Original Article

Prognostic impact of ground-glass opacity components in lung cancer with lymph node metastasis

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Background: In early-stage non-small cell lung cancer (NSCLC), the presence of a ground-glass opacity (GGO) component in the primary lesion on high-resolution computed tomography (CT) is recognized as a favorable prognostic factor. Even in NSCLC with a GGO component, lymph node metastases are occasionally detected during or after surgery. However, the prognostic impact of GGO components in these patients has not been clarified. We aimed to examine the prognostic significance of GGO components as radiological findings of primary lesions of completely resected NSCLC with pathological nodal involvement.

Methods: This study included 290 patients (11%) with pathological nodal involvement among 2,546 patients who underwent complete resection of NSCLC at our institution. Patients with an unknown primary lesion (T0) or centrally located lung cancer were excluded. The 290 patients were divided into two groups [i.e., the part-solid ("PS") and "Solid" groups] according to the radiological findings of the primary lesion, and their clinicopathological characteristics and prognoses were compared. Furthermore, a multivariate analysis was performed using the Cox proportional hazards model to examine the factors affecting the overall survival (OS).

Results: The OS in the PS group (n=58) was significantly longer than that in the Solid group (n=232; P=0.039). However, multivariate analysis only revealed age [hazard ratio (HR) =1.77; 95% confidence interval (CI): 1.15–2.72] and the clinical T factor (HR =1.58; 95% CI: 1.01–2.47), but not the radiological findings of primary lesions, as the independent prognostic factors. Furthermore, the OS did not differ significantly between the PS and Solid groups matched for the clinical T and N factors (n=58 patients each).

Conclusions: GGO components in the primary lesion, considered a decisive prognostic factor in early-stage NSCLC, did not affect the prognosis of patients with NSCLC and pathological nodal involvement.

Keywords: Non-small cell lung cancer (NSCLC); pathological nodal involvement; high-resolution computed tomography (high-resolution CT); overall survival (OS); prognosis

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Introduction

Background

Radiological findings of non-small cell lung cancer (NSCLC) on high-resolution computed tomography (CT) can be classified into pure ground-glass, part-solid (PS), and solid types. In the eighth edition of the TNM classification, the ground-glass opacity (GGO) component (representing a pathological lepidic growth pattern) was not included in the tumor diameter (1). Since then, several retrospective studies have investigated the prognostic significance of GGO components in early-stage NSCLC (2-11). Most of these studies have demonstrated that pure solid-type nodules, which do not contain GGO components, have a distinctive malignant behavior and worse prognosis than PS-type nodules in clinical stage I disease.

Rationale and knowledge gap

Lymph node involvement is one of the most decisive factors for poor prognosis and a critical factor in the TNM classification (12). Moreover, several parameters related to lymph node involvement, such as the extent of nodal invasion, number of involved nodes, and invasion pattern, have been reported to affect the prognosis (13-16). Even in NSCLC with a GGO component, which is considered to have a good prognosis, patients occasionally present with lymph node metastases. It is important to know the prognosis and background of such patients in order to select the best surgical procedure and postoperative therapy plan. However, the prognostic impact of GGO components on primary lesions is yet to be fully elucidated in patients having NSCLC with lymph node involvement.

Objective

The purpose of this study was to clarify the prognostic significance of the presence of the GGO component in primary lesions in completely resected NSCLC with pathological nodal involvement. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-144/rc).

Highlight box

Key findings

- Multivariate analysis revealed that the presence of ground-glass opacity (GGO) components was not an independent prognostic factor in patients with node-positive non-small cell lung cancer (NSCLC). The overall survival did not differ significantly between patients with or without GGO components after matching for the clinical T and N factors.

What is known and what is new?

- In patients with early-stage NSCLC, the GGO component is a decisive favorable prognostic factor.
- However, the GGO component was not a favorable prognostic factor in patients with NSCLC and pathological lymph node metastases.

What is the implication, and what should change now?

- The prognostic impact of the GGO component in node-positive NSCLC was different from that in early-stage NSCLC. Our results suggest that the subsequent prognosis of part-solid lesions after tumor cell metastasis to the lymph nodes was comparable to that of solid lesions. We should be careful to avoid underestimating the malignant potential of the disease based on the presence or absence of GGO components alone.

Methods

Study population

This retrospective study was conducted in accordance with the Declaration of Helsinki (as revised in 2013), and was approved by the Institutional Review Board of the Cancer Institute Hospital of the Japanese Foundation for Cancer Research in Tokyo, Japan (approval No. 2022-GB-112). The need to obtain written informed consent from each patient was waived because of the retrospective nature of the study, and the anonymity of the patients was ensured.

