1, the result showed that central location (OR 6.409, 95% CI: 1.813–22.649, P=0.004), solid nodule (OR 8.354, 95% CI: 1.074–64.995, P=0.043) and visceral pleural invasion (OR 3.378, 95% CI: 1.542–7.399, P=0.002) were independent predictors for pathological lymph node involvement. In Model 2 with primary tumor SUV_{max}, central location (OR 5.784, 95% CI: 1.584–21.114, P=0.008), SUV_{max} (increase of 1 unite, OR 1.147, 95% CI: 1.035–1.272, P=0.009) and visceral pleural invasion (OR 3.044, 95% CI: 1.369–6.769, P=0.006) were significantly associated with lymph node involvement.

ROC curve was performed. Model 2 (AUC =0.811, 95% CI: 0.744–0.878) showed a little better diagnostic accuracy than Model 1 (AUC =0.766, 95% CI: 0.690–0.841), statistical significant difference was not exhibited (P=0.065) (Figure 1A). In addition, ROC area under the curve of primary tumor SUV_{max} for lymph node involvement was 0.770 (95% CI: 0.698–0.841) (Figure 1B). An optimal cut-off value was identified as 4.45 by ROC curve, the sensitivity and specificity were 85.4% and 63.2%, respectively.

Multivariate analysis of 175 lung adenocarcinomas indicated that the following three predictors were significant association with lymph node metastasis: central location (OR 7.946, 95% CI: 1.657–38.106, P=0.010), SUV_{max} (increase of 1 unite, OR 1.249, 95% CI: 1.119–1.394, P<0.001), and visceral pleural invasion (OR 2.840, 95% CI:

Table 3 Multivariate analysis of risk factors for lymph node involvement

Variable	Multivariate analysis					
	Model 1		Model 2		Model 3	
	Odds ratio	P	Odds ratio	P	Odds ratio	P
Tumor size (1 cm increase)	1.223 (0.716–2.008)	0.461	1.007 (0.564–1.797)	0.982	0.941 (0.505–1.754)	0.849
Elevated CEA (vs. normal)	2.093 (0.858–5.108)	0.105	1.781 (0.706–4.492)	0.222	2.124 (0.799–5.644)	0.131
Central location (vs. peripheral)	6.409 (1.813–22.649)	0.004	5.784 (1.584–21.114)	0.008	7.946 (1.657–38.106)	0.010
Solid nodule type (vs. GGO)	8.354 (1.074–64.995)	0.043	4.575 (0.550–38.059)	0.159	3.804 (0.443–32.641)	0.223
Visceral pleural invasion (vs. absent)	3.378 (1.542–7.399)	0.002	3.044 (1.369–6.769)	0.006	2.840 (1.246–6.476)	0.013
Tumor SUV _{max} (1 unite increase)	–		1.147 (1.035–1.272)	0.009	1.249 (1.119–1.394)	<0.001
Micropapillary and solid patterns (vs. absent)	–		–		1.949 (0.780–4.872)	0.153

SUV_{max}, the maximum standardized uptake value; GGO, ground-glass opacity.

