0003-4975/$36.00
https://doi.org/10.1016/j.athoracsur.2022.11.040

Lung: Research

# Importance of Lymph Node Evaluation in ≤2-cm Pure-Solid Non-Small Cell Lung Cancer

Soohwan Choi, MD,[1,2,*] Dong Woog Yoon, MD,[1,3,*] Sumin Shin, MD,[1,4] Hong Kwan Kim, MD,[1] Yong Soo Choi, MD,[1] Jhingook Kim, MD,[1] Young Mog Shim, MD,[1] and Jong Ho Cho, MD[1]

## ABSTRACT

**BACKGROUND** The prevalence of lymph node (LN) metastasis in small-sized lung cancer varies depending on the tumor size and proportion of ground-glass opacity. We investigated occult LN metastasis and prognosis in patients with small-sized non-small cell lung cancer (NSCLC), mainly focusing on the pure-solid tumor.

**METHODS** We retrospectively reviewed patients with ≤2-cm clinical N0 NSCLC who underwent lung resection with curative intent from 2003 to 2017. Among them we analyzed patients who also underwent adequate complete systematic LN dissection. Pathologic results and disease-free survival of the radiologically mixed ground-glass nodule (mGGN) and pure-solid nodule (PSN) groups were analyzed.

**RESULTS** Of 1329 patients analyzed, 591 had mGGNs and PSNs. As tumor size increased, patients in the mGGN group showed no difference in LN metastasis: ≤1 cm, 2.27%; 1.0 to 1.5 cm, 2.19%; and 1.5 to 2.0 cm, 2.18% ($P = .999$). However the PSN group showed a significant difference in LN metastasis as the tumor size increased: ≤1 cm, 2.67%; 1.0 to 1.5 cm, 12.46%; and 1.5 to 2.0 cm, 21.31% ($P < .001$). In the multivariate analysis tumor size was a significant predictor of nodal metastasis in the PSN group but not in the mGGN group. In terms of 5-year disease-free survival, the mGGN group showed a better prognosis than the PSN group (94.4% vs 71.2%, $P < .001$).

**CONCLUSIONS** We need to conduct a thorough LN dissection during surgery for small-sized NSCLC, especially for pure-solid tumors ≥ 1 cm.

(Ann Thorac Surg 2024;117:586-93)


Lymph node (LN) status is an invaluable component of TNM (tumor, node, metastasis) staging of non-small cell lung cancer (NSCLC).[1,2] To evaluate LN status, lobectomy with systematic mediastinal LN dissection has been a standard treatment for stage IA NSCLC.[3] However with a recent early detection program using high-resolution computed tomography (CT), diagnosis of early-stage NSCLC has increased.[4] Therefore many studies are underway to determine the optimal LN evaluation for better prognosis of early-stage NSCLC.

The relationship between tumor size and LN metastasis in early-stage NSCLC has been investigated. Some authors have argued that NSCLC < 1 cm in size shows no LN metastasis and that LN dissection procedures are not always necessary considering its associated complications.[5-7] In addition Oda and colleagues[8] reported an LN metastasis rate of 20.8% in adenocarcinomas 11 to 20 mm in size but a rate of 0% in tumors ≤ 10 mm. Seok and associates[9] reported no cases of LN metastasis in patients with solid tumors sized ≤ 5 mm. However Pani and associates[10] recommended that LN evaluation should always be performed when possible, even for

The Supplemental Material can be viewed in the online version of this article [10.1016/j.athoracsur.2022.11.040] on http://www.annalsthoracicsurgery.org.

Accepted for publication Nov 21, 2022.

*Drs S. Choi and Yoon are co-first authors.

[1]Department of Thoracic and Cardiovascular Surgery, Samsung Medical Center, SungkyunKwan University School of Medicine, Seoul, Korea; [2]Department of Thoracic and Cardiovascular Surgery, Hanyang University Guri Hospital, Hanyang University College of Medicine, Seoul, Korea; [3]Department of Thoracic and Cardiovascular Surgery, Chung-ang University Hospital, Seoul, Korea; and [4]Department of Thoracic and Cardiovascular Surgery, School of Medicine, Ewha Womans University, Mok-dong Hospital, Seoul, Korea

Address correspondence to Dr Cho, Department of Thoracic and Cardiovascular Surgery, Samsung Medical Center, 81 Irwon-ro, Gangnam-gu, Seoul, 06351, Korea; email: jongho.cho@gmail.com.

sub-centimeter NSCLC, unless surgeons have accurate histologic information, which is rarely available preoperatively or intraoperatively. The controversy over optimal LN evaluation in patients with small-sized early-stage NSCLC is still ongoing.

The use of invasive tumor size as a T-descriptor was recommended in the eighth edition of the TNM classification for NSCLC.[11] Accordingly ground-glass opacity (GGO) on CT, which generally corresponds to lepidic architecture on pathologic examination, was excluded in the current clinical staging system. However it was reported that the presence or absence of a GGO component is an independent prognostic indicator,[12] and Watanabe and colleagues[13] suggested that tumors with GGO and pure-solid tumors should be evaluated separately. Studies on whether surgical LN dissection should be performed differently according to the presence of GGO in early-stage NSCLC are scarce.

Therefore in this study we investigated the rate of LN metastasis of ≤2 cm NSCLC based on tumor size and the presence of GGO and evaluated the factors associated with LN metastasis. Furthermore we compared the prognosis of these patients according to the presence of GGO.