We retrospectively reviewed 2,546 patients with NSCLC who underwent resection of a complete lobe or more with lobe-specific or systematic mediastinal nodal dissection at our institution between 2010 and 2018. Of these, 312 (12%) patients had pathologically confirmed hilar and/or mediastinal node involvement. Twenty-two patients whose imaging evaluation of the primary lesion was complex due to a hilar location or the presence of an unknown primary lesion (T0) were excluded. Ultimately, 290 patients with available data were included in this study. The medical records of all patients were reviewed for the following clinicopathological factors: age, sex, pack-year smoking status, tumor size, surgical procedure, carcinoembryonic antigen (CEA) level, adjuvant chemotherapy, radiological and pathological nodal involvement, histological type, and epidermal growth factor receptor (EGFR) mutation

status. The clinical and pathological stages were determined according to the eighth edition of the TNM classification (17). The surgical approach included thoracoscopic or open thoracotomy, determined based on the time period and the surgeon's preference. Postoperative surveillance was performed using chest and abdominal CT and laboratory testing every 6–12 months.

Radiographic evaluation

All patients underwent contrast-enhanced CT using a 64-channel multidetector CT scanner (Revolution HD, GE Medical Systems, Milwaukee, WI, USA) under the following settings: gantry rotation speed, 0.5 s per rotation; collimation, 0.625 mm; table incrementation speed, 39.37 mm/s with a 0.984 helical pitch; and tube voltage, 120 kV. The CT images were reconstructed with a section thickness of 1.25 mm and viewed on standard lungs (level: –600 HU; width: 1,500 HU) and mediastinal windows (level: 30 HU; width: 400 HU). PS-type lesions were defined as tumors consisting of GGO and solid components, while solid lesions were defined as tumors consisting of only solid components. Four investigators performed the radiographic evaluation; these comprised two experienced thoracic radiologists (K.O. and Yoshinao Sato) and two experienced thoracic surgeons (S.T. and M.N.). Consolidation-to-tumor ratio (CTR) was defined as the ratio of the maximum size of consolidation to the maximum tumor size. GGO-like shadows, which extended in only one direction on the peripheral side of the solid lesions, were considered secondary shadows reflecting poor lung inflation rather than GGO components. Disagreements among the investigators were resolved through a discussion and consensus. Lymph nodes enlarged to ≥10 mm along the short axis on CT images or those showing an abnormal accumulation on positron emission tomography-CT were suspected to indicate metastasis. Mediastinal lymph nodes meeting the above criteria were pathologically evaluated by endobronchial ultrasound-guided transbronchial needle aspiration.

Pathological evaluation

The resected specimens were histologically classified according to the World Health Organization International Histological Classification of Tumors. The EGFR mutation status was evaluated using the Cobas EGFR Mutation Kit v2 (Roche Diagnostics, Tokyo, Japan); it was determined in 94% of the study cohort, and decisions regarding treatment strategies after relapse using EGFR tyrosine kinase inhibitors were based on these results.

Statistical analysis

Categorical variables are presented as frequencies and percentages; these were compared using the chi-square test. Continuous variables are presented as medians and ranges; these were compared using the Mann-Whitney *U* test. The overall survival (OS) was measured from the date of surgery to the date of death from any cause or the last follow-up. Data for patients who were alive on July 30, 2021, or were lost to follow-up were censored. The OS was estimated using the Kaplan-Meier method, while differences among groups were determined using the log-rank test. A multivariate analysis was performed using the Cox proportional hazards model to examine the factors affecting the OS. Clinically relevant variables that could be measured before surgery were selected as the covariates based on a priori knowledge of the prognostic factors after limiting the number of items and checking the correlations among them to avoid overfitting and multicollinearity. Two-sided P values of <0.05 indicated statistical significance. All statistical analyses were performed using JMP Pro14.0.0 (SAS Institute, Cary, NC, USA).

Results

Comparisons of patient characteristics between the PS and Solid groups

Of the 290 eligible patients, 58 (20%) had PS-type primary lesions (PS group), and 232 (80%) had solid type primary lesions (Solid group) (*Figure 1*). No patients had pure GGO lesions. The patients' background characteristics are shown in *Table 1*. Compared with the Solid group, the PS group included more women, never-smokers, and patients with adenocarcinomas. While no significant differences in the total tumor size were noted between the groups, the solid component size was significantly smaller in the PS group than in the Solid group. The median CTR in the PS group was 0.75, with a range of 0.30–1.0. The cN1–2 status rate was significantly higher in the Solid group than in the PS group. The surgical procedure, the extent of mediastinal lymph node dissection, and the extent of pathological nodal involvement (pN1 or pN2) were not significantly different between the two groups.

