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Frequency of Lymph Node Metastasis According to the Size of Tumors in Resected Pulmonary Adenocarcinoma with a Size of 30 mm or Smaller

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Background: This study analyzed the relation between the tumor size and the lymph node metastasis in adenocarcinoma of the lung with a size of 30 mm or smaller.

Methods: Four hundred thirteen patients who had undergone curative resection for lung adenocarcinoma were enrolled. If the tumor presented ground-glass opacities on the preoperative high-resolution computed tomography, both the total size including ground-glass opacities and the solid size alone were measured. To calculate the rates of lymph node metastasis by the tumor size, the tumors were divided into six groups by their sizes: 5 mm or less, 6 to 10 mm, 11 to 15 mm, 16 to 20 mm, 21 to 25 mm, and 26 to 30 mm.

Results: The average numbers of dissected lymph nodes and dissected lymph node stations were 17 and 5, respectively. Seventy-five patients (18%) were postoperatively discovered to have positive nodes. The rates of node metastasis in each total size group were 0/1 (0%), 0/29 (0%), 5/77 (7%), 17/121 (14%), 27/101 (27%), and 26/84 (31%), respectively. The rates of node metastasis in each solid size group were 0/37 (0%), 1/53 (2%), 9/88 (10%), 17/104 (16%), 23/78 (30%), and 25/53 (47%), respectively. The area under the curve of receiver operating characteristic curves for the total size was measured as 0.701, and that for the solid size was measured as 0.777. By multivariate analysis, solid size, maximum standardized uptake value, and lymphovascular invasion were independent significant predictive factors.

Conclusions: Solid size, maximum standardized uptake value, and lymphovascular invasion were independent predictors for lymph node metastasis of lung adenocarcinoma. The size of the solid component explained the relation between the tumor size and the lymph node metastasis more accurately than that explained by the total tumor size on high-resolution computed tomography.

Key Words: Tumor size, Lymph node metastasis, Adenocarcinoma.

(J Thorac Oncol. 2014;9: 818–824)

Tumor size and lymph node status are recognized to be the most powerful predictors of prognosis and are fundamental elements in the tumor-node-metastasis (TNM) staging system. Generally, larger tumors have been known to be more closely associated with lymph node involvement in solid tumors including lung cancer.[1,2] However, a positive correlation between the tumor size and lymph node metastasis does not necessarily exist in all types of lung cancer. Some studies have reported that small squamous cell carcinoma tumors are not generally related to lymph node metastasis, but small adenocarcinoma tumors tend to present with lymph node metastasis.[3,4]

The number of cases of early detection of lung cancer has recently been increasing with the help of computed tomography (CT) screening and regular health examinations for lung cancer.[5,6] Lung cancer detected by means of CT screening is more likely to be small in size and peripherally located, and also to present with mainly an adenocarcinoma histology, especially from the in situ component.[5,7] Accordingly, the pathologic characteristics or prognosis of this type of lung cancer have been extensively studied, and surgeons have made attempts to minimize the volume of lung that is to be resected on the basis of size.

In making decisions on limited resection, considering that the size of the tumor cannot be the sole factor to be evaluated—given the risk of unknown lymph node status even with small tumors, research on the association between lymph node metastasis and the size of adenocarcinoma with a ground-glass opacities (GGOs) component would be beneficial for predicting prognosis and making reliable decisions on the basis of limited resections.

Therefore, this study analyzed the relation between the tumor size and lymph node metastasis in adenocarcinoma of the lung with a size of 30 mm or smaller on preoperative CT.

PATIENTS AND METHODS

Patient Population

This study is a retrospective review of a prospective lung cancer database. Patients enrolled in this study had undergone curative resection at Seoul National University Bundang Hospital from January 2004 to December 2012 and were diagnosed pathologically with lung adenocarcinoma. Patients who underwent neoadjuvant therapy and

patients who presented with tumors larger than 30 mm were excluded from this study. This study was approved by the Institutional Review Board of Seoul National University Bundang Hospital. Informed consent was waived because it was a retrospective review.