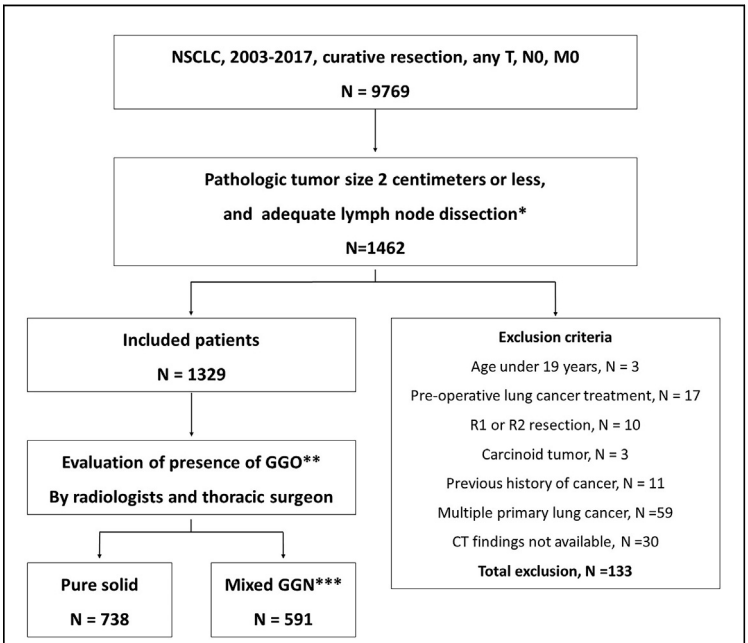


**FIGURE 1** Study participants. *Adequate lymph node (LN) dissection; dissection of a minimum of 3 LN stations, including 7 station LNs and more than 6 LNs in total. **GGO, ground-glass opacity. ***GGN, ground-glass nodule. (CT, computed tomography; NSCLC, non-small cell lung cancer.)

**TABLE 1 Baseline Characteristics of Patients in the Mixed Ground-Glass Nodule and Pure-Solid Nodule Groups**

| Characteristics | Total (N = 1329) | Mixed Ground-Glass Nodule (n = 591) | Pure-Solid Nodule (n = 738) | *P* |
|---|---|---|---|---|
| Age, y | 59.8 ± 9.5 | 58.5 ± 9.2 | 60.9 ± 9.7 | <.001 |
| Male sex | 680 (51.1) | 260 (44) | 420 (56.9) | <.001 |
| Tumor size, cm | 1.5 ± 0.36 | 1.45 ± 0.35 | 1.54 ± 0.36 | <.001 |
| 0-1.0 cm | 163 (12.3) | 88 (14.9) | 75 (10.2) | |
| 1-1.5 cm | 571 (43) | 274 (46.4) | 297 (40.2) | |
| 1.5-2.0 cm | 595 (44.8) | 229 (38.7) | 366 (49.6) | |
| Preoperative positron emission tomography | 1132 (85.2) | 503 (85.1) | 629 (85.2) | .951 |
| Preoperative invasive mediastinal staging procedures | 138 (10.4) | 23 (3.9) | 115 (15.6) | <.001 |
| Histologic type | | | | <.001 |
| Adenocarcinoma | 1059 (79.7) | 556 (94.1) | 503 (68.2) | |
| Squamous cell carcinoma | 139 (10.5) | 4 (0.7) | 135 (18.3) | |
| Other | 131 (9.9) | 31 (5.2) | 100 (13.6) | |
| Extent of surgery | | | | <.001 |
| Lobectomy | 1106 (83.2) | 433 (73.3) | 673 (91.2) | |
| Sublobar resection | 223 (16.8) | 158 (26.7) | 65 (8.8) | |
| No. of dissected lymph nodes | 16.3 ± 7.3 | 15.4 ± 7.1 | 16.9 ± 7.4 | <.001 |
| Lymph node metastasis | | | | <.001 |
| Total | 130 (9.8) | 13 (2.2) | 117 (15.9) | |
| N1 | 65 (4.9) | 6 (1) | 59 (8) | |
| N2 | 65 (4.9) | 7 (1.2) | 58 (7.9) | |
| Adjuvant therapy | | | | <.001 |
| Chemotherapy + radiotherapy | 28 (2.1) | 3 (0.5) | 25 (3.4) | |
| Chemotherapy | 91 (6.8) | 8 (1.4) | 83 (11.2) | |
| Radiotherapy | 9 (0.7) | 1 (0.2) | 8 (1.1) | |
| None | 1201 (90.4) | 579 (98) | 622 (84.3) | |

Values are mean ± SD or n (%).