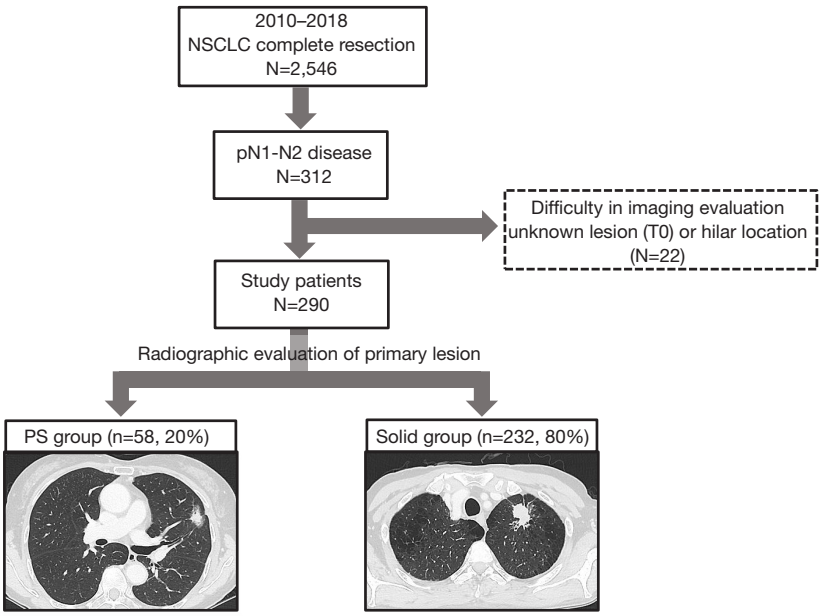

Figure 1 Flow diagram of the study patients. NSCLC, non-small cell lung cancer; PS, part-solid.

Comparison of the prognosis between the PS and Solid groups

Figure 2 shows the OS curves for the PS and Solid groups. The median observation period was 54 (interquartile range, 41–76) months. The OS was significantly longer in the PS group than in the Solid group (P=0.04; *Figure 2*). The 5-year OS rates were 83% and 66% in the PS and Solid groups, respectively.

Multivariate analysis of the preoperative factors for OS

Radiological findings of the primary lesion were strongly associated with sex, smoking history, solid component size, clinical N factor, histological type, and EGFR mutation status (*Table 1*). Therefore, we performed a multivariate analysis to determine which of the following preoperative factors affected the OS: age, sex, smoking history, radiological findings of the primary lesion, clinical T factor, clinical N factor, and serum CEA level (*Table 2*). We found that only age [hazard ratio (HR) =1.77; 95% confidence interval (CI): 1.15–2.72] and the clinical T factor (HR =1.58; 95% CI: 1.01–2.47) were independent prognostic factors for the OS, whereas the radiological appearance of the primary lesion was not.

Comparison of the prognosis between the PS and Solid groups with matching clinical stages

We compared the OS between the PS and Solid groups matched for the clinical T and N factors (n=58 patients each; *Table 3*). No significant differences were observed in the OS between the two groups (*Figure 3*). The 5-year OS rates were 83% and 78% in the PS and Solid groups, respectively.

Discussion

Key findings

In this study, we investigated the prognostic impact of GGO components in the primary lesions of 290 patients with pN1–2 NSCLC. The OS was significantly higher in the PS group than in the Solid group. However, compared to the Solid group, the PS group differed in patient background, with more patients who were female, and had no history of smoking, smaller solid size, clinical N0, adenocarcinoma, and EGFR mutations. Because the presence of GGO components was strongly associated with other factors, a multivariate analysis was used to identify the factors affecting the OS. It revealed age and the clinical

Table 1 Patient characteristics of the Part-solid and Solid groups

Characteristics	Radiological findings of the primary lesion		P value
	Part-solid (n=58)	Solid (n=232)	
Age, years	65 [37–78]	67 [29–79]	0.12†
Sex			<0.001
Male	20 [34]	154 [66]	
Female	38 [66]	78 [34]	
Smoking history			0.003
Yes	29 [50]	164 [71]	
No	29 [50]	68 [29]	
Total tumor size, mm	30 [10–69]	31 [9–84]	0.34†
Solid component size, mm	22 [7–46]	31 [9–84]	<0.001†
Consolidation-to-tumor ratio	0.75 [0.30–1.0]	1.0 [1.0–1.0]	<0.001†
Clinical N factor			<0.001
cN0	52 [90]	142 [61]	
cN1 or cN2	6 [10]	90 [39]	
Surgical procedure			0.13
Lobectomy	54 [93]	199 [86]	
Bi-lobectomy/ pneumonectomy	4 [7]	33 [14]	
Extent of mediastinal lymph node dissection			0.49
Lobe-specific	41 [71]	153 [66]	
Systematic	17 [29]	79 [34]	
Adjuvant chemotherapy			0.19
Yes	20 [34]	60 [26]	
No	38 [66]	172 [74]	
Pathological N factor			0.55
pN1	24 [41]	106 [46]	
pN2	34 [59]	126 [54]	
Histological type			<0.001
Adenocarcinoma	57 [98]	159 [69]	
Other	1 [2]	73 [31]	
EGFR mutation status‡			<0.001
Yes	38 [67]	64 [30]	
No	19 [33]	152 [70]	

