

# Lepidic growth component as a favorable prognostic factor in non-small cell lung cancer of $\leq 3$ cm

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## Abstract

**Background:** Many non-small cell lung cancer (NSCLC) tumors present complex histology with various components. The effects of the lepidic growth component (LGC) on the prognosis of NSCLC have not been investigated. Here, we investigated whether an LGC is a relevant prognostic factor for NSCLC.

**Methods:** This study retrospectively investigated the clinicopathologic characteristics of 379 patients with NSCLC  $\leq 3$  cm who underwent complete surgical resection between 2004 and 2016 at the University of Yamanashi Hospital. The histologic subtypes were classified into NSCLC with or without an LGC. We evaluated the effect of an LGC on the clinicopathologic features and 5-year overall survival of patients with NSCLC.

**Results:** On final pathology, 214 (56%) of 379 patients had an LGC, and 165 (44%) did not. Sex, smoking history, ground-glass opacity component, pathologic invasive size, lymph node metastasis, pleural invasion, vessel invasion, pathologic stage, and histologic type were significantly different between the groups. Multivariate analysis of 5-year overall survival, identified age (hazard ratio [HR], 1.07; 95% confidence interval [CI], 1.035–1.105;  $p < 0.001$ ), pathologic invasive size (HR, 1.548; 95% CI, 1.088–2.202;  $p = 0.015$ ) and LGC (HR, 2.11; 95% CI, 1.099–4.051;  $p = 0.025$ ) as independent prognostic factors. When the pathologic invasive size was matched, the 5-year overall survival of the LGC and non-LGC groups was 93% and 77%, respectively ( $p = 0.006$ ).

**Conclusions:** LGC is a significantly favorable prognostic factor for NSCLC with a pathologic invasive size of  $\leq 3$  cm.

## KEYWORDS

lepidic growth component, non-small cell lung cancer, pathology, prognostic factor, survival analysis

## INTRODUCTION

The development of imaging technology, such as computed tomography (CT), has increased the identification and surgical treatment of small-sized non-small cell lung cancer (NSCLC) in recent years.<sup>1</sup> Previous studies have reported that small-sized NSCLC with ground-glass opacity (GGO) is non-invasive with little vessel invasion or lymph node metastasis and has an improved prognosis compared to tumors without GGO<sup>2–11</sup>; this is because the GGO

component is usually pathologically equivalent to a lepidic growth component (LGC).<sup>2,12–15</sup> Therefore, some researchers have suggested that the stage of NSCLC can be determined by the GGO component.<sup>4,7,11</sup>

A GGO component is likely to be a prognostic and important factor in deciding the surgical procedure. However, there are some problems in determining whether a GGO component is present in a nodule on CT. First, although GGO is characterized by an increase in lung attenuation without obscuring the underlying structures,<sup>2,16</sup> there

is no clear indicator of whether a nodule contains a GGO component. Second, infiltration of surrounding inflammatory cells, mucus, some papillary adenocarcinomas, and poor aeration of the lungs on pathological findings may be recognized as GGOs on CT.<sup>17</sup> Third, if there is only a small area of GGO, it is up to the surgeon's subjectivity to determine whether the shadow indicates GGO. Moreover, a GGO component does not necessarily correspond to an LGC.<sup>4</sup> Therefore, although GGO is important in deciding whether or not to perform sublobar resection, it is difficult to identify the stage of NSCLC considering the GGO component.

Pathologically, a LGC consists of bland pneumocyte cells growing along the surface of alveolar walls.<sup>18</sup> Lepidic adenocarcinoma was formerly called bronchoalveolar carcinoma (BAC), but in 2011, a new classification was introduced, and BAC was subdivided into new classifications, such as adenocarcinoma in situ, minimally invasive adenocarcinoma, lepidic predominant adenocarcinoma, and invasive mucinous adenocarcinoma (IMA).<sup>14,15</sup> Therefore, BAC with mucus was classified as IMA separate from invasive non-mucinous adenocarcinoma, which consists of lepidic, acinar, papillary, solid, and micropapillary adenocarcinomas.<sup>14</sup> In previous studies investigating the effects of an LGC on the clinicopathologic features and prognosis of NSCLC, IMA was included in BAC, or those studies were limited to lung adenocarcinoma rather than NSCLC.<sup>4,5,9,11,19-22</sup> One of the limitations of using adenocarcinoma for prognostication in previous studies is that the prognosis was thought to differ depending on the histologic type. Some studies have shown that adenocarcinomas have a better prognosis than squamous cell carcinomas.<sup>6,11,23</sup> In contrast, adenocarcinoma without a GGO component has an equivalent risk of postoperative recurrence compared with squamous cell carcinoma.<sup>6</sup> Therefore, lung adenocarcinoma may not have an improved prognosis compared to squamous cell carcinoma,

