Risk factors of lymph node metastasis in patients with non-small cell lung cancer ≤ 2 cm in size: A monocentric population-based analysis

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Abstract
Aim: This study was designed to determine the risk factors of lymph node metastasis in non-small cell lung cancer (NSCLC) patients with tumors ≤ 2 cm, using the Shanghai Chest Hospital Lung Cancer Database.

Methods: Five hundred and eighteen patients with NSCLC ≤ 2 cm were included in this study, and were classified into lymph node-positive and lymph node-negative groups. Univariate and multivariate logistic regression analyses were performed to select the independent risk factors for lymph node metastasis in NSCLC patients.

Results: No evidence of metastasis was found in tumors ≤ 1 cm, all positive results were in tumors sized 1–2 cm. Imaging characteristics, including solid and part-solid nodules, were strongly associated with lymph node metastasis (odds ratio [OR] 24.959, 95% confidence interval [CI] 5.999–103.835, \( P < 0.001 \); OR 12.559, 95% CI 3.564–44.259, \( P < 0.001 \)) and subgroup logistic analysis (OR 21.384, 95% CI 5.058–90.407, \( P < 0.001 \); OR 11.632, 95% CI 3.290–41.126, \( P < 0.001 \)). Greater lymph node metastasis was observed in non-adeno non-squamous carcinoma. The presence of pleural invasion and carcinoembryonic antigen levels indicated lymph node dissection. Similar results were revealed in subgroup analysis in tumors ≤ 2 to > 1 cm.

Conclusion: Size had a great impact on lymph node metastasis, especially tumors of 1–2 cm. Preoperative imaging, non-adeno non-squamous carcinoma, pleural invasion, and carcinoembryonic antigen all indicated lymph node dissection. There was no discrepancy between N1 and N2 positive lymph nodes.

Introduction
Lung cancer is the leading cause of death all over the world, but particularly in China.¹ Standard lobectomy with systemic lymph node dissection has become the recommended surgical treatment for clinical stage I non-small cell lung cancer (NSCLC) since a randomized controlled trial performed in 1995 recommended lobectomy as the best approach for stage I NSCLC patients.² The wide use of computed tomography (CT) has allowed for the detection of more small-sized nodules, especially greater quantities of small-sized ground grass opacities (GGOs)³ thus, the use of classic and traditional anatomic resection (lobectomy) for lymph node dissection is being challenged.

It is well-known that lymph node evaluation of lung cancer can be classified into two groups, systemic lymph node dissection (SND) and lymph node sampling,⁴,⁵ both of which play a significant role in evaluating lymph node metastasis and pathological N stage of lung cancer. It is difficult for surgeons to decide whether lymph node dissection is appropriate for patients with relatively good radiographic results but a poor general condition.

In this study, we retrospectively analyzed small-sized (≤ 2 cm) tumors in NSCLC patients who underwent lobectomy and lymph node dissection at the Shanghai Chest Hospital from 2012 to 2014 to determine the potential risk factors for lymph node metastasis in such patients.
Methods

Patients

We retrospectively collected the records of consecutive patients with NSCLC tumors \( \leq 2 \) cm who had undergone lobectomy and lymph node dissection (including SND and lymph node sampling) at Shanghai Chest Hospital from 2012 to 2014. Inclusion criteria were: (i) single NSCLC, patient underwent anatomic resection and lymph node dissection, proven by final pathology; (ii) the tumor was \( \leq 2 \) cm; and (iii) lymph node dissection included SND and lymph node sampling. Patients were excluded for: (i) multiple lung cancer or small cell lung cancer, (ii) suspicious lymphadenectasis (hilum and/or mediastinum lymph node \( \geq 1 \) cm in size) detected by CT scan or other techniques, and (iii) local or distant metastasis.

All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from each patient to permit genetic analysis of biological samples.

