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Pathological high malignant grade is higher risk of recurrence in pN0M0 invasive lung adenocarcinoma, even with small invasive size

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Abstract

Introduction: Tumor size is an absolute recurrence risk in lung cancer. Although morphological features also reflect recurrence risk, its significance among lower-risk cases characterized by small size is unknown. We aimed to evaluate the relationship between pathological invasive tumor size and morphological features, and their prognostic impact by considering them simultaneously in lung adenocarcinoma.

Patients and methods: We retrospectively reviewed 563 pN0M0 patients with pathological invasive size of ≤40 mm. The patients were classified by pathological invasive size and pathological malignant grading using the proportion of subhistological components. The prognostic impact was evaluated using recurrence-free survival (RFS) and overall survival (OS). The impact on prognosis was evaluated using uni- and multivariate analyses.

Results: The proportion of histological grade changed according to invasive tumor size. Patients with high malignant grade (G3) showed worse RFS than those with low and intermediate malignant grade (G1+2) with invasive size ≤20 mm. The 5-year RFS (G1+2 vs. G3) in 5–10 mm was 96.0% vs. 83.3% (HR = 5.505, 95% CI = 7.156–1850, $p < 0.001$) and in 10–20 mm was 87.8% vs. 67.1% (HR = 2.829, 95% CI = 4.160–43.14, $p < 0.001$). G3 patients were significantly bigger in invasive size and included more pleural/lymphatic/vascular invasion and recurrence. Multivariate analysis indicated pathological G3 status was significantly associated with worse RFS (HR = 2.097, 95% CI = 1.320–3.333, $p = 0.002$).

Conclusions: Invasive tumor size and pathological malignant grade overlap in invasive adenocarcinoma. G3 patients are more likely to have pleural/lymphatic/vascular invasion and significantly worse RFS compared to G1/G2 cases, even with a small invasive size of ≤20 mm.

KEYWORDS
early stage, IASLC, lymphovascular invasion, surgery, TNM

INTRODUCTION

Adenocarcinoma is the most frequent histological type of non-small-cell lung cancer (NSCLC). The standard curative treatment is complete resection for nodal-negative cases, and the risk of recurrence mainly depends on pathological tumor size and morphological features. In lung adenocarcinoma, both the pathological invasive tumor size and the International Association for the Study of Lung Cancer (IASLC) pathological grade using the proportion of subhistological components reflect the risk of recurrence. However, categorizations based on invasive tumor size and

pathological features have been established independently. They are different concepts, and their methodologies for categorization also vary. Tumor size is a conventional and gold-standard method for evaluating the risk of recurrence, whereas the IASLC pathological grade is relatively new. No study has evaluated their association and whether the pathological malignant grading system is valid even in lower-risk cases characterized by small tumor size.

Thus, this study aimed to evaluate the relationship between pathological invasive tumor size and the latest IASLC pathological grade, and the prognostic impact of each status in completely resected pN0M0 adenocarcinoma of the lung.

METHODS

Study design and patients

This retrospective study evaluated patients with lung cancer who underwent resection at Hiroshima University Hospital between January 2007 and December 2018. Only patients with confirmed primary lung adenocarcinoma without nodal/distant metastasis were included. Due to the small number of patients, those with pathological invasive size >50 mm were not included. Patients with variant types of adenocarcinoma, post-preoperative chemotherapy/chemoradiotherapy, missing complete pathological data, no follow-up information, or non-R0 resection were also excluded. Patients with adenocarcinoma in situ (AIS) and minimally invasive adenocarcinoma (MIA) were excluded because they were not included in the latest IASLC pathological malignant grading system.