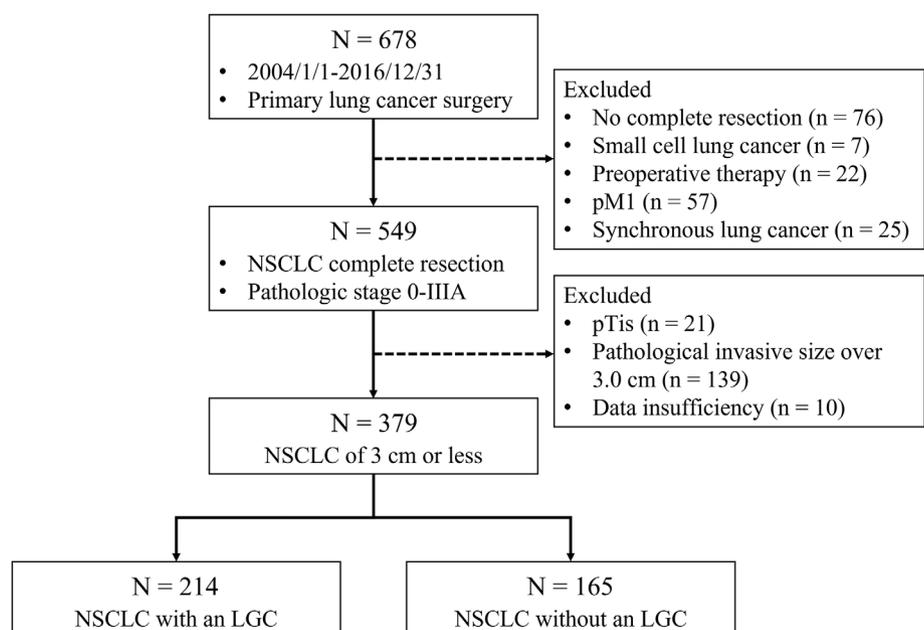
and the prognosis of adenocarcinoma with an LGC may be better than that of other NSCLCs. Therefore, we investigated the effect of an LGC, excluding IMA, on the clinicopathologic features and prognosis of NSCLC rather than lung adenocarcinoma.

## METHODS

### Study population

We retrospectively analyzed the medical histories of patients who underwent radical surgical resection for NSCLC at the University of Yamanashi Hospital (Yamanashi, Japan) between January 2004 and December 2016. This study was approved by the Institutional Review Board of the University of Yamanashi, Japan, (IRB number: 2021-2469) in June 2021, and informed consent was obtained from all participants by opt-out. The inclusion criterion was participants with complete resected NSCLC with a pathologic invasive size  $\leq 3$  cm regardless of pathological stage. The exclusion criteria were as follows: participants with (a) diagnosis of small cell lung cancer of any size, adenocarcinoma in situ, or synchronous lung cancer; (b) previous preoperative chemotherapy or radiotherapy; (c) stage IV disease; and (d) insufficient data lacking clinical, pathological, or prognostic information. The flowchart of the patient selection process is presented in Figure 1. Thirteen patients (1.9%) with pM1 had multiple pulmonary metastases, frank pleural metastases, or malignant pleural effusions. These patients underwent sublobar resection for biopsy because bronchoscopic, CT-guided, or pleural effusion biopsies were non-diagnostic. Forty-four patients (6.5%) with cM0 were diagnosed with pM1 because they had malignant pleural effusions or pleural dissemination. All tumors in those