The patients were divided into two groups: lymph node-positive and lymph node-negative. The baseline characteristics of these patients were gender, age, smoking history, family history, tumor location, imaging characteristics, pathology, size of tumor, pleural invasion (PI), the number of harvested lymph nodes, and serum tumor marker (carcinoembryonic antigen [CEA]) level, all of which were collected from the Shanghai Chest Hospital Lung Cancer database. Family history was defined whether there was the malignancy in a family member or not. Imaging characteristics included pure ground-grass nodules (pGGN), mixed ground-grass nodules (mGGN), and solid nodules. Pathology was classified into adenocarcinoma (ADC), squamous cell carcinoma (SCC), and other types of lung cancer according to final pathology. The size of tumor was divided into \( \leq 1 \) and \( \leq 2 \) cm in accordance with the 8th Tumor Node Metastasis (TNM) Classification for Lung Cancer. CEA level was tested before surgery and a normal level was considered \(< 5.0 \mu \text{g/L} \).

Statistical analysis

Pearson \( \chi^2 \) and Fisher’s exact tests and \( t \)-tests were conducted to analyze the categorical and continuous variables, respectively. Univariable and multivariable logistic regression analyses were performed to select the independent risk factors for lymph node metastasis in NSCLC. Subgroup analysis was also performed according to the size of tumor, and the univariate and multivariate logistic regressions were subsequently analyzed. Statistical significance was set at \( P < 0.05 \). All analyses were performed using SPSS version 20.0 (IBM Corp., Armonk, NY, USA).

Results

A total of 518 patients with NSCLC tumors \( \leq 2 \) cm were included in this study: 53 patients with positive lymph nodes and 465 with negative lymph nodes, proven by final pathology. The positive rate of N2 was 2.12% (11/518), the

Table 1  Clinicopathological characteristics of lymph node positive and negative groups and univariate logistic regression analysis in clinical T1a NSCLC patients

| Characteristic | LN(−)(%) | LN(+) (%) | Univariable logistic |
|---------------|----------|-----------|---------------------|
| Gender        |          |           |                     |
| Male          | 184 (39.6) | 23 (43.4) | 0.590               |
| Female        | 281 (60.4) | 30 (56.6) | —                   |
| Age           |          |           |                     |
| \( \leq 60 \)  | 291 (62.6) | 30 (56.6) | 0.396               |
| \( >60 \)     | 174 (37.4) | 23 (43.4) | —                   |
| Smoke history |          |           |                     |
| No            | 405 (87.1) | 43 (81.1) | 0.229               |
| Yes           | 60 (12.9)  | 10 (18.9) | —                   |
| Family history|          |           |                     |
| No            | 453 (97.4) | 51 (96.2) | 0.612               |
| Yes           | 12 (2.6)   | 2 (3.8)   | —                   |
| Location      |          |           |                     |
| RUL           | 172 (37.0) | 17 (32.1) | 0.477               |
| RML           | 36 (7.7)   | 5 (9.4)   | —                   |
| RLL           | 78 (16.8)  | 7 (13.2)  | —                   |
| LUL           | 112 (24.1) | 16 (30.2) | —                   |
| Imaging       |          |           |                     |
| LLL           | 67 (14.4)  | 8 (15.1)  | <0.001              |
| pGGN          | 255 (54.8) | 3 (5.7)   | —                   |
| mGGN          | 57 (12.3)  | 9 (17.0)  | —                   |
| Solid         | 153 (32.9) | 41 (77.3) | —                   |
| Pathology     |          |           |                     |
| ADC           | 440 (94.6) | 46 (86.8) | 0.008               |
| SCC           | 12 (2.6)   | 1 (1.9)   | —                   |
| Others        | 13 (2.8)   | 6 (11.3)  | —                   |
| Size          |          |           |                     |
| \( \leq 1 \) cm | 122 (26.2) | 0 (0)     | 0.966               |
| \( \leq 2 \) cm | 343 (73.8) | 53 (100.0)| —                   |
| PI            |          |           |                     |
| No            | 431 (92.7) | 24 (45.3) | <0.001              |
| Yes           | 34 (7.3)   | 29 (54.7) | —                   |
| HLN           |          |           |                     |
| Average       | 6.85      | 7.13      | 0.589               |
| CEA           |          |           |                     |
| Normal        | 424 (91.2) | 41 (77.4) | <0.001              |
| Abnormal      | 41 (8.8)  | 15 (22.6) | —                   |