Preoperative Evaluations

A contrast-enhanced chest CT or high-resolution CT was performed in all the patients preoperatively. For partly solid GGOs, the images were photographed with a window level of −600 Hounsfield Units (H) and a window width of 2000 H as the lung window. GGO was defined as a hazy increase in lung attenuation without obscuring the underlying bronchial or vascular structures, and solid attenuation was defined as an increase in lung attenuation obscuring the underlying structures.[8] If the tumor presented GGOs, both the total size including GGOs and the solid size were measured. Otherwise, only the total size of the tumor was measured. All measurements were performed retrospectively by a radiologist and surgeons who did not know the pathologic results. The largest transverse cross-sectional diameter of the area of GGO in the lung window and the remaining solid area in mediastinal window image were measured. For manual diameter measurements, we used the electronic calipers function of our picture archiving and communication system on the axial image in which the GGO had the greatest dimension. Readers were advised to zoom in on the nodule for more accurate analysis. Spiculations were included in the determination of the largest transverse cross-sectional diameter of the speculated nodule (Fig. 1). To calculate the rates of lymph node metastasis by the tumor size, the tumors were divided into six groups by their sizes: 5 mm or less, 6 to 10 mm, 11 to 15 mm, 16 to 20 mm, 21 to 25 mm, and 26 to 30 mm. Adenocarcinoma with GGOs was grouped in the same manner but separately by the total size and the solid size.

As a standard staging procedure, positron emission tomography/CT was performed with an integrated positron emission tomography/CT scanner (Discovery VCT; GE Healthcare, Milwaukee, WI) and the maximum standardized uptake value (SUVmax) of the main tumor was assessed.

The tumor locations were assessed with bronchoscopy, and if the bronchoscopic findings showed a visible lesion, it was defined as central. If no visible lesion was found, it was defined as peripheral.

Surgical Treatment

Lobectomy combined with mediastinal lymph node dissection by thoracotomy or video-assisted thoracic surgery was performed as the standard surgical procedure. However, segmentectomy was selectively performed in patients with a partly solid GGO that was 10 mm or smaller. All patients underwent mediastinal lymph node dissection. This study also excluded patients who presented less than six lymph nodes or who did not undergo dissection of the hilar, subcarinal, and paratracheal (right side), or aortopulmonary window lymph nodes (left side).

Pathology

Diagnostic evaluation of lymph node metastasis was done using hematoxylin and eosin staining. The status of lymph node involvement was recorded as N1 or N2 depending on their locations, and its count was also recorded. The histopathological classification of the specimens was done on the basis of the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society classification of lung adenocarcinoma.[9] The tumors were classified as adenocarcinoma in situ, minimally invasive adenocarcinoma, and invasive adenocarcinoma. Visceral pleural invasion was assessed in all the cases, using the guidelines of the 7th edition of the TNM classification for lung cancer. Lymphovascular invasion was also examined.

Statistical Analysis

The Student's t test and analysis of variance were used to compare the distribution of continuous data, and Fisher's exact or χ^2 tests were used to compare the frequencies of categorical measures among different groups. Receiver operating characteristic curves and the area under the curve (AUC) of the total size, solid size, and SUVmax were generated to determine the cutoff value and whether the total size or solid size was more highly predictive of lymph node metastasis. The statistical analysis was performed using IBM SPSS 20.0 software (IBM Co., Chicago, IL). All p values less than 0.05 were considered to be statistically significant.