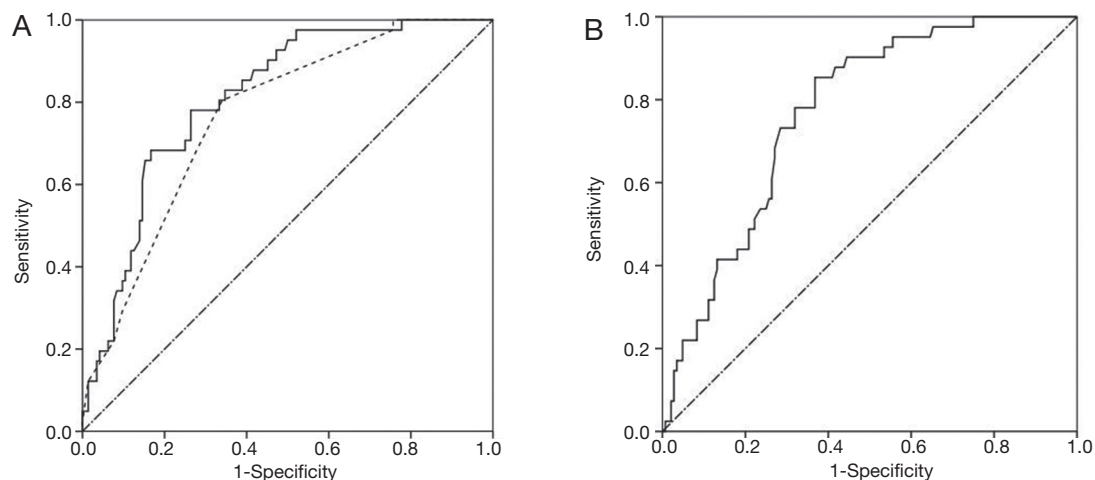


Figure 1 ROC curves for lymph node involvement. (A) ROC curves for predicting lymph node involvement for Model 1 (dotted line) and Model 2 (full line). AUC was 0.766 (95% CI: 0.690–0.841) for Model 1 and 0.811 (95% CI: 0.744–0.878) for Model 2, this demonstrated a little better diagnostic accuracy of Model 2 compared to Model 1 ($P=0.065$); (B) ROC curve for predicting lymph node involvement for primary tumor SUV_{max}. The optimal cut-off value was 4.45. AUC was 0.770 (95% CI: 0.698–0.841, $P<0.001$). ROC, Receiver operating characteristic; SUV_{max}, the maximum standardized uptake value; AUC, area under the curve.

1.246–6.476, $P=0.013$), as shown in Model 3. The presence of micropapillary and solid patterns was not significant association with pathological node-positive ($P=0.153$) in multivariate analysis.

Correlations between SUV_{max} and other variables

The correlations between clinicalpathological variables and SUV_{max} were calculated by Spearman's correlation test. Only moderate correlation was found between nodule type and SUV_{max} ($r=0.59$, $P<0.001$). Tumor size was related

to SUV_{max} ($r=0.42$, $P<0.001$). For lung adenocarcinoma, correlation between adenocarcinoma pattern and SUV_{max} of primary tumor was 0.36 ($P<0.001$). Serum CEA, visceral pleural invasion and histology revealed weak correlations with SUV_{max} (Table 4).

Discussion

Except of radical lobectomy, SBRT was acceptable for stage I NSCLC patients with limited pulmonary function and inoperable medical condition (4–6). However, conflicting

Table 4 Correlations between all variables and P values

Variable	SUV _{max}	Serum CEA	Tumor size	Nodule type	Visceral pleural invasion
Serum CEA	0.29 (<0.001)	–	–	–	–
Tumor size	0.42 (<0.001)	0.19 (0.011)	–	–	–
Nodule type	0.59 (<0.001)	0.19 (0.10)	0.22 (0.002)	–	–
Visceral pleural invasion	0.22 (<0.001)	0.10 (0.194)	0.20 (0.007)	0.12 (0.104)	–
Adenocarcinoma patterns	0.36 (<0.001)	0.05 (0.529)	0.12 (0.128)	0.24 (0.001)	0.04 (0.631)
Histology	0.20 (0.006)	0.02 (0.817)	0.05 (0.477)	0.12 (0.111)	–0.08 (0.261)

SUV_{max}, the maximum standardized uptake value.

results of local recurrence and overall survival were reported in several previous studies (5,6,21). Controversy remained about the lymph node involvement in these clinical N0 patients. Although FDG-PET/CT was applied to screening out node-positive patients, occult lymph node involvement was unavoidable (10-12). Therefore, in this study, we retrospectively assessed the association between clinical/pathological variables and lymph node involvement in potential SBRT candidates.

Central location tumors were inclined to have pathological node-positive in our study. The incidence of occult lymph node metastasis was 61.5% for central location, only 19.2% for peripheral location. The results were consistent with the findings in previous reported studies (15,16,22,23). Therefore, selecting patients with tumor centrally located for SBRT should be more careful to rule out lymph node involvement.

Visceral pleural invasion was considered as a poor prognostic factor in NSCLC, and correlated with higher frequency of lymph node involvement (24,25). Gorai and his colleagues confirmed that the incidence of skip N2 was associated with visceral pleural invasion in clinical IA NSCLC patients (26). The similar result was obtained in the current study, visceral pleural invasion was an independent risk factor for pathological nodal involvement.

FDG-PET/CT played an important role in lymph node staging, preoperative evaluation of lymph node condition mostly depended on lymph node FDG uptake. Moreover, the SUV_{max} of primary tumor could predict lymph node involvement in several studies. Downey and his colleagues identified that patients with lymph node involvement had a higher SUV_{max} of primary tumor than patients without nodal involvement (27). In 2011, Kanzaki and his colleagues showed that SUV_{max} of primary tumor was the risk factor in occult mediastinal lymph node metastasis for NSCLC patients with

clinical N0–1 (28). Li illustrated that primary tumor SUV_{max} would help for selecting patients for SBRT (29).