ADC, adenocarcinoma; HLN, harvested lymph node; LLL, left lower lobe; LN, lymph node; LUL, left upper lobe; mGGN, mixed ground-grass nodules; NSCLC, non-small cell lung cancer; pGGN, pure ground-grass nodules; PI, pleural invasion; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe; SCC, squamous cell carcinoma.
positive rate of N1 was 2.90% (15/518), and positive rate of N1 and N2 was 5.21% (27/518). In total, 3565 lymph nodes were harvested, including 2176 for N2 and 1389 for N1. The average number of harvested lymph nodes was 6.88, with averages of 4.20 for N2 and 2.88 for N1. The clinicopathological characteristics of the groups are listed in Table 1. A surprising result was that there were no lymph node metastases < 1 cm. Univariate logistic analysis was performed to determine the potential risk factors for lymph node metastasis. Compared to the lymph node-negative group, the lymph node-positive group demonstrated significant differences in imaging characteristics (P < 0.001), pathological type (P = 0.008), PI (P < 0.001), and high CEA level (P < 0.001), while there were no discrepancies with other variables (Table 1). After univariate logistic regression analysis, the potential risk factors were entered into multivariable analysis using SPSS version 20.0. Specifically, the imaging containing solid or mGGN characteristics had a strong relationship to lymph node metastasis. In detail, mGGN and solid nodules definitely indicated local and mediastinal lymph node metastasis when compared to pGGN (odds ratio [OR] 24.959, 95% confidence interval [CI] 5.999–103.835, P < 0.001; OR 12.559, 95% CI 3.564–44.259, P = 0.004, respectively). Regarding the pathology subtype, SCC did not display any difference (P = 0.463), while other types demonstrated a discrepancy (OR 3.745, 95% CI 1.078–13.010, P = 0.038) compared to ADC. PI (OR 14.827, 95% CI 6.565–33.490, P < 0.001) and CEA (OR 3.704, 95% CI 1.518–9.037, P = 0.004) were also risk factors of lymph node metastasis according to the results of multivariate logistic analysis (Table 2).

We also conducted subgroup analysis of tumor size, because lymph node metastasis did not occur in tumors ≤ 1 cm in our study compared to tumors sized ≤ 2 to > 1 cm. Univariate and multivariate logistic analyses were successively performed in the subgroup of ≤ 2 to > 1 cm. Similar to our previous results, mGGN and solid nodules played significant roles in indicating potential lymph node metastasis against pGGN (OR 21.384, 95% CI 5.058–90.407, P < 0.001; OR 11.632, 95% CI 3.290–41.126, P < 0.001, respectively). There was no statistical difference in lymph node metastasis between SCC and ADC (P = 0.382), but other types of lung cancer had a stronger tendency to metastasize compared to ADC (OR 3.712, 95% CI 1.035–13.319, P = 0.044). PI (OR 12.001, 95% CI 5.293–27.212, P < 0.001) and CEA (OR 3.218, 95% CI 1.321–7.843, P = 0.010) were associated with lymph node metastasis (Table 3).

In this study, we also compared the clinicopathological characteristics of N1-positive, N2-positive (mediastinal lymph node), and N1+2-positive groups according to the status of metastasis. It was surprising that there were no apparent differences in statistics, except for the N1+2-positive group in which a greater number of lymph nodes were harvested during dissection (Table 4). With respect to N1 and N2 subgroups, we sought to determine the potential risk factors using univariate and multivariate logistic analyses. Disappointingly, there seemed to be no discrepancy in statistics between N1-positive and N2-positive (including N1+2) groups (Table 5).

### Discussion

Lymph node status in NSCLC, especially pathological status, is of great importance, not only for prognosis but also to guide postoperative therapeutic strategy. Lymph node dissection is often indicated and is indeed essential, especially during surgery for cT1a-2bN0-1M0 NSCLC.
Tumor size is considered an important risk factor for lymph node metastasis, and can be detected by preoperative radiology.\textsuperscript{2} Zhang \textit{et al.} demonstrated a prevalence of lymph node metastasis of 7.4\% in tumors 1–2 cm, and 3.8\% in tumors < 1 cm.\textsuperscript{8} In this study, 53 patients had pathological lymph node metastasis of tumors 1–2 cm, while there was no evidence of metastasis in tumors < 1 cm. This finding could indicate a tendency of lymph node metastasis to increase with tumor size, especially in tumors ≤ 2 cm. These results were consistent with those determined by Asamura \textit{et al.}.\textsuperscript{9}

In this study, preoperative imaging characteristics, pathology subtype, PI, and serum CEA level before surgery were considered independent risk factors indicating lymph node metastasis in NSCLC patients. Similar results were found in subgroup analysis of tumor size.