RESULTS

Patient Characteristics

This study enrolled 413 patients who were diagnosed with adenocarcinoma of the lung from January 2004 to
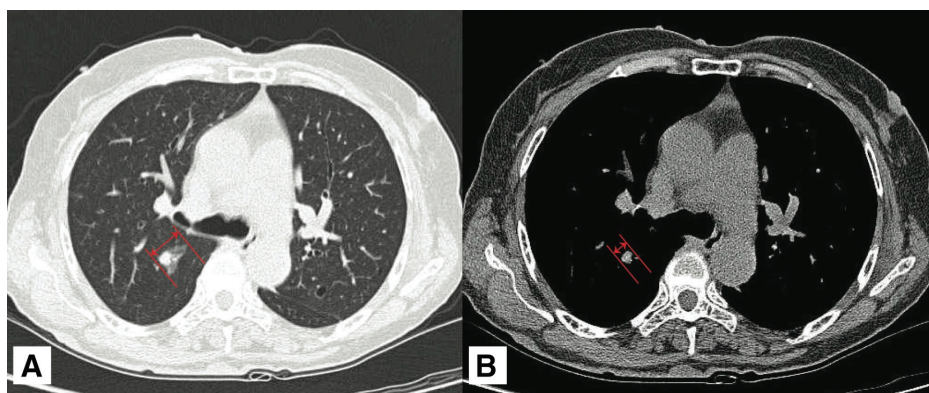

FIGURE 1. *A,* Axial image of computed tomography shows 22-mm mixed ground-glass opacity in right upper lobe on lung window. *B,* Axial image of computed tomography shows 10-mm solid area in right upper lobe on mediastinal window.

December 2012 (Table 1). Among them, 198 patients (48%) were male and 215 patients (52%) were female. The mean age was 62.0 years (range, 26–84). Two hundred forty-seven of those patients (60%) were never smokers, 106 patients (26%) were exsmokers, and 60 patients (14%) were current smokers. Surgical resection that was more extensive than segmentectomy was performed in 379 patients (92%) and segmentectomy was performed in 34 patients (8%).

One hundred ninety-one patients (46%) presented partly solid GGO nodules on preoperative CT, and 222 patients (54%) presented 100% solid tumors. In terms of in situ lesions on pathologic examination, 155 patients (38%) presented tumors combined with an in situ component, whereas 258 patients (62%) presented 100% invasive tumors.

Forty-two patients who had partly solid GGO lesions on preoperative CT revealed no in situ lesion on pathologic findings; in contrast, six patients with only a solid lesion on CT showed an in situ lesion on pathologic findings after surgery.

Tumor Size

Of the 413 patients enrolled in the study, the median total size of the tumor was 20.0 (6.0–30.0) mm, whereas the median size of the solid component was only 17.0 (0.0–30.0) mm. After the tumors were divided into six groups by their total sizes (≤5, 6–10, 11–15, 16–20, 21–25, and 26–30 mm), the numbers of patients in each group were calculated to be 0 (0%), 30 (7%), 77 (19%), 121 (29%), 101 (25%), and 84 (20%), respectively. The tumors were also classified according to the sizes of only the solid component in the same manner, and the numbers of patients in each group were 37 (9%), 53 (13%), 88 (21%), 104 (25%), 78 (19%), and 53 (13%), respectively. The total tumor sizes of those 37 patients were measured, and there were 11 patients in the 6 to 10 mm group,

13 in the 11 to 15 mm group, eight in the 16 to 20 mm, two in the 21 to 25 mm, and three in the 26 to 30 mm groups.

Frequency of Lymph Node Metastasis

The average numbers of dissected lymph nodes and dissected lymph node stations were 17.6 (range, 6–57) and 4.6, respectively. Seventy-five patients (18%) were postoperatively discovered to have positive nodes. Forty-one of those patients (10%) were diagnosed with pathologically positive N1 nodes, and 34 patients (8%) were diagnosed with pathologically positive N2 nodes. The average number of involved lymph nodes was 4.4 (1–12) in patients who experienced lymph node metastasis. The mean total number of dissected lymph nodes was 16.8 and 8.8 in the lobectomy and segmentectomy group, and there were no positive nodes in the segmentectomy group.