Data are presented as number [percentage] or median [range]. †, Mann-Whitney *U* test; ‡, 17 unknown patients were excluded. EGFR, epidermal growth factor receptor.

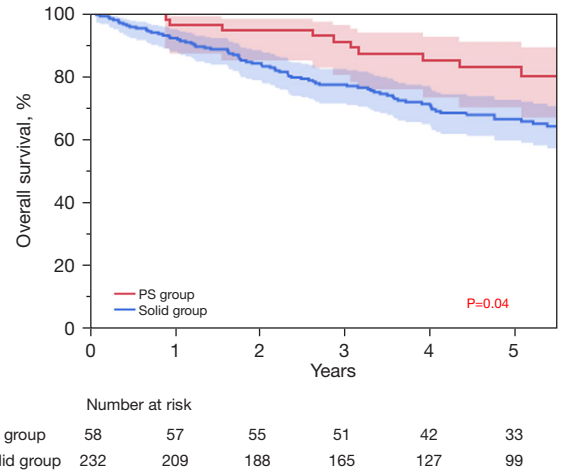

Figure 2 OS curves according to the radiographic appearance of the primary lesions for the entire patient population. The 5-year OS rate was 83% (95% CI: 77.7–88.2%) in the PS group and 66% (95% CI: 63.1–69.7%; P=0.04) in the Solid group. PS, part-solid; OS, overall survival; CI, confidence interval.

Table 2 Multivariate analysis of the preoperative factors for the OS

Factors	Hazard ratio (95% CI)	P value
Age, years		
<70	1.00	
≥71	1.77 (1.15–2.72)	0.009
Sex		
Male	1.00	
Female	1.11 (0.67–1.81)	0.69
Smoking history		
No	1.00	
Yes	1.15 (0.69–1.90)	0.60
Radiological findings of the primary lesion		
Part-solid type	1.00	
Solid type	1.40 (0.76–2.59)	0.28
Clinical T factor		
cT1	1.00	
cT2–cT4	1.58 (1.01–2.47)	0.046
Clinical N factor		
cN0	1.00	
cN1–cN2	1.24 (0.79–1.96)	0.35
CEA, ng/mL		
<5.0	1.00	
≥5.1	1.22 (0.81–1.84)	0.34

CEA, carcinoembryonic antigen; CI, confidence interval; OS, overall survival.

Table 3 Clinical stage of the matched cohort from the Part-solid and Solid groups

Characteristics	Radiological findings of the primary lesion		P value
	Part-solid (n=58)	Solid (n=58)	
Clinical T factor			>0.99
cT1	45 (78%)	45 (78%)	
cT2–cT4	13 (22%)	13 (22%)	
Clinical N factor			>0.99
cN0	52 (90%)	52 (90%)	
cN1–cN2	6 (10%)	6 (10%)	

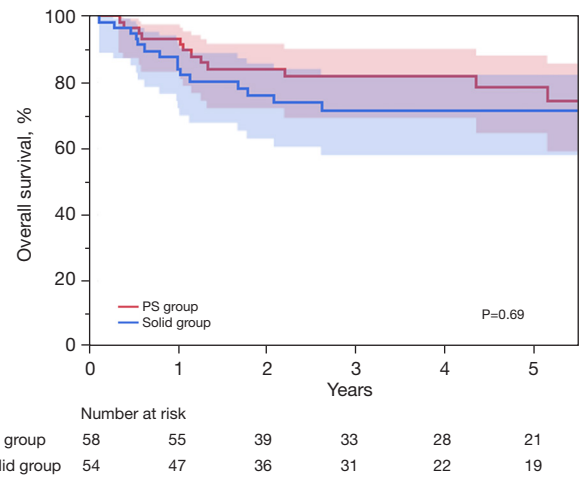

Figure 3 OS curves according to the radiographic appearance of the primary lesions for patient cohorts matched for the clinical stage. The 5-year OS rate was 83% (95% CI: 77.7–88.8%) in the PS group and 78% (95% CI: 72.5–83.7%; P=0.69) in the Solid group. PS, part-solid; OS, overall survival; CI, confidence interval.