Regarding imaging characteristics, mGGN and solid nodules were correlated with a higher rate of local and mediastinal lymph node metastasis when compared to pure GGO, evident by the appearance of a solid component in the imaging scans, strongly indicating the existence of a much more invasive component or pathological subtype. Thus, the characteristics of preoperative CT scanning could represent a much more convenient and reliable strategy for deciding whether to perform lymph node dissection during surgery.

There was no statistical difference between ADC and SCC, but other types of pathology demonstrated statistic

| Characteristic   | Univariate |          |          |          |          |          |
|------------------|------------|----------|----------|----------|----------|----------|
|                  | B         | SE       | Wald     | P        | OR       | 95\% CI  |
| Gender           |           |          |          |          |          |          |
| Male             | 0.973     |          |          |          |          |          |
| Female           | —         |          |          |          |          |          |
| Age              |           |          |          |          |          |          |
| ≤60              | 0.932     |          |          |          |          |          |
| >60              | —         |          |          |          |          |          |
| Smoking history  |           |          |          |          |          |          |
| No               | 0.350     |          |          |          |          |          |
| Yes              | —         |          |          |          |          |          |
| Family history   |           |          |          |          |          |          |
| No               | 0.635     |          |          |          |          |          |
| Yes              | —         |          |          |          |          |          |
| Location         |           |          |          |          |          |          |
| RUL              | 0.462     |          |          |          |          |          |
| RML              | —         |          |          |          |          |          |
| RLL              | —         |          |          |          |          |          |
| LUL              | —         |          |          |          |          |          |
| Imaging          |           |          |          |          |          |          |
| LLL              | —         |          |          |          |          |          |
| pGGN             | <0.001    | 3.063    | 0.736    | 17.335   | <0.001   | 21.384   |
| mGGN             | —         | 2.454    | 0.644    | 14.053   | <0.001   | 11.632   |
| Solid            | —         |          |          |          |          |          |
| Pathology        |           |          |          |          |          |          |
| ADC              | 0.021     | —        |          |          |          |          |
| SCC              | —         | -0.976   | 1.117    | 0.764    | 0.382    | 0.377    |
| Others           | —         | 1.312    | 0.652    | 4.049    | 0.044    | 3.712    |
| PI               |           |          |          |          |          |          |
| No               | <0.001    | 2.485    | 0.418    | 35.395   | <0.001   | 12.001   |
| Yes              | —         |          |          |          |          |          |
| HLN              | 0.864     | —        |          |          | —        |          |
| CEA              |           |          |          |          |          |          |
| Normal           | <0.001    | 1.169    | 0.454    | 6.615    | 0.010    | 3.218    |
| Abnormal         | —         |          |          |          |          |          |
| Constant         | —         | -4.874   | 0.645    | 57.075   | <0.001   | 0.008    |

ADC, adenocarcinoma; CEA, carcinoembryonic antigen; CI, confidence interval; LLL, left lower lobe; HLN, harvested lymph node; LUL, left upper lobe; mGGN, mixed ground-grass nodules; NSCLC, non-small cell lung cancer; pGGN, pure ground-grass nodules; PI, pleural invasion; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe; SCC, squamous cell carcinoma; SE, standard error.
significance in subgroup analysis, with ORs of > 5 to > 6 indicating a close relationship with lymph node metastasis. With regard to ADC, although several types of ADC, such as adenocarcinoma in situ and minimally invasive adenocarcinoma, did not tend to spread to lymph nodes\textsuperscript{10} and GGO-predominant tumors displayed a low incidence of mediastinal lymph node metastasis,\textsuperscript{11} it is well-known that invasive adenocarcinoma possesses the metastatic ability to progress to regional lymph nodes and even occult lymph node metastasis.\textsuperscript{12} Subtypes, such as micropapillary-predominant adenocarcinoma, are even related to a higher likelihood of metastasis and poor prognosis.\textsuperscript{13}

Pleural invasion is another significant risk factor associated with a greater tendency for lymph node metastasis, with the highest ORs in univariate and multivariate logistic analyses. Not only were more lymph nodes involved, but PI also indicated a high risk of systemic metastasis because the tumor cells could be reabsorbed by the parietal pleura after desquamating from visceral pleura.\textsuperscript{14,15}