Correlation between Total Tumor Size and LN Metastasis

The proportions of node metastasis in each total size group in order from the smallest diameter to the largest (≤5, 6–10, 11–15, 16–20, 21–25, and 26–30 mm) were 0/1 (0%), 0/30 (0%), 5/77 (7%), 17/121 (14%), 27/101 (27%), and 26/84 (31%), respectively, which showed a statistically significant increase in the rate of the lymph node metastasis with increasing tumor size ($p < 0.001$) (Table 2).

Correlation between Solid Component Size and LN Metastasis

The rates of node metastasis in each invasive size group were 0/37 (0%), 1/53 (2%), 9/88 (10%), 17/104 (16%), 23/78 (30%), and 25/53 (47%), respectively, which also showed a statistically significant increase in the rates of lymph node metastasis with increasing solid component size ($p < 0.001$) (Table 2).

Comparison of Predictability of LN Metastasis by Total Size and Solid Size

Predictability of lymph node metastasis was evaluated by using a receiver operating characteristic curve. The AUC for the total size of the tumor was measured as 0.701 (95% CI = 0.641–0.761), and that for the solid size of the tumor was measured as 0.777 (95% CI = 0.724–0.829; Fig. 2). This result showed that the use of the solid size would produce more accurate predictions of lymph node metastasis. For the ever-smokers and nonsmokers, the AUC for the total tumor size and the solid size were 0.680/0.740 and 0.713/0.800, respectively.

Correlation between Tumor Size and Node Location

In terms of the metastatic nodes by location, the frequency of N1 involvement was the same in the 26 to 30 mm group as in the 21 to 25 mm group on the basis of the solid size of the tumors (Table 3). However, there was a positive correlation presented between the frequency of N2 involvement and the solid size of the tumor. There was no metastatic N2 found in the tumors smaller than 10 mm.

TABLE 1. Patient Characteristics	
Variables	**Frequency**
Sex, *n* (%)	
Male	198 (47.9)
Female	215 (52.1)
Age, yr, mean (range)	62.0 (26–84)
Smoking, *n* (%)	
Never	247 (59.8)
Exsmoker	106 (25.7)
Current smoker	60 (14.5)
Consistency on CT, *n* (%)	
Partly solid	191 (46.2)
Pure solid	222 (53.8)
Consistency on pathology, *n* (%)	
Including in situ component	155 (37.5)
Invasive only	258 (62.5)
Extent of surgery, *n* (%)	
Lobectomy	378 (91.8)
Segmentectomy	34 (8.2)
CT, computed tomography.	

TABLE 2. Correlation between Tumor Size and LN Metastasis

Size (mm)	≤5	5<, ≤10	10<, ≤15	15<, ≤20	20<, ≤25	25<, ≤30	*p*
Total size, *n* (%)	0 (0.0)	30 (7.0)	77 (18.6)	121 (29.3)	101 (24.5)	84 (20.3)	
Positive LN, *n* (%)	0 (0.0)	0 (0.0)	5 (6.5)	17 (14.0)	27 (26.7)	26 (30.9)	<0.001
Solid size, *n* (%)	37 (9.0)	53 (12.8)	88 (21.3)	104 (25.2)	78 (18.9)	53 (12.8)	
Positive LN, *n* (%)	0 (0.0)	1 (1.9)	9 (10.2)	17 (16.3)	23 (29.5)	25 (47.2)	<0.001

LN, lymph node.

Stations of Metastatic LNs According to Tumor Locating Lobes

Multistation N1 lymph node metastasis was common in the tumors located in the right upper lobe or left lower lobe (Table 4). In N2 lymph node metastasis, the upper zone was a common site of LN metastasis from the right upper lobe tumors, the aortopulmonary zone from the LUL tumors, and the subcarinal zone from the tumors located in both lower lobes.