Estimation of pathological invasive tumor size and malignant grade

Pathological diagnosis was performed by two pathologists (K.K. and Yu.T.) according to the 2015 World Health Organization classification.[1] The variant type of adenocarcinoma was defined, and the subhistology component in adenocarcinoma was recorded quantitatively at 5% intervals according to the IASLC proposal.[2] Pathological invasive tumor size was measured in the resected specimen directly or calculated as the proportion of invasive component in the whole tumor size, including the noninvasive tumor component as recommended.[3] The IASLC pathological grade was determined according to the ratio of the subhistological components.[4] Synchronous or asynchronous multiple lesions were diagnosed as another primary or intrapulmonary metastasis/recurrence according to the IASLC proposal.[5,6]

Statistical analysis

The prognostic impact was evaluated using recurrence-free survival (RFS) and overall survival (OS). RFS was defined as the period from the day of the operation to the day of recurrence or death from any cause. OS was defined as the period from the day of the operation to the day of death from any cause. RFS and OS curves were generated using the Kaplan–Meier method and compared using the log-rank test. The significance of frequencies was evaluated using the Chi-square or Yates-square test. Patient age and invasive tumor size as continuous variables were compared using the Mann–Whitney *U*-test. The prognostic impact of each variable was evaluated via univariate and multivariate analyses using the Cox proportional hazards model with a backward stepwise procedure. Statistical analyses were performed using SPSS (version 20.0; IBM Corp.). All tests were two-tailed, and a p value less than 0.05 was considered significant.

RESULTS

Distribution and clinicopathological features

In total, 576 pN0M0 patients were initially evaluated and categorized according to pathological invasive size (>5 and ≤10 mm, >10 and ≤20 mm, >20 and ≤30 mm, >30 and ≤40 mm, or >40 and ≤50 mm) and pathological grade (G1, G2, or G3). Those with invasive sizes >40 and ≤50 mm were excluded because of the small number of patients. Finally, 563 patients were included in the analysis. The patient distribution according to invasive size and pathological grade is shown in Figure 1(a), and the clinicopathological characteristics are shown in Table 1. The distribution of invasive size

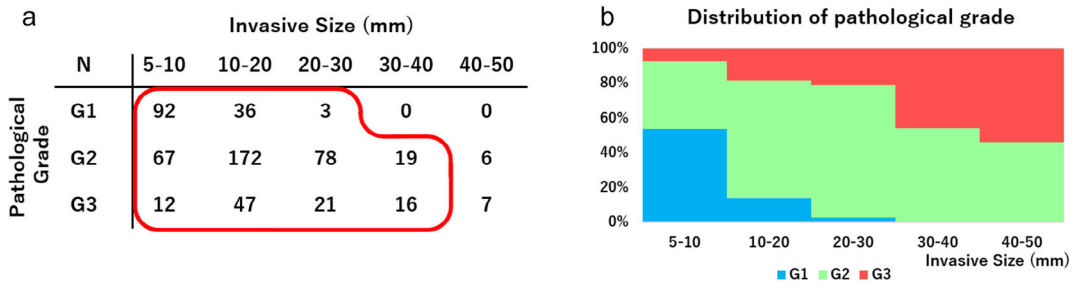

FIGURE 1 Distribution of the 576 patients according to invasive tumor size and pathological malignant grading. A total of 563 patients (surrounded by red squares) were evaluated (a). Bar graph indicating the percentage of each pathological grade according to invasive tumor size (b)

TABLE 1 Patient characteristics of analyzed cases ($N = 563$)

Characteristic	Number of cases (%)
Age, years	
Median (interquartile range)	69 (64–75)
Sex	
Male/female	305 (54.2)/258 (45.8)
Smoking status	
Ex- or current smoker	302 (53.6)
Never smoked	261 (46.4)
Surgical procedure	
Lobectomy	333 (59.1)
Segmentectomy	171 (30.4)
Wedge resection	59 (10.5)
Pathological invasive tumor size	
>5 and ≤10 mm	171 (30.4)
>10 and ≤20 mm	255 (45.3)
>20 and ≤30 mm	102 (18.1)
>30 and ≤40 mm	35 (6.2)
T descriptor	
T1a/T1b/T1c	161 (28.6)/214 (38.0)/75 (13.3)
T2a/T2b/T3	93 (16.5)/0 (0)/20 (3.6)
Pathological grade	
G1/G2/G3	131 (23.3)/336 (59.7)/96 (17.1)
Pleural invasion	
Pl0	479 (85.1)
Pl1/Pl2/Pl3	58 (10.3)/9 (1.6)/17 (3.0)
Lymphatic invasion	
Negative/positive	492 (87.4)/71 (12.6)
Vascular invasion	
Negative/positive	453 (80.5)/110 (19.5)
Intrapulmonary metastasis	
Negative/positive	551 (97.9)/12 (2.1)
Recurrence	
Negative/positive	501 (89.0)/62 (11.0)

and pathological grade overlapped; the larger the invasive size, the less and more the proportion of G1 and G3 changed, respectively (Figure 1(b)).