It is well known that there is a relationship between the serum CEA level and mediastinal lymph node metastasis in patients with clinical stage I A NSCLC.\textsuperscript{16,17} Inoue \textit{et al.} reported that higher CEA levels corresponded with higher five-year mortality among patients with NSCLC tumors ≤

**Table 4** Clinicopathological characteristics of N1-positive, N2-positive, and N1+2-positive groups

| Characteristics | N1(%) | N2(%) | N1 + 2(%) | P   |
|----------------|-------|-------|-----------|-----|
| Gender         |       |       |           |     |
| Male           | 6 (40.0) | 5 (45.5) | 12 (44.4) | 0.951 |
| Female         | 9 (60.0)  | 6 (54.5)  | 15 (55.6)  | —    |
| Age            |       |       |           |     |
| ≤60            | 10 (66.7) | 4 (36.4)  | 16 (59.3)  | 0.282 |
| >60            | 5 (33.3)  | 7 (63.6)  | 11 (40.7)  | —    |
| Smoking history|       |       |           |     |
| No             | 12 (80.0) | 10 (90.9) | 21 (77.8)  | 0.718 |
| Yes            | 3 (20.0)  | 1 (9.1)   | 5 (22.2)   | —    |
| Family history |       |       |           |     |
| No             | 15 (100)  | 11 (100)  | 25 (92.6)  | 0.368 |
| Yes            | 0 (0)     | 0 (0)     | 2 (7.4)    | —    |
| Location       |       |       |           |     |
| RUL            | 5 (33.4)  | 2 (18.2)  | 10 (37.0)  | 0.986 |
| RML            | 2 (13.3)  | 1 (9.1)   | 2 (7.4)    | —    |
| RLL            | 2 (13.3)  | 2 (18.2)  | 3 (11.1)   | —    |
| LUL            | 4 (26.7)  | 4 (26.3)  | 8 (29.7)   | —    |
| LLL            | 2 (13.3)  | 2 (18.2)  | 4 (14.8)   | —    |
| Imaging        |       |       |           |     |
| pGGN           | 2 (13.3)  | 1 (9.1)   | 0 (0)      | 0.117 |
| mGGN           | 0 (0)     | 2 (18.2)  | 7 (25.9)   | —    |
| Solid          | 13 (86.7) | 8 (72.7)  | 20 (74.1)  | —    |
| Pathology      |       |       |           |     |
| ADC            | 13 (86.6) | 10 (90.9) | 23 (85.2)  | 0.527 |
| SCC            | 1 (6.7)   | 0 (0)    | 0 (0)      | —    |
| Others         | 1 (6.7)   | 1 (9.1)   | 4 (14.8)   | —    |
| PI             |       |       |           |     |
| No             | 6 (40.0)  | 5 (45.5)  | 13 (48.1)  | 0.879 |
| Yes            | 9 (60.0)  | 6 (54.5)  | 14 (51.9)  | —    |
| HLN            |       |       |           |     |
| Average        | 6.27     | 5.18     | 8.41       | 0.038 |
| CEA            |       |       |           |     |
| Normal         | 11 (73.3) | 9 (81.8)  | 18 (66.7)  | 0.634 |
| Abnormal       | 4 (26.7)  | 2 (18.2)  | 9 (33.3)   | —    |

ADC, adenocarcinoma; CEA, carcinoembryonic antigen; HLN, harvested lymph node; LLL, left lower lobe; LUL, left upper lobe; mGGN, mixed ground-grass nodules; pGGN, pure ground-grass nodules; PI, pleural invasion; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe; SCC, squamous cell carcinoma.