**TABLE 2 Baseline Characteristics and Pattern of Recurrence Stratified by Lymph Node Metastasis**

| Variable | Mixed Ground-Glass Nodule | | | | Pure-Solid Nodule | | | |
|---|---|---|---|---|---|---|---|---|
| | Total (N = 591) | Pathologic N0 (n = 578) | Pathologic N+ (n = 13) | *P* | Total (N = 738) | Pathologic N0 (n = 621) | Pathologic N+ (n = 117) | *P* |
| Baseline characteristics | | | | | | | | |
| Age, y | 58.46 ± 9.18 | 58.42 ± 9.19 | 60.54 ± 9.04 | .253 | 60.85 ± 9.66 | 61.41 ± 9.5 | 57.87 ± 10 | <.001 |
| Sex, male | 260 | 253 (43.8) | 7 (53.8) | .469 | 420 | 348 (56) | 72 (61.5) | .271 |
| Tumor size | | | | .999 | | | | <.001 |
| 0-1.0 cm | 88 | 86 (14.9) | 2 (15.4) | | 75 | 73 (11.8) | 2 (1.7) | |
| 1-1.5 cm | 274 | 268 (46.4) | 6 (46.2) | ... | 297 | 260 (41.9) | 37 (31.6) | |
| 1.5-2.0 cm | 229 | 224 (38.8) | 5 (38.5) | | 366 | 288 (46.4) | 78 (66.7) | |
| Preoperative positron emission tomography | 503 (85.1) | 493 (85.3) | 10 (76.9) | .402 | 629 (85.2) | 532 (85.7) | 97 (82.9) | .44 |
| Preoperative invasive mediastinal stage | 23 (3.9) | 21 (3.6) | 2 (8.7) | .03 | 115 (15.6) | 93 (15) | 22 (18.8) | .295 |
| Histologic type | | | | .884 | | | | .127 |
| Adenocarcinoma | 556 (94.1) | 544 (94.1) | 12 (92.3) | | 503 | 417 (67.1) | 86 (73.5) | |
| Squamous cell carcinoma | 4 (0.7) | 4 (0.7) | 0 | ... | 135 | 113 (18.2) | 22 (18.8) | |
| Other | 31 (5.2) | 30 (5.2) | 1 (7.7) | ... | 100 | 91 (14.7) | 9 (7.7) | |
| Extent of surgery | | | | .028 | | | | .24 |
| Lobectomy | 433 | 420 (72.7) | 13 (100) | | 673 | 563 (90.7) | 110 (94) | |
| Sublobar resection | 158 | 158 (27.3) | 0 | ... | 65 | 58 (9.3) | 7 (6) | |
| Adjuvant therapy | | | | <.001 | | | | <.001 |
| Chemotherapy + radiotherapy | 3 (0.5) | 0 | 3 (23.1) | | 25 (3.4) | 0 | 25 (21.4) | |
| Chemotherapy | 8 (1.4) | 3 (0.5) | 5 (38.5) | | 83 (11.2) | 14 (2.3) | 69 (59) | |
| Radiotherapy | 1 (0.2) | 1 (0.2) | 0 | | 8 (1.1) | 2 (0.2) | 6 (5.1) | |
| None | 579 (98) | 574 (99.3) | 5 (38.5) | | 622 (84.3) | 605 (97.4) | 17 (14.5) | |
| Recurrence | | | | | | | | |
| Event of recurrence | 12 (2) | 8 (1.4) | 4 (30.8) | | 131 (17.8) | 82 (13.2) | 49 (41.9) | |
| Pattern of recurrence | | | | .232 | | | | .034 |
| Local | 2 (16.7) | 2 (25) | 0 (0) | | 6 (4.6) | 6 (7.3) | 0 (0) | |
| Regional | 3 (25) | 2 (25) | 1 (25) | ... | 37 (28.2) | 18 (22) | 19 (38.8) | |
| Distant only | 2 (16.7) | 0 (0) | 2 (50) | ... | 49 (37.4) | 35 (42.7) | 14 (28.6) | |
| Multiple (regional + distant) | 5 (41.7) | 4 (50) | 1 (25) | | 39 (29.8) | 23 (28) | 16 (32.7) | |

Values are mean ± SD or n (%).

## MATERIAL AND METHODS

**PATIENT ENROLLMENT.** We retrospectively analyzed the medical records of patients who underwent curative surgical resection for clinical N0 NSCLC at a single center from January 2003 to December 2017. Among them, cases in which the tumor size was ≤2 cm and that underwent adequate LN dissection were enrolled. Adequate LN dissection was defined as the dissection of a minimum of 3 LN stations, including station 7 LNs and more than 6 LNs total.[14,15] We then excluded patients younger than 19 years (n = 3); those who received preoperative lung cancer treatment (n = 17); those who underwent R1 or R2 resection (n = 10); those with carcinoid tumors (n = 3), previous history of lung cancer (n = 11), and multiple primary lung cancers (n = 59); and those for whom CT findings were not available (n = 30). Finally, 1329 patients were enrolled (Figure 1).

A radiologist and thoracic surgeon then reviewed the preoperative CTs and categorized patients into the mixed ground-glass nodule (mGGN) and pure-solid nodule (PSN) groups. mGGN was defined as a lung lesion containing any GGO, which had been previously described as a hazy increase in lung attenuation without obscuring the underlying bronchial or vascular structures inside the tumor. In contrast PSN was defined as a lung lesion with only solid attenuation, which was previously described as increased lung attenuation obscuring the underlying structures.[9,16] In a subgroup analysis a lesion consisting of 100% GGO was categorized into the pure GGO group, whereas lesions containing both a solid part and GGO were categorized into the part-solid group. Preoperative invasive mediastinal LN staging procedures, such as endobronchial ultrasound or mediastinoscopy, were performed in cases of a central lesion or a strong suspicion of nodal disease.

The Institutional Review Board of Samsung Medical Center approved this study (IRB no. 2022-01-101). The need for informed consent was waived due to the retrospective nature of the study.