Validation of classification by invasive size or pathological grading

Categorization by invasive tumor size or pathological grading was a valuable classification method in all 563 cases. RFS was significantly different according to invasive size, except in those with >20 and ≤30 mm versus with >30 and ≤40 mm invasive size. The 5-year RFS rates were as follows: >5 and ≤10 mm versus >10 and ≤20 mm: 95.1% versus 84.4%, hazard ratio (HR) = 1.726, 95% confidence interval (CI) = 1.704–9.346, $p = 0.00144$; >10 and ≤20 mm versus >20 and ≤30 mm: 84.4% versus 72.5%, HR = 1.783, 95% CI = 2.074–10.49, $p < 0.001$; >20 mm and ≤30 mm versus >30 and ≤40 mm: 72.5% versus 63.9%, HR = 1.596, 95% CI = 0.8782–4.985, $p = 0.0956$ (Figure 2(a)).

RFS was also significantly different between any pathological grade. The 5-year RFS rates according to the pathological grade were as follows: G1 versus G2: 93.6% versus 85.2%, HR = 1.553, 95% CI = 1.236–6.830, $p = 0.0145$; G2 versus G3: 85.2% versus 66.5%, HR = 2.548, 95% CI = 5.342–26.05, $p < 0.001$ (Figure 2(b)). Similar results were observed for OS. Invasive size partially stratified cases with significance, and patients with G3 status had particularly poor OS (Supporting Information Figure S1(a),(b)).

Prognostic impact of G3 status on RFS and OS

Patients with G3 status showed the worst prognosis among the three grade categories (Figure 2(b) and Supporting Information S1(b)). Compared with the G1+G2 groups, the G3 patients included significantly more male patients, more ex- or current smokers, fewer T1a and more T2a patients, and more patients with pleural, lymphatic, or vascular invasion. Furthermore, invasive size and the number of recurrences were significantly larger and higher in the G3 patients, respectively (Table 2).

Among the patients with >5 and ≤10 mm or with >10 and ≤20 mm invasive size, those with G3 showed significantly worse RFS than those with G1+G2 status. The 5-year RFS was 83.3% versus 96.0% (HR = 5.505, 95% CI = 7.156–1850, $p < 0.001$) in those with >5 and ≤10 mm invasive disease, while it was 67.1% versus 87.8% (HR = 2.829, 95% CI = 4.160–43.14, $p < 0.001$) in those with >10 and ≤20 mm invasive size (Figure 2(c),(d)). Meanwhile, although G3 patients also had poorer RFS than G1+2 or G2 patients among those with >20 and ≤30 mm or >30 and ≤40 mm invasive size, the difference was not significant because of the small number of cases (Figure 2(e),(f)). Similar results were observed for OS (Supporting Information Figure S1 (c)–(f)). In several categories, the G3 patients were significantly more often accompanied by pleural, lymphatic, or vascular invasion than the G1, G2, or G1+2 patients (Figure 3). Univariate and multivariate analyses indicated that male sex, positive smoking history, pathological invasive size, and pathological G3 status were significantly associated with worse RFS (G3 status in multivariate analysis: HR= 2.097, 95% CI = 1.320–3.333, $p = 0.002$) (Table 3). Pathological G3 status was also significantly associated with worse OS (HR = 2.364, 95% CI = 1.305–4.283, $p = 0.005$) (Supporting Information Table S1).