**FIGURE 1** Patient flowchart. In total, 678 patients undergoing surgery for primary lung cancer were included in our study. Among them, 76 patients had incomplete resection, seven tumors were small cell lung cancer, 22 patients received preoperative therapy, 57 patients were diagnosed with pM1, 25 patients had synchronous lung cancer, 21 patients were diagnosed with pTis, 139 tumors were over 3 cm in pathologic invasive size, and 10 patients had incomplete data. Finally, a total of 379 patients were analyzed. Of these, 214 patients were assigned to the group of non-small cell lung cancer with a lepidic growth component, and 165 patients were assigned to the group without a lepidic growth component. LGC, lepidic growth component; NSCLC, non-small cell lung cancer.



patients had pleural invasion, and most tumors were extensively bordering the pleura even on preoperative CT. However, because there were no obvious pleural effusions or pleural disseminated nodules on preoperative CT, we performed surgery.

The medical records of each patient were reviewed retrospectively, and the pathological staging was re-evaluated according to the 8th edition of the TNM classification.

## Patient care

After the diagnosis of NSCLC through preoperative biopsy or intraoperative frozen sections, radical surgical resection was performed. We performed sublobar resection for peripheral NSCLC  $\leq 2$  cm, which is predominantly GGO on CT.<sup>2,3,8</sup> Postoperative adjuvant chemotherapy was administered to patients with NSCLC stage IA3 or above who wished to be treated. After surgery, we followed-up with patients at intervals of 3 to 6 months, while chest CT was performed every 6 to 12 months. Follow-up was more than 5 years unless a patient dropped out. The median follow-up period was 72 months (interquartile range, 60–101 months).

## Data abstraction

For all patients, medical records included information on age, sex, smoking history, surgical procedure, postoperative adjuvant chemotherapy, pathologic invasive size, lymph node metastasis, pleural involvement, vessel invasion, pathologic TNM status, and histology. Because there were many patients whose number of cigarettes smoked varied according to age, and also patients whose smoking index was not recorded in the database, this study evaluated the presence or absence of smoking without using the smoking index. We created a database of 379 patients who underwent radical surgical resection for NSCLC with a pathologic invasive size  $\leq 3$  cm.

## Pathological evaluation

Surgically resected specimens were fixed with 10% formalin and embedded in paraffin. Specimens sliced every 5 to 10 mm were stained with hematoxylin and eosin and microscopically examined. The histologic type was re-evaluated, and a pathologist (T.K.) and a clinician (H.M.) recorded all patterns of invasive non-mucinous adenocarcinomas (lepidic, acinar, papillary, solid, and micropapillary) at 5% increments following the 5th edition of the World Health Organization (WHO) classification of thoracic tumors.<sup>18</sup> Vascular invasion or lymphatic permeation was defined as a vessel invasion. The group of lung adenocarcinomas containing 5% or more LGC was defined as the LGC group, and the group of NSCLC with little or no LGC was defined as the non-LGC group. Because IMA was distinguished from

non-invasive adenocarcinoma because of its peculiarity according to the WHO classification, it was classified into the non-LGC group. If the area of an LGC was  $< 5\%$ , it would be difficult to determine if an LGC was present; therefore, we assigned these patients to the non-LGC group in our study. NSCLC with both an LGC and IMA was not present in this study.

## Statistical analyses

All statistical analyses were performed using SPSS version 26 (IBM). The  $\chi^2$ , Fisher's exact, or Mann–Whitney *U* tests were used to compare the clinicopathologic characteristics of the patients extracted in this study. The duration of overall survival (OS) was defined as the interval between the date of surgery and the last follow-up date or death from any cause. A Cox proportional hazards model was used to identify significant prognostic factors for 5-year OS. Variables that attained a *p*-value of  $< 0.05$  in the univariate analysis were included in the multivariate model, and a final model was developed using variables that had a *p*-value of  $< 0.05$ . Hazard ratios (HRs), which explained the relationship between a variable and 5-year OS, were reported. All estimates were reported with 95% confidence intervals (CIs). In addition, the LGC and non-LGC groups were matched by pathologic invasive size to compare the effect of an LGC on the clinicopathologic features and prognosis with no difference in pathologic invasive size. The  $\chi^2$ , Fisher's exact, or Mann–Whitney *U* tests were used to compare the clinicopathologic characteristics of the patients with matching pathologic invasive sizes. Survival was estimated using the Kaplan–Meier method, and the two groups were compared using the log-rank test. A *p*-value of  $< 0.05$  was defined to indicate statistical significance.