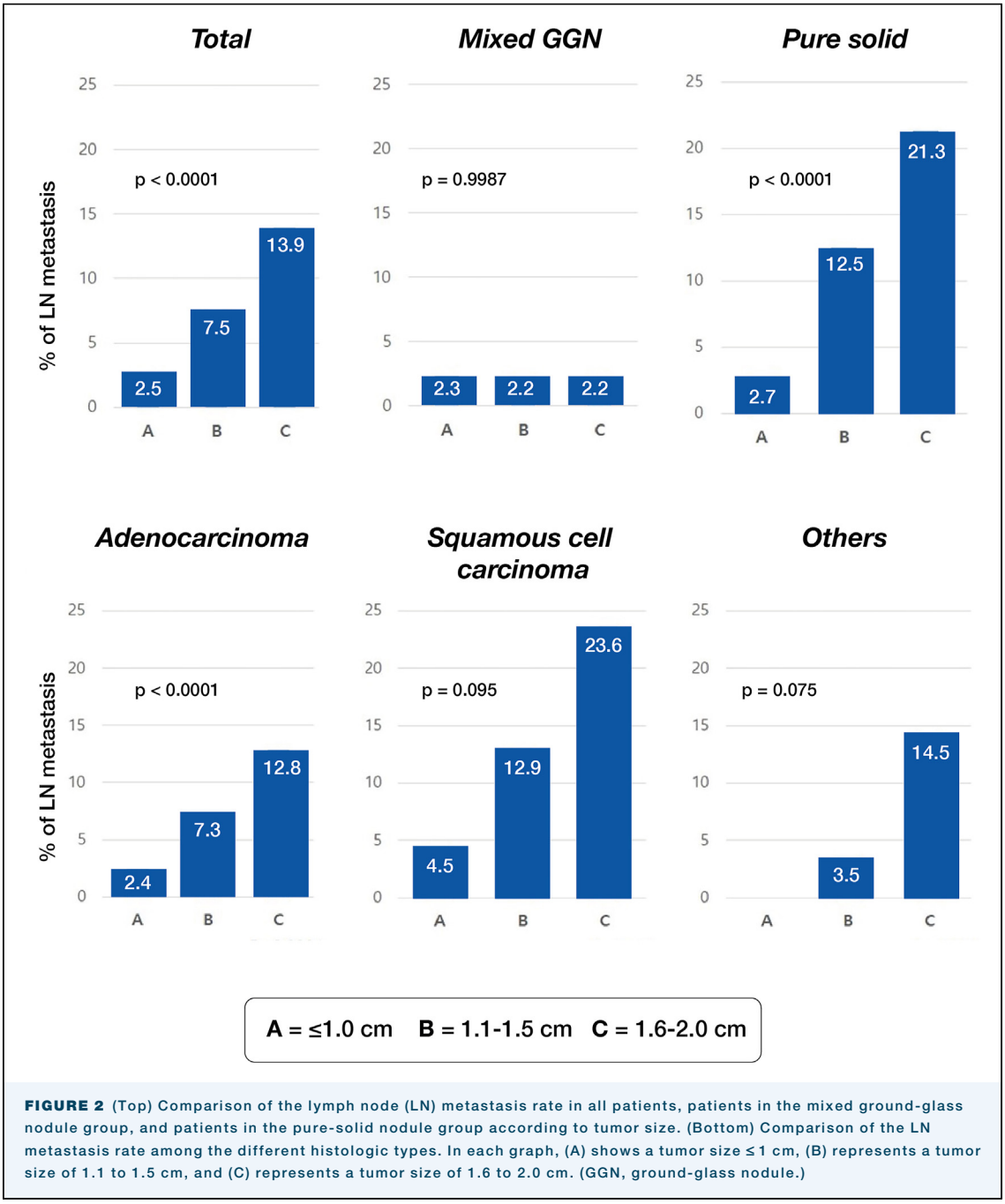


**FIGURE 2** (Top) Comparison of the lymph node (LN) metastasis rate in all patients, patients in the mixed ground-glass nodule group, and patients in the pure-solid nodule group according to tumor size. (Bottom) Comparison of the LN metastasis rate among the different histologic types. In each graph, (A) shows a tumor size ≤ 1 cm, (B) represents a tumor size of 1.1 to 1.5 cm, and (C) represents a tumor size of 1.6 to 2.0 cm. (GGN, ground-glass nodule.)

**SURGERY AND PATHOLOGIC EVALUATION.** All pulmonary resections and systematic LN dissections were conducted by thoracic surgeons at the Samsung Medical Center. Systematic LN dissection was conducted in the same manner in all patients, including removal of all lymphatic tissues within the defined anatomic landmarks of stations.

All intraoperative and postoperative specimens, including dissected LNs, were histologically examined after hematoxylin and eosin staining by pathologists in the Samsung Medical Center. We reviewed the electric medical records of the pathology reports of all patients. LN metastasis was recorded as either N1 or N2 depending on their location. The number of metastatic LNs and the number of all submitted LNs were recorded.