**Table 5** Univariate and multivariate logistic analyses of N1-positive and N2-positive groups

| Characteristics | Univariate | Multivariate |
|-----------------|------------|--------------|
|                 | B          | SE | Wald | df | P  | OR |
| Gender          |            |    |      |    |    |    |
| Male            | 0.696      | —  | —    | —  | —  | —  |
| Female          |            |    |      |    |    |    |
| Age             |            |    |      |    |    |    |
| ≤60             | 0.314      | —  | —    | —  | —  | —  |
| >60             |            |    |      |    |    |    |
| Smoking history |            |    |      |    |    |    |
| No              | 0.929      | —  | —    | —  | —  | —  |
| Yes             |            |    |      |    |    |    |
| Family history  |            |    |      |    |    |    |
| No              | 0.358      | —  | —    | —  | —  | —  |
| Yes             |            |    |      |    |    |    |
| Location        |            |    |      |    |    |    |
| RUL             | 0.732      | —  | —    | —  | —  | —  |
| RML             |            |    |      |    |    |    |
| RLL             |            |    |      |    |    |    |
| LUL             |            |    |      |    |    |    |
| LLL             |            |    |      |    |    |    |
| Imaging         |            |    |      |    |    |    |
| pGGN            | 0.983      | —  | —    | —  | —  | —  |
| mGGN            |            |    |      |    |    |    |
| Solid           |            |    |      |    |    |    |
| Pathology       |            |    |      |    |    |    |
| ADC             | 0.723      | —  | —    | —  | —  | —  |
| SCC             |            |    |      |    |    |    |
| Others          |            |    |      |    |    |    |
| PI              |            |    |      |    |    |    |
| No              | 0.696      | —  | —    | —  | —  | —  |
| Yes             |            |    |      |    |    |    |
| HLN             |            |    |      |    |    |    |
| Average         | 0.273      | —  | —    | —  | —  | —  |
| CEA             |            |    |      |    |    |    |
| Normal          | 0.825      | —  | —    | —  | —  | —  |
| Abnormal        |            |    |      |    |    |    |

ADC, adenocarcinoma; CEA, carcinoembryonic antigen; HLN, harvested lymph node; LLL, left lower lobe; LUL, left upper lobe; mGGN, mixed ground-grass nodules; pGGN, pure ground-grass nodules; PI, pleural invasion; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe; SCC, squamous cell carcinoma.
2 cm. In this study, an abnormal preoperative CEA level also showed a significant correlation to lymph node metastasis, which could be an indication to conduct lymph node dissection, even systemic dissection, when lower-lobar clinical stage I adenocarcinoma occurs, suggesting that high CEA levels are associated with upper mediastinal lymph node metastasis.

There are several techniques for lymph node dissection, including preoperative integrated fluorodeoxyglucose positron emission tomography/CT (PET/CT) and freezing sections of lymph nodes during surgery; however, it is much more feasible and practical for surgeons to make a decision using preoperative clinicopathological characteristics.

Although part of our study objective was to determine any difference between N1 and N2 patients, univariate and multivariate logistic analysis revealed no obvious discrepancy between these groups. Fewer lymph nodes were harvested in the N1 and N2 groups compared to the N1+2 group.

There were several limitations to this study. First, it was a retrospective analysis with a relatively limited number of patients and parameters, which may restrict the wide usage of our indications in clinics. Second, our research did not take recurrence and survival outcomes into consideration, which means that we may have overlooked some indications for lymph node dissection. This requires further investigation.

In conclusion, preoperative imaging characteristics are essential for indicating lymph node metastasis. Tumor size is also a significant risk factor for lymph node metastasis, especially in tumors of 1–2 cm. Non-adenocarcinoma and non-squamous subtypes of lung cancer (large cell lung cancer, carcinoid, etc.) demonstrate a higher risk of lymph node metastasis compared to ADC and SCC. PI and high preoperative CEA level are further risk factors for lymph node metastasis, indicating a need for dissection. There was no difference between N1 positive and N2 positive lymph nodes. Further research is required to determine whether there are any other potential risk factors for lymph node metastasis.

Disclosure
No authors report any conflict of interest.