## RESULTS

### Patient characteristics

The clinicopathologic characteristics of 379 patients are presented in Table 1. Among them, 214 (56%) patients were assigned to the LGC group and 165 (44%) to the non-LGC group. The LGC group was composed of significantly more female patients who never smoked. Although a GGO component was identified in 92% of the patients in the LGC group, it was also found in 16% of those in the non-LGC group, demonstrating that a GGO component did not necessarily correspond to an LGC in this study. The 27 tumors of the non-LGC group with GGO included 25 adenocarcinoma, one squamous cell carcinoma, and one adenosquamous carcinoma. The 25 adenocarcinomas consisted of five IMA and 20 papillary adenocarcinoma. In squamous cell carcinoma with GGO, inflammatory cell infiltration was observed around the tumor. Adenosquamous cell carcinoma with GGO showed pathologic findings similar to IMA. In

**TABLE 1** Patient characteristics based on the presence of a lepidic growth component

Variables	Non-small cell lung cancer of $\leq 3$ cm excluding adenocarcinoma in situ $n = 379$				p-value
	LGC		non-LGC		
	$n = 214$ (56)		$n = 165$ (44)		
Clinical characteristics of the patients					
Age, years	69	(63–75)	68	(62–73)	0.344
Sex					<0.001
Male	98	(46)	122	(74)	
Female	116	(54)	43	(26)	
Smoking history					<0.001
Never	125	(58)	33	(20)	
Current or former	89	(42)	132	(80)	
GGO component					<0.001
Absent	17	(8)	138	(84)	
Present	197	(92)	27	(16)	
Surgical procedure					0.168
Pneumonectomy	0	(0)	1	(1)	
Lobectomy	152	(71)	114	(69)	
Segmentectomy	37	(17)	21	(13)	
Wedge resection	25	(12)	29	(18)	
Adjuvant chemotherapy					0.426
No	197	(92)	148	(90)	
Yes	17	(8)	17	(10)	
Pathologic characteristics of patients					
Pathologic invasive size, mm	10	(5–18)	20	(15)	<0.001
Pathologic nodal status					<0.001
pN0	207	(97)	140	(85)	
pN1	4	(2)	16	(10)	
pN2	3	(1)	9	(5)	
Pleural invasion (pI)					0.015
Positive	32	(15)	41	(25)	
Negative	182	(85)	124	(75)	
Vessel invasion					<0.001
Positive	27	(13)	60	(36)	
Negative	187	(87)	105	(64)	
Pathologic stage (8th edition)					<0.001
IA1	113	(53)	17	(10)	
IA2	44	(21)	57	(35)	
IA3	22	(10)	33	(20)	
IB	28	(13)	33	(20)	
IIA	0	(0)	0	(0)	
IIB	4	(2)	16	(10)	
IIIA	3	(1)	9	(5)	
Histologic type					<0.001
Adenocarcinoma	214	(100)	96	(58)	
Squamous cell carcinoma	0	(0)	52	(32)	
Large cell carcinoma	0	(0)	3	(2)	
Adenosquamous carcinoma	0	(0)	3	(2)	
Large cell neuroendocrine carcinoma	0	(0)	4	(2)	

(Continues)

TABLE 1 (Continued)

Variables	Non-small cell lung cancer of $\leq 3$ cm excluding adenocarcinoma in situ $n = 379$				
	LGC		non-LGC		<i>p</i> -value
	$n = 214$ (56)		$n = 165$ (44)		
Typical carcinoid	0	(0)	4	(2)	
Pleomorphic carcinoma	0	(0)	3	(2)	

Note: The number in parentheses is given as  $n$  (%) or median (interquartile range) unless otherwise indicated. Abbreviations: GGO, ground glass opacity; LGC, lepidic growth component.