**FOLLOW-UP AFTER INITIAL SURGERY.** Patients were followed up regularly every 3 months for the first 2 years after surgery and every 6 months during the next 3 years with an annual CT. Depending on patient symptoms, brain CT or brain magnetic resonance imaging and other

**TABLE 3 Multivariable Analysis of Risk Factors for Lymph Node Metastasis**

| Variable | Odds Ratio (95% CI) | *P* |
|---|---|---|
| All patients | | |
| Sex, male | 0.74 (0.49-1.12) | .152 |
| Age | 0.97 (0.95-0.99) | .001 |
| Solidity | | |
| Mixed ground-glass nodule | 1 (Ref) | |
| Pure-solid nodule | 7.83 (4.28-14.35) | <.001 |
| Tumor size | | |
| ≤1 cm | 1 (Ref) | |
| 1< size ≤1.5 cm | 2.96 (1.03-8.50) | .044 |
| 1.5< size ≤2 cm | 5.35 (1.90-15.10) | .002 |
| Sublobar resection | 1.72 (0.77-3.88) | .188 |
| Histologic type | | |
| Adenocarcinoma | 1 (Ref) | |
| Squamous cell carcinoma | 1.15 (0.65-2.02) | .632 |
| Other | 0.55 (0.28-1.12) | .098 |
| Patients with mixed ground-glass nodules | | |
| Sex, male | 0.74 (0.48-1.15) | .182 |
| Age | 0.96 (0.94-0.98) | <.001 |
| Tumor size | | |
| ≤1 cm | 1 (Ref) | |
| 1< size ≤1.5 cm | 0.74 (0.19-3) | .678 |
| 1.5< size ≤2 cm | 0.63 (0.15-2.67) | .528 |
| Sublobar resection | 10.44 (0.79-137.94) | .075 |
| Cell type | | |
| Adenocarcinoma | 1 (Ref) | |
| Squamous cell carcinoma | 3.04 (0.1-95.23) | .632 |
| Other | 1.77 (0.33-9.4) | .506 |
| Patients with pure-solid nodules | | |
| Sex, male | 0.74 (0.48-1.15) | .182 |
| Age | 0.96 (0.94-0.98) | <.001 |
| Tumor size | | |
| ≤1 cm | 1 (Ref) | |
| 1< size ≤1.5 cm | 4.09 (1.11-15.12) | .035 |
| 1.5< size ≤2 cm | 8.24 (2.27-29.91) | .001 |
| Sublobar resection | 1.04 (0.46-2.36) | .93 |
| Histologic type | | |
| Adenocarcinoma | 1 (Ref) | |
| Squamous cell carcinoma | 1.26 (0.71-2.23) | .437 |
| Other | 0.55 (0.27-1.13) | .101 |

imaging techniques were used for the detection of recurrence.

**DATA ANALYSIS.** We analyzed patient characteristics, clinicopathologic factors, and prognosis. Solidity of the tumor was categorized as mGGN or PSN. Total pathologic tumor size was categorized as ≤1 cm, 1.0 to 1.5 cm, and 1.5 to 2.0 cm. Surgical extent was categorized as either lobectomy or sublobar resection, including wedge resection, and segmentectomy. Histologic type was categorized as adenocarcinoma, squamous cell carcinoma, or other.

Categorical variables were analyzed using the $\chi^2$ test or Fisher's exact test (when the expected frequency in one or more of the cells was <5). Continuous variables were compared using the Wilcoxon rank sum test. Disease-free survival (DFS) was analyzed using Kaplan-Meier survival curves. Differences among the survival curves were tested for statistical significance using the 2-tailed log-rank test. Univariable logistic regression analysis was performed to determine the odds ratio, and statistically significant variables were further analyzed in the multivariable analysis. $P < .05$ was considered statistically significant. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC) and R 4.0.0 (Vienna, Austria; http://www.R-project.org/).

## RESULTS

**BASELINE CHARACTERISTICS OF THE MGGN AND PSN GROUPS.** Of 1329 patients enrolled, 591 were in the mGGN group and 738 were in the PSN group. The median follow-up period was 35.3 months (interquartile range, 26.6-60.9), and the number of recurrences or deaths was 210. The mean tumor size was 1.5 ± 0.36, which was larger in the PSN group (1.54 ± 0.36) than in the mGGN group (1.45 ± 0.35, $P < .001$). Preoperative invasive mediastinal staging procedures, including endobronchial ultrasound or mediastinoscopy, were performed in 10.38% of cases and were more frequently performed in the PSN group (15.6%) than in the mGGN group (3.9%, $P < .001$). Sublobar resections (wedge resection or segmentectomy) were performed in 16.8% of cases and were more frequently performed in the mGGN group (26.7%) than the PSN group (8.8%, $P < .001$). More LNs were resected in the PSN group (16.9 ± 7.4) than in the mGGN group (15.4 ± 7.1, $P < .001$). LN metastasis was found in 9.8% and was significantly different between the 2 groups (mGGN, 2.2%; PSN, 15.9%; $P < .001$). Details are shown in Table 1.

In the subgroup analysis the mGGN group was analyzed by dividing it into the pure GGO and part-solid groups. There was no LN metastasis in the pure GGO group; the PSN group showed a higher rate of LN metastasis compared with the part-solid group. Subgroup analysis of patients, excluding those undergoing sublobar resection, showed similar results. Details are shown in Supplemental Table 1.

**FACTORS ASSOCIATED WITH LN METASTASIS AND RECURRENCE PATTERN.** Table 2 shows factors associated with LN metastasis. In the mGGN group, LN metastasis was found only in patients who underwent lobectomy. In the PSN group, patients with LN metastasis were younger ($P < .001$) and had larger tumors ($P < .001$) than pathologic N0 patients. In the analysis of recurrence pattern, patients with LN metastasis showed more regional and multiple (regional and distant) recurrences than pathologic N0 patients in the PSN group ($P = .034$). Subgroup analysis of patients was categorized into 3 groups (pure GGO, part-solid, and PSN groups), and another

subgroup analysis of patients undergoing lobectomy is shown in Supplemental Table 2.