Correlation of Other Factors with LN Metastasis

The mean SUVmax was 3.3, and mean SUVmax of the node-negative patients and node-positive patients were 2.4 and 4.9, respectively, which were significantly different ($p < 0.001$) (Table 5). However, there was no significant difference between N1- and N2-positive patients (4.9 in N1 versus 4.5 in N2, $p = 0.418$).

At a cutoff value of 2.5, patients with a high SUVmax (66 of 183, 36%) had a greater incidence of LN metastasis compared with that in those with a low value (9 of 230, 4%).

FIGURE 2. ROC curves showed the predictability of lymph node metastasis based on the total size and solid size. The AUC for the total size was 0.701 and that for the solid size was 0.777. ROC, receiver operating characteristic; AUC, area under the curve; CT, computed tomography.

The eight of 17 (47%) of the centrally located tumors and 67 of 396 (17%) of the peripheral tumors showed LN metastasis, respectively, and this was statistically significant. LN metastasis was evaluated according to tumor differentiation, and the frequencies of LN metastasis were 10% (6 of 63) in well, 18% (15 of 82) in moderate, and 35% (7 of 20) in poor differentiation. LN metastasis was found in 38 of 302 (13%) of the tumors with no visceral pleural invasion and 37 of 111 (37%) of the tumors with visceral pleural invasion. By multivariate analysis, solid size (cutoff value = 2.0), SUVmax (cutoff value = 2.5), and lymphovascular invasion were independent significant predictive factors for LN metastasis.

DISCUSSION

This study focused on analyzing the tumor size and its association with lymph node metastasis in lung adenocarcinoma with a size of 30 mm or smaller. Generally, the frequency of lymph node metastasis has been known to increase as the tumor size increases,[10–12] and the data from this study were in accordance with this, showing a sequential increase in the rate of node metastasis from the smallest tumor group (2%) to the largest tumor group (40%). There are several well-known factors for lymph node metastasis in non–small-cell lung cancer, such as the degree of differentiation, visceral pleural invasion, amount of GGO, lymphovascular invasion, and tumor size,[7,10,13–16] and rather than acting individually, these factors interact together and influence lymph node metastasis. In our study, solid size, SUVmax, and lymphovascular invasion were statistically independent risk factors for lymph node metastasis by multivariate analysis. Okada et al. identified 2.5 as an optimal cutoff value for the SUVmax to predict high-grade malignancy and concluded that SUVmax is a significant preoperative predictor for surgical outcomes in clinical stage IA adenocarcinoma.

However, until now, few studies have evaluated LN metastasis by precise tumor size in adenocarcinoma less than 30 mm. Especially, given that the detection of adenocarcinoma with GGO in asymptomatic patients has increased, it is important to evaluate the maximum size of a tumor that can be expected not to be associated with lymph node metastasis.

Lobectomy with systemic mediastinal lymph node dissection has been believed to be the appropriate surgical procedure for pathologic stage IA lung cancer because a prospective randomized trial was performed by the Lung Cancer Study Group.[17] However, it may not be appropriate to simply apply the old theory to the treatment of lung cancer recently detected by CT screening programs. Therefore, many studies on the feasibility of limited resection for small lung cancer
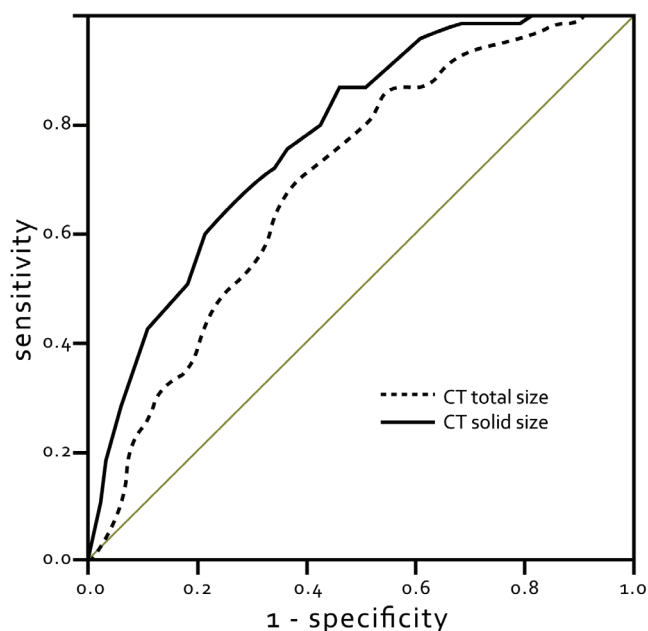
TABLE 3. Correlation between Solid Size of Tumor and Positive Lymph Node Location