TABLE 2 Five-year overall survival analysis of 379 patients with NSCLC of 3 cm or less

Variable	5-year overall survival					
	Univariate analysis			Multivariate analysis		
	HR	95%CI	<i>p</i> -value	HR	95%CI	<i>p</i> -value
Age, years	1.067	1.035–1.101	<0.001	1.07	1.035–1.105	<0.001
Sex, male (vs. female)	2.797	1.546–5.059	0.001	1.787	0.815–3.917	0.147
Smoking history, current or former (vs. never)	2.75	1.520–4.974	0.001	1.126	0.493–2.570	0.779
Surgical procedure, pneumonectomy or lobectomy (vs. limited surgery)	0.762	0.563–1.032	0.079			
Postoperative adjuvant chemotherapy, yes (vs. no)	0.978	0.422–2.266	0.958			
Pathological invasive size, mm	2.102	1.526–2.895	0.001	1.548	1.088–2.202	0.015
Lepidic growth component, absent (vs. present)	3.591	2.082–6.193	<0.001	2.11	1.099–4.051	0.025
Pathological type, others (vs. adenocarcinoma)	1.442	1.201–1.730	<0.001	1.181	0.932–1.495	0.169

Abbreviations: CI, confidence interval; HR, hazard ratio; NSCLC, non-small cell lung cancer.

contrast, 12 tumors of the 17 LGCs without GGO had LGC <10%. The characteristics of the remaining five tumors were as follows: four located in lower lobes and one located in the middle lobe, all five were peripheral lung cancer, four were in small women, and all five had acinar adenocarcinoma.

Patient groups did not differ by surgical procedures and postoperative adjuvant chemotherapy. The pathologic invasive size of the LGC group was significantly smaller than that of the non-LGC group, as were the frequencies of lymph node metastasis, pleural invasion, and vessel invasion. Although several adenosquamous cell carcinomas with a pathologic invasive size  $\geq 3$  cm contained LGCs, the histologic types were all adenocarcinomas in the LGC group, with the non-LGC group composed of adenocarcinomas, squamous cell carcinomas, large cell carcinomas, adenosquamous carcinomas, large cell neuroendocrine carcinomas, typical carcinomas, and pleomorphic carcinomas. In the non-LGC group, 17 patients had IMA.

## Survival analysis

Table 2 reveals the results of multivariate analysis to identify prognostic factors that affect the 5-year OS of NSCLC. The multivariate analysis revealed that older patients, patients with NSCLC with a larger pathologic invasive size, or patients with NSCLC without an LGC had higher mortality, thereby identifying these as significant independent

prognostic factors for survival. Sex, smoking history, and histologic type were not significant prognostic factors in the multivariate analysis.

When the LGC and non-LGC groups were matched by pathologic invasive size, only vessel invasion and histologic type differed significantly between the groups (Table 3). The 5-year OS rate was significantly better in the LGC group than in the non-LGC group (Figure 2).

When the 379 patients were divided into LGC group with GGO, non-LGC group with GGO, LGC group without GGO, and non-LGC group without GGO, the 5-year OS rate was significantly better in the LGC group with GGO than in the non-LGC group without GGO (Figure 3).

Of 214 patients with NSCLC in the LGC group, there was no significant difference in the 5-year OS rate between the 121 patients with an LGC  $\geq 50\%$  and 93 patients with an LGC < 50% (Figure 4).

## DISCUSSION

Because lepidic adenocarcinoma is considered a non-invasive adenocarcinoma,<sup>2,12–15</sup> pathologic invasive size, excluding the LGC that affects the prognosis of NSCLC more than the entire tumor size, determines the T stage of NSCLC.<sup>24</sup> However, some previous studies have reported that the LGC affects the prognosis of lung adenocarcinoma; therefore, this study was not limited to adenocarcinoma and