To investigate the risk factors for LN metastasis, we analyzed the differences in LN metastasis rate for clinicopathologic parameters, including tumor size and histologic type. In all patients as the tumor size increased, the LN metastasis rate increased. Tumors sized ≤1 cm showed an LN metastasis rate of 2.45%, and tumors sized 1.5 to 2.0 cm showed a higher rate of 13.95% ($P < .001$). In the mGGN group the LN metastasis rate was not significantly different among the different size groups ($P = .998$). However, in the PSN group as the tumor size increased, the LN metastasis rate increased markedly (from 2.67% to 21.31%; $P < .001$). In the analysis according to histologic type, the adenocarcinoma, squamous cell carcinoma, and other groups all showed an increased LN metastasis rate as the tumor size increased. Schematic graphs are shown in Figure 2. Results of the subgroup analysis are shown in Supplemental Figure 1.

We also conducted multivariable logistic regression analysis. Tumor sizes of 1 to 1.5 cm and 1.5 to 2.0 cm were independent significant factors for LN metastasis in the PSN group but not in the mGGN group. Details are shown in Table 3. The subgroup analysis of patients undergoing lobectomy showed similar results. Details are shown in Supplemental Table 3.

**SURVIVAL ANALYSIS.** In the DFS analysis of all patients, the 5-year DFS graph showed a significant difference according to the presence of GGO (mGGN 94.4% vs PSN 71.2%, $P < .001$) (Figure 3). Subgroup analysis of the mGGN group revealed that the sublobar resection group had better patient outcomes compared with the lobectomy group. However in the PSN group DFS showed no difference between the lobectomy and sublobar resection groups (Supplemental Figure 2).

## COMMENT

LN evaluation using lymphadenectomy is indisputably a valuable and integral part of lung cancer surgery. In clinical N0 patients, systematic complete lymphadenectomy is performed for removal of micrometastasis of cancer and accurate pathologic staging, which can benefit patients who will be treated with adjuvant therapy. Although invasive mediastinal LN staging procedure is recommended before surgical resection for most patients with clinical stage I or II lung cancer,[17] it has several challenges, including complications and difficulties of quality control.[18] With this background, we started our study and found that LN evaluation is necessary in small-sized NSCLC, especially in cases of PSNs on CT. The cutoff tumor size that requires thorough lymphadenectomy was difficult to define in our study. However we believe that lesions ≥1 cm require lymphadenectomy for LN evaluation because of a pathologic nodal upstaging rate of more than 10% (12.46%). Furthermore, tumors with PSNs sized 1.6 to 2.0 cm had a pathologic nodal upstaging rate of 21.31%. These results imply that certain patients with preoperative stage IA1 and IA2 actually have stage II to III NSCLC and that they would benefit from other treatment modality including chemotherapy.

In previous studies LN metastasis was reported to be affected by specific histologic types and by tumor size.[19,20] In our study all histologic types of NSCLC showed an increased LN metastasis rate as tumor size increased, although statistically significant differences were not noted in squamous cell carcinoma and other groups. Sakurai and coworkers[19] showed that the LN metastasis rate in peripheral small squamous cell carcinoma was 0% (for ≤1 cm) and 14% (for 1-2 cm). However in our study a group of squamous cell carcinomas presented as PSNs showed an 18.4% LN metastasis rate. Furthermore squamous cell carcinoma sized 1.5 to 2 cm demonstrated an LN metastasis rate of 23.6%. These results were in agreement with those of Pani and colleagues,[10] and we believe that LN evaluation should be performed appropriately even in small-sized NSCLC because an exact histologic type analysis is not possible using frozen tissue or intraoperatively, regardless of histologic type.

In this study the PSN group exhibited a worse prognosis than the mGGN group and a different LN metastasis rate variance according to tumor size. Although we measured total pathologic size including the noninvasive component, these results were in line with those of

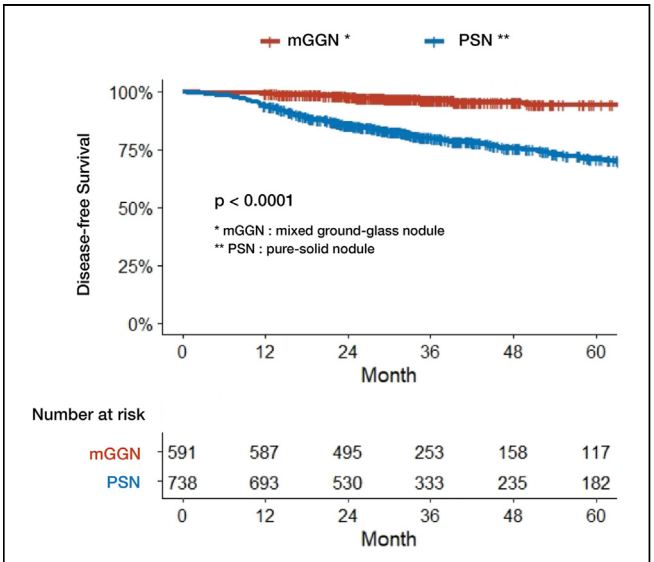


**FIGURE 3** Disease-free survival according to the presence of ground-glass opacity in all patients. (mGGN, mixed ground-glass nodule; PSN, pure-solid nodule.)

previous reports, which showed distinct clinicopathologic characteristics according to the presence of GGO.[12] Our findings also support the need for GGO to be added to the current T-descriptor as an additional prefix, as others have insisted.[21,22] Further confirmatory studies are necessary. In the subgroup analysis of mGGN patients, the sublobar resection group had a better prognosis compared with the lobectomy group. These results were in line with the results of JCOG 0802,[23] but an insufficient follow-up period of the sublobar resection group was limitation of our analysis.