References
1 Jemal A, Bray F, Center MM et al. Global cancer statistics. (Published erratum appears in CA Cancer J Clin 2011; 61: 134). CA Cancer J Clin 2011; 61: 69–90.
2 Ginsberg RJ, Rubinstein LV. Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer. Lung Cancer Study Group. Ann Thorac Surg 1995; 60: 615–22.
3 Son JY, Lee HY, Kim JH et al. Quantitative CT analysis of pulmonary ground-glass opacity nodules for distinguishing invasive adenocarcinoma from non-invasive or minimally invasive adenocarcinoma: The added value of using iodine mapping. Eur Radiol 2016; 26: 43–54.
4 Adachi H, Sakamaki K, Nishii T et al. Lobe-specific lymph node dissection as a standard procedure in surgery for non-small-cell lung cancer: A propensity score matching study. J Thorac Oncol 2017; 12: 85–93.
5 Moon Y, Sung SW, Namkoong M, Park JK. The effectiveness of mediastinal lymph node evaluation in a patient with ground glass opacity tumor. J Thorac Dis 2016; 8: 2617–25.
6 Lardinois D, De Leyn P, Van Schil P et al. ESTS guidelines for intraoperative lymph node staging in non-small cell lung cancer. Eur J Cardiothorac Surg 2006; 30: 787–92.
7 Bao F, Yuan P, Yuan X, Lv X, Wang Z, Hu J. Predictive risk factors for lymph node metastasis in patients with small size non-small cell lung cancer. J Thorac Dis 2014; 6: 1697–703.
8 Zhang Y, Sun Y, Shen L et al. Predictive factors of lymph node status in small peripheral non-small cell lung cancers: Tumor histology is more reliable. Ann Surg Oncol 2013; 20: 1949–54.
9 Asamura H, Nakayama H, Kondo H, Tsuchiya R, Shimosato Y, Naruke T. Lymph node involvement, recurrence, and prognosis in resected small, peripheral, non-small cell lung carcinomas: Are these carcinomas candidates for video-assisted lobectomy? J Thorac Cardiovasc Surg 1996; 111: 1125–34.
10 Travis WD, Brambilla E, Noguchi M et al. International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society International Multidisciplinary Classification of Lung Adenocarcinoma. J Thorac Oncol 2011; 6: 244–85.
11 Haruki T, Aokage K, Miyoshi T et al. Mediastinal nodal involvement in patients with clinical stage I non-small-cell lung cancer: Possibility of rational lymph node dissection. J Thorac Oncol 2015; 10: 930–6.
12 Kanzaki R, Higashiyama M, Fujiwara A et al. Occult mediastinal lymph node metastasis in NSCLC patients diagnosed as clinical N0-1 by preoperative integrated FDG-PET/CT and CT: Risk factors, pattern, and histopathological study. Lung Cancer 2011; 71: 333–7.
13 Russell PA, Wainer Z, Wright GM, Daniels M, Conron M, Williams RA. Does lung adenocarcinoma subtype predict patient survival? A clinicopathological study based on the new International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society international multidisciplinary lung adenocarcinoma classification. J Thorac Oncol 2011; 6: 1496–504.
14 Manach D, Riquet M, Medioni J, Le Pimpec-Barthes F, Dujon A, Danel C. Visceral pleura invasion by non-small cell lung cancer: An underrated bad prognostic factor. Ann Thorac Surg 2001; 71: 1088–93.
15 Riquet M, Badoual C, Le Pimpec Barthes F et al. Visceral pleura invasion and pleural lavage tumor cytology by lung cancer: A prospective appraisal. Ann Thorac Surg 2003; 75: 353–5.
16 Koike T, Koike T, Yamato Y, Yoshiya K, Toyabe S. Predictive risk factors for mediastinal lymph node metastasis in clinical stage IA non-small-cell lung cancer patients. J Thorac Oncol 2012; 7: 1246–51.
17 Grunnet M, Sorensen JB. Carcinoembryonic antigen (CEA) as tumor marker in lung cancer. Lung Cancer 2012; 76: 138–43.
18 Inoue M, Minami M, Shiono H, Sawabata N, Ideguchi K, Okumura M. Clinicopathologic study of resected, peripheral, small-sized, non-small cell lung cancer tumors of 2 cm or less in diameter: Pleural invasion and increase of serum carcinoembryonic antigen level as predictors of nodal involvement. J Thorac Cardiovasc Surg 2006; 131: 988–93.
19 Kaseda K, Asakura K, Kazama A, Ozawa Y. Risk factors for predicting occult lymph node metastasis in patients with clinical stage I non-small cell lung cancer staged by integrated fluorodeoxyglucose positron emission tomography/computed tomography. World J Surg 2016; 40: 2976–83.
20 Li W, Yang XN, Liao RQ et al. Intraoperative frozen sections of the regional lymph nodes contribute to surgical decision-making in non-small cell lung cancer patients. J Thorac Dis 2016; 8: 1974–80.