**TABLE 3** Patients' characteristics after matching pathologic invasive size

Variables	LGC		Non-LGC		p-value
	n = 81		n = 81		
Age, years	70	(62–74)	66	(62–73)	0.332
Sex					0.871
Male	51	(63)	50	(62)	
Female	30	(37)	31	(38)	
Smoking history					0.505
Never	25	(31)	29	(36)	
Current or former	56	(69)	52	(64)	
Surgical procedure					0.051
Pneumonectomy	0	(0)	1	(1)	
Lobectomy	63	(78)	50	(62)	
Segmentectomy	12	(15)	14	(17)	
Wedge resection	6	(7)	16	(20)	
Postoperative adjuvant chemotherapy					0.339
No	69	(85)	73	(90)	
Yes	12	(15)	8	(10)	
Pathologic invasive size, mm	1.8	(1.1–2.2)	1.8	(1.1–2.1)	0.742
Pathologic nodal status					0.105
pN0	77	(96)	69	(85)	
pN1	2	(2)	5	(6)	
pN2	2	(2)	7	(9)	
Pleural invasion (pI)					0.257
Positive	21	(26)	15	(19)	
Negative	60	(74)	66	(81)	
Vessel invasion					0.012
Positive	14	(17)	28	(35)	
Negative	67	(83)	53	(65)	
Pathologic stage (8th edition)					0.397
IA1	17	(21)	17	(21)	
IA2	26	(32)	26	(32)	
IA3	15	(19)	12	(15)	
IB	19	(23)	14	(17)	
IIA	0	(0)	0	(0)	
IIB	2	(2)	5	(6)	
IIIA	2	(2)	7	(9)	
Histologic type					<0.001
Adenocarcinoma	81	(100)	57	(70)	
Squamous cell carcinoma	0	(0)	19	(23)	
Large cell carcinoma	0	(0)	1	(1)	
Adenosquamous carcinoma	0	(0)	1	(1)	
Large cell neuroendocrine carcinoma	0	(0)	2	(2)	
Typical carcinoid	0	(0)	1	(1)	

Note: The numbers in parentheses is given as n (%) or median (interquartile range) unless otherwise indicated.  
Abbreviation: LGC, lepidic growth component.

investigated the effect of the LGC on the prognosis of NSCLC.<sup>5,9,19,20</sup> In this study, the LGC was a favorable prognostic factor for NSCLC in the multivariate analysis.

Furthermore, when the pathologic invasive size was matched, the prognosis of NSCLC with an LGC was significantly better than that without an LGC. Therefore,

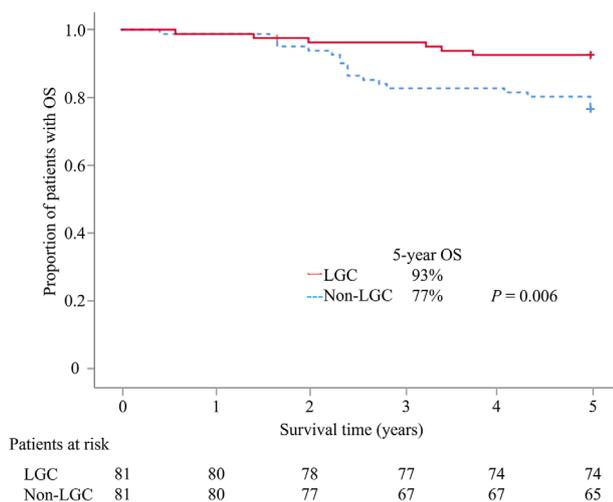
pathologic invasive size and LGC may both be variables influencing the T stage of NSCLC.

Vessel invasion, especially lymphatic infiltration, is not a good prognostic factor for NSCLC.<sup>25</sup> In this study, vessel invasion was frequently observed in the non-LGC group; therefore, vessel invasion might affect the poor prognosis of NSCLC without an LGC.