Our study has some limitations. First our study is retrospective, and there is the possibility of selection bias compared with a randomized study. However to our knowledge this is the largest dataset published of patients with NSCLC sized $\leq 2$ cm. Second various factors that could affect LN metastasis, such as vascular and visceral pleura invasion, tumor differentiation, positron emission tomography and CT findings, and adenocarcinoma subtype, were not investigated. However we sought to focus on the representative parameters, such as tumor size and solidity on preoperative CT. Third we categorized all patients into either the mGGN or PSN group, and information on the particular solid component size or proportion of solid component was not analyzed. This is because this study focused on tumor solidity rather than on the percent of GGO or the related ratio to the size of the entire tumor. Further studies, including data on the proportion of solid components, are warranted.

We demonstrated that tumor size and the absence of GGO are independent risk factors for LN metastasis in patients with small-sized NSCLC and that the rate of LN metastasis increases as the tumor size increases in patients with PSNs. Adequate LN evaluation should be performed in patients with small-sized NSCLC, especially in those with PSNs $\geq 1$ cm.

## FUNDING SOURCES

The authors have no funding sources to disclose.

## DISCLOSURES

The authors have no conflicts of interest to disclose.

## REFERENCES

1. Detterbeck FC, Boffa DJ, Kim AW, Tanoue LT. The eighth edition lung cancer stage classification. *Chest*. 2017;151:193-203.

2. Goldstraw P, Crowley J, Chansky K, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM classification of malignant tumours. *J Thorac Oncol*. 2007;2:706-714.

3. 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;60:615-622 [discussion: 622-613].

4. National Lung Screening Trial Research Team, Aberle DR, Adams AM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med*. 2011;365:395-409.

5. Allen MS, Darling GE, Pechet TT, et al. Morbidity and mortality of major pulmonary resections in patients with early-stage lung cancer: initial results of the randomized, prospective acosog z0030 trial. *Ann Thorac Surg*. 2006;81:1013-1019 [discussion: 1019-1020].

6. Veronesi G, Maisonneuve P, Pelosi G, et al. Screening-detected lung cancers: is systematic nodal dissection always essential? *J Thorac Oncol*. 2011;6:525-530.

7. Mokhles S, Macbeth F, Treasure T, et al. Systematic lymphadenectomy versus sampling of ipsilateral mediastinal lymph-nodes during lobectomy for non-small-cell lung cancer: a systematic review of randomized trials and a meta-analysis. *Eur J Cardiothorac Surg*. 2017;51:1149-1156.

8. Oda M, Watanabe Y, Shimizu J, et al. Extent of mediastinal node metastasis in clinical stage I non-small-cell lung cancer: the role of systematic nodal dissection. *Lung Cancer*. 1998;22:23-30.

9. Seok Y, Yang HC, Kim TJ, et al. Frequency of lymph node metastasis according to the size of tumors in resected pulmonary adenocarcinoma with a size of 30 mm or smaller. *J Thorac Oncol*. 2014;9:818-824.

10. Pani E, Kennedy G, Zheng X, et al. Factors associated with nodal metastasis in 2-centimeter or less non-small cell lung cancer. *J Thorac Cardiovasc Surg*. 2020;159:1088-1096.

11. Travis WD, Asamura H, Bankier AA, et al. The IASLC Lung Cancer Staging Project: proposals for coding T categories for subsolid nodules and assessment of tumor size in part-solid tumors in the forthcoming eighth edition of the TNM classification of lung cancer. *J Thorac Oncol*. 2016;11:1204-1223.

12. Hattori A, Hirayama S, Matsunaga T, et al. Distinct clinicopathologic characteristics and prognosis based on the presence of ground glass opacity component in clinical stage IA lung adenocarcinoma. *J Thorac Oncol*. 2019;14:265-275.

13. Watanabe Y, Hattori A, Nojiri S, et al. Clinical impact of a small component of ground-glass opacity in solid-dominant clinical stage IA non-small cell lung cancer. *J Thorac Cardiovasc Surg*. 2022;163:791-801. e4.

14. NCCN clinical practice guidelines in oncology (NCCN guidelines®) non-small cell lung cancer (version 5.2022). 2022. Accessed September 26, 2022. https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1450

15. Gajra A, Newman N, Gamble GP, Kohman LJ, Graziano SL. Effect of number of lymph nodes sampled on outcome in patients with stage I non-small-cell lung cancer. *J Clin Oncol*. 2003;21:1029-1034.

16. Tsutani Y, Miyata Y, Nakayama H, et al. Prognostic significance of using solid versus whole tumor size on high-resolution computed tomography for predicting pathologic malignant grade of tumors in clinical stage IA lung adenocarcinoma: a multicenter study. *J Thorac Cardiovasc Surg*. 2012;143:607-612.

17. Ettinger DS, Wood DE, Aisner DL, et al. NCCN guidelines insights: non-small cell lung cancer, version 2.2021. *J Natl Compr Canc Netw*. 2021;19:254-266.