In our retrospective study, we found that the risk of lymph node metastasis in clinical N0 patients with tumor less than 4 cm was related to primary tumor SUV_{max}. Multivariate analysis confirmed primary tumor SUV_{max} was an independent predictor for occult nodal disease. Comparing the prediction models of lymph node involvement with ROC curve, model with the factor of SUV_{max} displayed higher efficiency than model without. There were 69 patients whose primary tumors were less than 2 cm, nine patients had occult lymph node metastasis, six were N1 and three were N2. Univariate analysis showed that elevated serum CEA and primary tumor SUV_{max} were associated with occult lymph node involvement. Therefore, primary tumor SUV_{max} might be applied for eliminating lymph node involvement for clinical stage I NSCLC patients. Although a controversial conclusion was obtained in Akthar study, which showed that occult lymph node involvement was not associated with tumor SUV_{max}, only 79 of 105 patients tumor SUV_{max} were described, and only eight pathological node-positive patients happened in their series, so the negative result should be referred carefully (15).

Correlations between primary tumor SUV_{max} and tumor biological behaviors were explored. In Suzawa and colleagues study, they revealed that tumor size correlated significantly with SUV_{max}, irrespective of the histology (30). In our series, we detected that nodule type was median correlation with tumor SUV_{max}, a weak correlation was found with tumor size. These findings suggested that the FDG uptake of primary tumor were mostly dependent on tumor size and nodule type. Hence, SUV_{max} of primary tumor might reflect tumor malignant grade.

Tumor size was widely used in selecting potential patients for SBRT, which was suitable for clinical N0 patients with

tumor less than 5 cm. Hung and colleagues identified that tumor size was a good predictor of lymph node metastasis in lung adenocarcinoma of 3 cm or smaller (31). In 2013, Chen showed that larger tumor size was found in patients with mediastinal lymph node disease than those without mediastinal lymph node involvement (22). However, primary tumor size in predicting lymph node involvement was not widely accepted. The percentage of pathological nodal positive was 17.1% in the cases of small tumor less than 2 cm in Nakamura study (13). Likewise, we detected that the whole tumor size was larger in those with lymph node involvement, but there was not significance in multivariate analysis when considered as a continuous variable.

In Tsutani and colleagues study, solid tumor size became a predictor of nodal involvement rather than whole tumor size, and they confirmed that the solid component in tumor promoted the presence of lymph node metastasis (11). Miyasaka reported that the consolidation/tumor diameter ratio was related to pathological nodal involvement in clinical N0 NSCLC patients (12). In this study, only one of thirty-six patients with GGO staged into N2, who was confirmed with intrapulmonary and mediastinal lymph node involvement at the same time. A higher rate of nodal disease was found in solid tumor. However, we detected that solid nodule type was median correlation with tumor SUV_{max} , and the role of solid nodule type in predicting lymph node metastasis was neglected when taking into account primary tumor SUV_{max} .

Several studies focused on the association between history and lymph node involvement. Comparing with squamous cell lung cancer, lung adenocarcinoma was more possible to find out nodal involvement (28). For adenocarcinoma, the presence of micropapillary and solid patterns promoted lymph node metastasis (20,31). In our study, we found that tumor histology was not associated with lymph node involvement. Then, the association between adenocarcinoma patterns and lymph node metastasis was analyzed, the presence of micropapillary and solid patterns was significantly association with lymph node involvement in univariate analysis, but it was not considered as an independent predictor. Meanwhile, a weak correlation was found between primary tumors SUV_{max} with adenocarcinoma patterns.

Certainly, this is a retrospective single institution study to explored risk factors of lymph node involvement. We identified the SUV_{max} of primary tumor could predict lymph node involvement, further prospective survey should

conduct to verify the conclusion. In the current series, consecutive patients was enrolled based on the criteria of patients with clinical stage I NSCLC (cT1-2aN0M0), but the number of patients with central location and squamous cell lung cancer was too small, investigations with a larger scale of patients was need to control selection bias. Visceral pleural invasion was an independent predictor, rather than the evaluation of visceral pleural invasion from CT and FDG-PET/CT. Hence, the role of visceral pleural invasion in predicting lymph node involvement was limited before surgery.

In conclusion, primary tumor SUV_{max} was a predictor of lymph node involvement for patients with clinical stage I NSCLC (cT1-2aN0M0). Moreover, primary tumor SUV_{max} was mostly dependent on tumor size and nodule type. SUV_{max} was a more effective and measurable predictor in evaluating occult lymph node involvement. Centrally located tumor and visceral pleural invasion were related to a higher rate of nodal metastasis. Lobectomy and systemic lymph node dissection should be performed in these patients, instead of SBRT.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The study was approved by Institutional Review Board at Beijing Cancer Hospital (2015KT04) and written informed consent was obtained from all patients.

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