Solid Size (mm)	≤5	5<, ≤10	10<, ≤15	15<, ≤20	20<, ≤25	25<, ≤30
N0, n (%)	37 (10.9)	52 (15.4)	79 (23.4)	87 (25.7)	55 (16.3)	28 (8.3)
N1, n (%)	0 (0.0)	1 (2.4)	2 (4.9)	10 (24.4)	14 (34.1)	14 (34.1)
N2, n (%)	0 (0.0)	0 (0.0)	7 (20.6)	7 (20.6)	9 (26.5)	11 (32.4)

tumors are being carried out.[5,18] The major concern at this point is that a critical range for the tumor diameter with which there is no lymph node metastasis found should be identified. If we could identify tumors within this size range preoperatively, limited resection without lymph node dissection could be performed safely for these cases. Oda et al.[11] reported a 22% incidence of node metastasis among 524 patients with non–small-cell lung cancer and noted that none of the patients with adenocarcinoma with a size of 10 mm or smaller presented lymph node metastasis, whereas there was a 20.8% incidence of lymph node metastasis in adenocarcinoma tumors with a size of 11 to 20 mm. Tsutani et al.[16] suggested that pathologic node-negative criteria such as a solid tumor size less than 8 mm on high-resolution CT may be helpful for avoiding systemic lymphadenectomy for clinical stage IA lung adenocarcinoma. We determined that there was no lymph node metastasis found in tumors with a solid component size of 5 mm or smaller, and only one patient experienced lymph node metastasis among 53 patients who had a tumor with a solid size of 10 mm or smaller. This patient, in fact, presented a 7-mm-sized invasive component, which means that all the patients with a solid tumor size smaller than 7 mm had no lymph node metastasis. On the basis of the findings from the present study, lymph node dissection seems to be unnecessary in tumors with an invasive size of 5 mm or smaller.

Another important aim of this study was analyzing whether the total size or the solid size of the tumor is a more reliable factor for predicting lymph node metastasis. In patients with adenocarcinoma combined with an in situ component, although both the total tumor size and the solid component size were found to be important factors for lymph node involvement, the size of the solid component has generally been considered a more reliable factor. Furthermore, the solid component shown on preoperative CT was closely correlated with the invasive component on pathologic examination. Yanagawa et al. showed that the total tumor size was not correlated with disease-free survival (DFS), whereas the invasive tumor size was significantly correlated with DFS. They reported that DFS in patients with an invasive tumor smaller than 5 mm was 100% and noted that the invasive tumor size is a very useful predictor of recurrence.[19] The present study also found that the size of the solid component is a more useful factor than the total tumor size for predicting lymph node metastasis. Therefore, as a factor for predicting lymph node metastasis, the evaluation of the solid size, rather than the total tumor size, is suggested in patients with adenocarcinoma with an in situ component.

A high SUVmax of a tumor is known to be correlated with advanced stage, poor survival, or recurrence in adenocarcinoma.[20] Miyata et al. identified an optimal cutoff value of 2.5 for the SUVmax to predict high-grade malignancy and reported 21.4% LN metastasis in patients with an SUVmax of greater than 2.5. They concluded that a high SUVmax significantly correlated with a high carcinoembryonic antigen level, lymphatic invasion, vascular invasion, pleural invasion, and lymph node metastasis.[21] In present study, the mean SUVmax of node-positive patients was significantly higher than that of the node-negative patients, and 36% of the patients with an SUVmax of 2.5 or greater had LN metastasis.