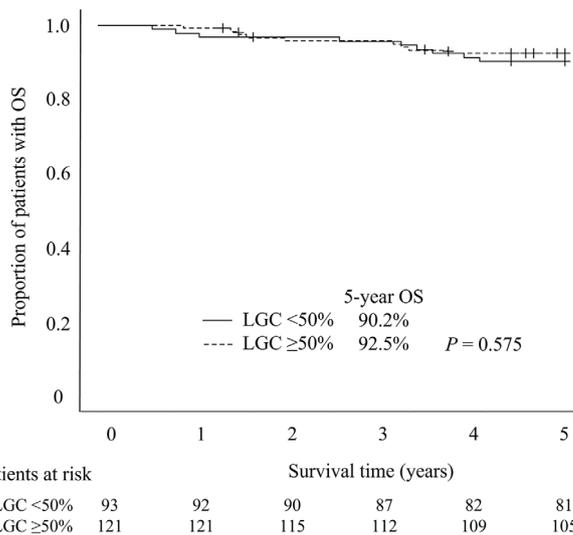
Lung adenocarcinoma has a better prognosis than squamous cell carcinoma.<sup>4,5,9,11,19-22</sup> However, the eighth edition of the TNM classification does not distinguish between histologic types for the pathologic stage of NSCLC.<sup>26</sup> In addition, lung

adenocarcinoma without GGO has a similar prognosis to squamous cell carcinoma.<sup>6,11</sup> In this study, the histologic type was not a significant prognostic factor in the multivariate analysis that compared the effect of LGC and histologic type on the prognosis of NSCLC, suggesting that the difference in prognosis between adenocarcinoma without an LGC and NSCLC can be attributed to adenocarcinoma.

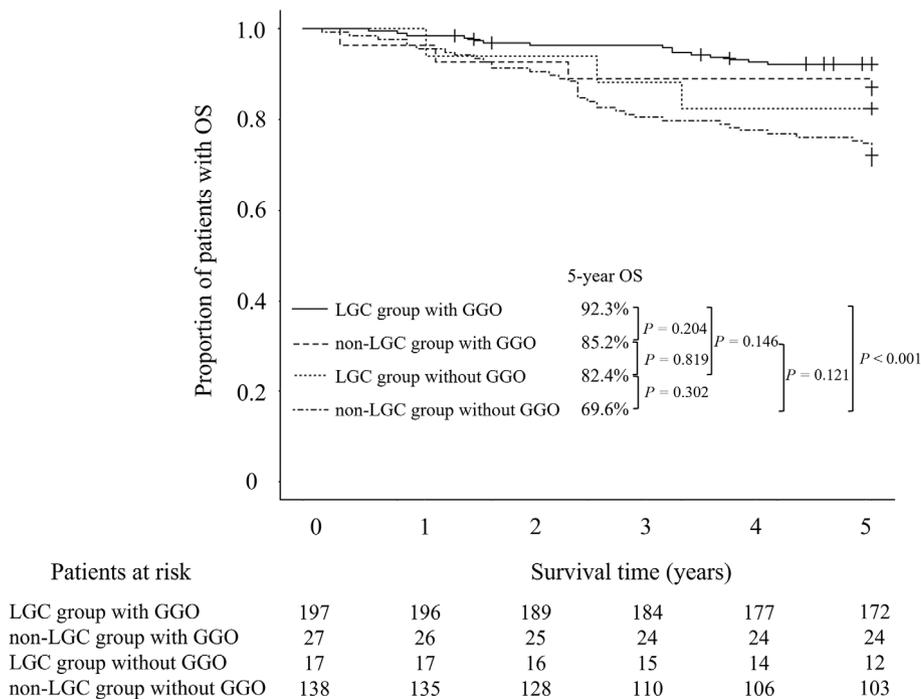
When the pathologic invasive size was matched, there was a trend toward more sublobar resection in the non-LGC



**FIGURE 2** Kaplan–Meier curve of 5-year overall survival (OS) divides 162 patients into two subgroups: Tumors with and without a lepidic growth component (LGC), after matching by pathologic invasive size. The 5-year OS of tumors with an LGC was 93%, and that of tumors without an LGC was 77% ( $p = 0.006$ ).



**FIGURE 4** Kaplan–Meier curve of 5-year overall survival (OS) divides 214 patients into two subgroups: tumors with a lepidic growth component (LGC) <50% and an LGC ≥50%. The 5-year OS of tumors with an LGC <50% was 90.2%, and that of tumors with an LGC ≥50% was 92.5% ( $p = 0.575$ ).