18. Ost DE, Niu J, Zhao H, Grosu HB, Giordano SH. Quality gaps and comparative effectiveness in lung cancer staging and diagnosis. *Chest*. 2020;157:1322-1345.

19. Sakurai H, Asamura H, Watanabe S, Suzuki K, Tsuchiya R. Clinicopathologic features of peripheral squamous cell carcinoma of the lung. *Ann Thorac Surg*. 2004;78:222-227.

**20.** 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;20:1949-1954.

**21.** Kidane B. The hazy road to improved (prognostic) vision: the role of the ground-glass opacity component in clinical T stage. *J Thorac Cardiovasc Surg*. 2017;154:2111-2112.

**22.** Joubert P, Travis WD. Prognostic impact of ground-glass opacity/lepidic component in pulmonary adenocarcinoma: a hazy staging dilemma. *J Thorac Oncol*. 2022;17:19-21.

**23.** Saji H, Okada M, Tsuboi M, et al. Segmentectomy versus lobectomy in small-sized peripheral non-small-cell lung cancer (JCOG0802/WJOG4607L): a multicentre, open-label, phase 3, randomised, controlled, non-inferiority trial. *Lancet*. 2022;399:1607-1617.



0003-4975/$36.00
https://doi.org/10.1016/j.athoracsur.2023.01.035

## A "Solid" Rationale for Lymphadenectomy in Small, Peripheral Lung Cancers

**INVITED COMMENTARY:**

The relationship of tumor size to occult lymph node metastasis is well described.[1] In this issue of *The Annals of Thoracic Surgery*, Choi and colleagues[2] introduce important implications regarding the radiologic appearance of non-small cell lung cancers $\leq$ 2 cm with a retrospective review of data collected in a single institution Comparing mixed ground-glass nodules with pure-solid nodules (PSN), they report higher rates of occult nodal metastases as the tumor size increased, but only for the PSN group.

The data presented by the authors are quite valuable. It arguably would have been more clinically useful if "size" was defined radiographically rather than pathologically. Additionally we would like more granular data regarding size of the solid component in the mixed ground-glass nodule group, a better predict of behavior, and differences in positron emission tomography uptake of the lesions. These radiographic characteristics contribute to our ability to estimate preoperative risk and help guide surgical strategies for lymphadenectomy. We believe the location of relevant N1 and N2 stations is likely more important than the overall total number of nodes harvested.

The study is timely, given recent publications demonstrating comparable survival of sublobar resection with lobectomy for tumors of the size described here.[3,4] It is particularly sobering in this study that in the PSN group the rate of occult lymph node metastases was 15.9%, the recurrence rate was 17.8%, and the 5-year disease-free survival rate was just 71.2% in this relatively young cohort of patients. If sublobar resection is broadly adopted, will surgeons fail to identify these patients in the future and will outcomes be even worse? That would be a travesty, especially now that we have more effective adjuvant strategies for these patients. The 21% rate of occult nodal metastases in patients with PSN 1.5 to 2.0 cm in size arguably even calls for a more thorough and tailored strategy for preoperative bronchoscopic lymph node assessment, because patients with nodal metastases would be eligible for neoadjuvant therapy. To conclude, we congratulate the authors on their work, because we believe that in addition to offering valuable data, their study is hypothesis-generating and will undoubtedly serve as a reference for the development of future studies to investigate the ideal method of targeted lymphadenectomy for patients with small tumors.

### FUNDING SOURCES

The authors have no funding sources to disclose.

### DISCLOSURES

Brendon M. Stiles reports a relationship with Astra Zeneca, Merck, and Pfizer that includes: consulting, advisory boards; with Gala Therapeutics and Medtronic that includes: consulting; with Bristol Myers Squibb, Genentech, Arcus Biosciences, and Regeneron that includes: advisory boards; with Bristol Myers Squibb and Bristol Myers Squibb Foundation that includes: research funding; with Xalud, PPD, and Pfizer that includes: wife: stock and salary; and with Lung Cancer Research Foundation and LUNGevity that includes: board, science advisory board. J. Humberto Rodriguez-Quintero has no conflicts of interest to disclose.

Brendon M. Stiles, MD
J. Humberto Rodriguez-Quintero, MD

Montefiore Medical Center
Albert Einstein College of Medicine
3400 Bainbridge
Bronx, NY 10467
email: brstiles@montefiore.org

### REFERENCES

**1.** Graham AN, Chan KJM, Pastorino U, Goldstraw P. Systematic nodal dissection in the intrathoracic staging of patients with non–small cell lung cancer. *J Thorac Cardiovasc Surg*. 1999;117:246-251.

**2.** Choi S, Yoon DW, Shin S, et al. Importance of lymph node evaluation in ≤2-cm pure-solid non-small cell lung cancer. *Ann Thorac Surg*. 2024;117:586-593.

**3.** Saji H, Okada M, Tsuboi M, et al. Segmentectomy versus multicentre, open-label, phase 3, randomised, controlled, non-inferiority trial. *Lancet*. 2022;399:1607-1617.

**4.** Altorki NK, Wang X, Wigle D, et al. Perioperative mortality and morbidity after sublobar versus lobar resection for early-stage non-small-cell lung cancer: post-hoc analysis of an international, randomised, phase 3 trial (CALGB/Alliance 140503). *Lancet Respir Med*. 2018;6:915-924.