TABLE 4. Station of Metastatic Lymph Nodes According to Tumor Locating Lobes

	RUL (n = 138)	RML (n = 44)	RLL (n = 78)	LUL (n = 94)	LLL (n = 68)
N1, n (%)					
Hilar	1 (5.3)	0 (0.0)	1 (8.3)	1 (4.8)	0 (0.0)
Interlobar	5 (26.3)	2 (28.6)	6 (50.0)	2 (9.5)	0 (0.0)
Lobar	7 (36.8)	4 (57.1)	3 (25.0)	16 (76.2)	1 (11.1)
Hilar + interlobar	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)
Hilar + lobar	2 (10.5)	0 (0.0)	1 (8.3)	1 (4.8)	1 (11.1)
Interlobar + lobar	2 (10.5)	1 (14.3)	1 (8.3)	0 (0.0)	4 (44.4)
Hilar + interlobar + lobar	2 (10.5)	0 (0.0)	0 (0.0)	1 (4.8)	2 (22.2)
N2, n (%)					
Upper	6 (85.7)	1 (16.7)	0 (0.0)	1 (9.1)	0 (0.0)
Subcarinal	1 (14.3)	1 (16.7)	3 (100.0)	0 (0.0)	3 (42.9)
AP window	0 (0.0)	0 (0.0)	0 (0.0)	8 (72.7)	2 (28.6)
Two stations	0 (0.0)	4 (66.7)	0 (0.0)	0 (0.0)	2 (28.6)
Three stations	0 (0.0)	0 (0.0)	0 (0.0)	2 (18.2)	0 (0.0)

RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe, LUL, left upper lobe; LLL, left lower lobe; AP, aortopulmonary.

TABLE 5. Univariate and Multivariate Analyses of Positive Node

	Node Negative	Node Positive	Univariate Analysis	Multivariate Analysis HR (95% CI)
Total size, *n* (%)			<0.001	0.888 1.190 (0.106–13.339)
≤2.0	206 (90.4)	22 (9.6)		
>2.0	132 (71.4)	53 (28.6)		
Solid size, *n* (%)			<0.001	0.048 9.627 (0.923–100.390)
≤2.0	255 (90.4)	27 (9.6)		
>2.0	83 (63.4)	48 (36.6)		
SUVmax, *n* (%)			<0.001	0.001 16.885 (3.166–90.054)
≤2.5	221 (96.1)	9 (3.9)		
>2.5	117 (63.9)	66 (36.1)		
Differentiation, *n* (%)			0.045	0.221 0.31 (0.112–1.660)
Well	57 (90.5)	6 (9.5)		
Moderate/poor	80 (78.4)	22 (21.6)		
VPI, *n* (%)			<0.001	0.181 2.183 (0.696–6.845)
No	264 (87.4)	38 (12.6)		
Yes	74 (66.7)	37 (33.3)		
LVI, *n* (%)			<0.001	0.024 3.816 (1.188–12.253)
No	231 (93.1)	17 (6.9)		
Yes	107 (64.8)	58 (35.2)		

VPI, visceral pleural invasion; LVI, lymphovascular invasion; SUVmax, maximum standardized uptake value; HR, hazard ratio; CI, confidence interval.

CONCLUSIONS

Solid size, SUVmax, and lymphovascular invasion were independent predictors for lymph node metastasis of lung adenocarcinoma. There was no lymph node metastasis detected in patients with adenocarcinoma combined with an in situ component in which the solid component size was 5 mm or smaller. The size of the solid component explained the relation between the tumor size and the lymph node metastasis more accurately than that explained by the total tumor size. On the basis of the results from this study, a reliable guideline could be established to avoid unnecessary limited resection or lymph node dissection.

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