**FIGURE 3** Kaplan–Meier curve of 5-year overall survival (OS) divides 379 patients into four subgroups: Lepidic growth component (LGC) group with ground glass opacity (GGO), non-LGC group with GGO, LGC group without GGO, and non-LGC group without GGO. The 5-year OS of LGC group with GGO was 92.3%, that of non-LGC group with GGO was 85.2%, that of LGC group without GGO was 82.4, and that of non-LGC group without GGO was 69.6%.

group (Table 3); however, this difference was not significant ( $p = 0.051$ ). Of 379 patients, 49 had recurrent lung cancer. Of the patients who relapsed, three patients with LGC and seven without LGC underwent reduced surgery. Three patients with LGC and two patients without LGC had local recurrence, four patients without LGC had distant recurrence, and one patient without LGC had both local and distant recurrence. In surgery, we try to keep the margin larger than the tumor diameter, but in all cases of local recurrence, the margin was  $<1$  cm. The characteristics of the seven patients without LGC who had recurrence were as follows: all but one patient had a total tumor diameter of 2 cm or more, three patients had pleural invasion, two patients had solid adenocarcinoma, two patients had squamous cell carcinoma, and one patient was pN1. The 5-year survival rate for patients without LGC before tumor size matching was 72.1%; among those patients, the 5-year survival rate was 74.8% and was 66% for patients who underwent lobectomy and sublobar resection, respectively ( $p = 0.248$ ). Although there was no significant difference because of the small number of patients, sublobar resection tended to have a negative impact on prognosis in patients without LGC.

Previous studies have reported that GGO of different sizes have different prognoses, and LGCs may also have different prognoses depending on size. However, in this study, LGCs of different sizes did not affect prognosis. One reason may be that the number of patients was small and therefore, the LGC group could only be divided into two groups,  $\geq 50\%$  and  $<50\%$ . Future studies are needed with a larger number of patients.

Previous studies have reported LGCs that do not correspond to GGO: peritumoral inflammatory cell infiltrates, mucus, some papillary adenocarcinoma, and poor alveolar aeration. In this study, inflammatory cell infiltration around squamous cell carcinoma, mucus of IMA, some papillary adenocarcinoma, and poor air retention in the lower or middle lobe because of gravity were also recognized as GGO on preoperative CT despite the absence of LGC.

Our study had some limitations. This retrospective study was conducted at a single institution. Ten patients were excluded, primarily because of a lack of clinical or pathologic data. Because LGC is evaluated by histopathologic examination, it is often not considered in determining the surgical procedure. However, if future studies show that an LGC affects the surgical procedure, it may be possible to investigate LGCs in preoperative or intraoperative pathologic examinations, and it may alter the surgical procedure. In recent years, it has become possible to collect relatively large specimens even with bronchoscopic biopsy,<sup>27</sup> therefore; it may be possible to evaluate the presence or absence of LGCs preoperatively. However, although intraoperative rapid pathological examination can make a histopathological diagnosis to some extent, it is often difficult to accurately distinguish between lepidic and papillary adenocarcinoma. Therefore, the development of a method to accurately evaluate the lepidic growth component by intraoperative rapid pathological examination is a future issue.

In conclusion, patients with NSCLC with an LGC have a better prognosis than those without an LGC. According to the eighth edition of the TNM classification, for patients with an NSCLC of 3 cm or less, the T stage of NSCLC is determined by the pathologic invasive diameter and pleural invasion, but the T stage of NSCLC considering an LGC may offer a more accurate prognosis.

## DISCLOSURES

The authors have nothing to disclose.

## CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest associated with this manuscript.

## AUTHOR CONTRIBUTIONS

All authors had full access to the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: D.S. Acquisition of data: H.M., H.M., T.K., H.S., A.S., Y.O. and U.T. Analysis and interpretation of the data: D.S. Drafting of the manuscript: D.S. Critical revision of the manuscript for important intellectual content: D.S., H.M., T.K. and H.N. Statistical analysis: D.S.

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## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author, D.S., on reasonable request.

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## ETHICAL APPROVAL AND INFORMED PATIENT CONSENT

This study was approved by the Institutional Review Board of the University of Yamanashi, Japan, (IRB number: 2021–2469) in June 2021, and informed consent was obtained from all participants by opt-out.

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