T factor, but not the presence of GGO components in the primary lesion, as independent prognostic factors. In other words, the radiological findings of the primary tumor reflect other preoperative factors, and the radiological findings of the primary tumor itself do not affect the prognosis. In addition, because the solid component size and clinical N status were significantly different between the PS group and the Solid group, we compared the OS between the groups in patients with matched clinical T and N factors. The result showed no significant differences in OS between the two. Our results indicated that the prognosis was better in patients with GGO components than in those without, even in NSCLC with pathological nodal involvement; however, this was not due to the presence of the GGO component itself, but rather due to confounding factors.

Comparison with similar research

Several studies have revealed the favorable prognostic impact of GGO components (2-11). In some of these studies, such as that by Hattori *et al.*, a GGO component was a decisive prognostic factor in multivariate analysis, considering other factors in clinical stage IA adenocarcinomas (2). Our study from the same period also indicated that the OS was significantly better in patients with clinical stage IA adenocarcinomas with PS nodules than in patients with solid nodules (5). Ye *et al.* compared the prognoses of pure solid and PS (and pure GGO lesions) groups in a stage-independent population, including a few patients with lymph node metastases. They reported that the PS (and pure GGO lesions) group had a better prognosis than the pure solid group (3). Previous studies from multiple institutions established the status of the GGO component as a decisive prognostic factor for stage IA disease. However, although approximately 10% of the cases with pathological nodal involvement were included in these studies, they were not evaluated in depth.

Explanations of findings

In our cohort, most patients (80%; 232/290) had solid-type lesions. In general, solid-type lesions are known to have higher malignant potential than PS lesions (4). However, our results suggest that even for PS lesions, the subsequent prognosis after tumor cell metastasis to the lymph nodes is comparable to that for solid lesions. While this may be a reasonable result, given the strength of the N factor as a prognostic factor, it is interesting to note the different prognostic impact of the presence of GGO in previous studies on early-stage NSCLC.

Implications and actions needed

Our results may also be helpful for the selection of appropriate surgical procedures. Recently, small lesions with GGO components have increasingly been treated with sublobar resection, in accordance with the expectation that they have a favorable prognosis (17). However, this prediction must be revised in patients with pathological

lymph node involvement. We must be cautious about the notion that PS lesions have a uniformly favorable prognosis as compared to solid lesions. In our cohort, 90% of the cases in the PS group were clinically node-negative but pathologically node-positive. Although the same criteria were used to clinically diagnose nodal status, the rate of underestimation of nodal status was significantly higher in the PS group than in the Solid group. This finding may be a limitation of imaging for the diagnosis of lymph node metastasis. More sensitive modalities are needed, especially in the era of induction chemo-immunotherapy. In addition, it is possible that the high number of upstages in the PS group is due to the stereotype that NSCLC with GGO components is less likely to metastasize to the lymph nodes. This bias may influence the diagnosis based on CT and PET findings. Even when performing a sublobar resection for PS lesions, it is essential to accurately evaluate the lymph node status intraoperatively.

Strengths and limitations

To the best of our knowledge, no reports exist on the prognostic significance of GGO components in primary lesions, particularly those focusing on patients with NSCLC with lymph node metastases. The present report is the first on the topic, and we suggest that the prognostic impact of GGO components on patients with pN1–2 NSCLC is considerably different from that on patients with early-stage NSCLC. This study had some limitations. First, this was a retrospective analysis of a dataset from a single institute. The number of patients, particularly in the PS group, was relatively small. Further extensive studies with additional cases may provide more definitive conclusions. Second, radiographic discrimination between PS and solid lesions is occasionally challenging. We reached a consensus after a complete discussion in some cases, with peripheral GGO-like shadows reflecting poor lung inflation or obstructive pneumonia. Third, we only included patients who underwent mediastinal lymph node dissection and had pathologically confirmed lymph node metastasis. Therefore, applying our results to develop a generalized preoperative strategy in clinical practice may not be easy.

Conclusions

This is the first report on the prognostic significance of the radiological findings of primary lesions in patients with node-positive NSCLC. The presence of the GGO component, considered a decisive prognostic factor in early-stage NSCLC, did not affect the prognosis of patients having NSCLC with lymph node metastases.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-144/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-144/dss

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-144/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-144/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of the Cancer Institute Hospital, Japanese Foundation for Cancer Research (No. 2022-GB-112) and individual consent for this retrospective analysis was waived.

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