Impact of G3 status on T descriptor

Tumor, node and metastasis (TNM) stage is the gold standard for predicting the risk of recurrence, and invasive tumor size is merely one of the factors determining T

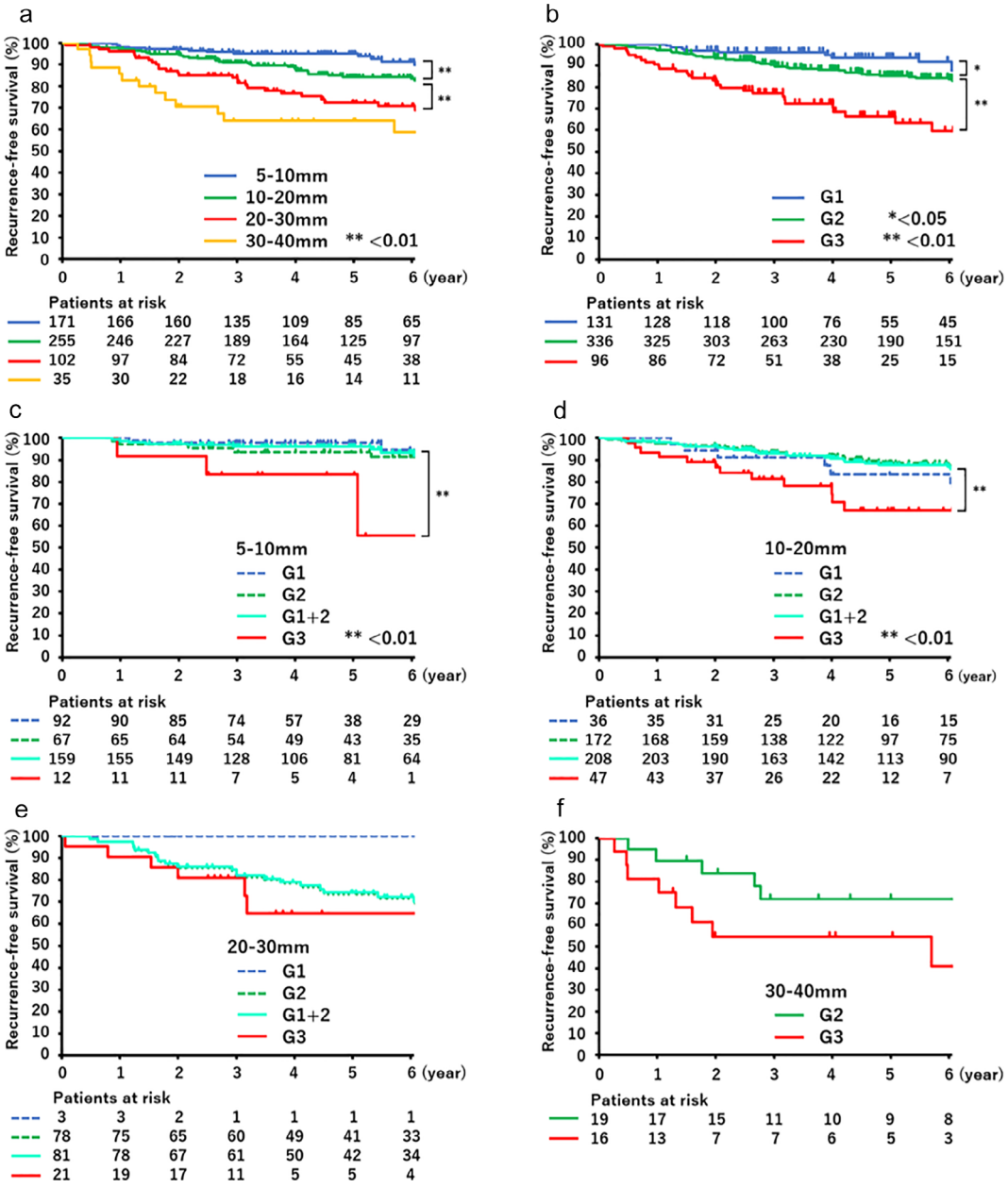

FIGURE 2 Recurrence-free survival curves by invasive tumor size (a) and by pathological grade (b). Recurrence-free survival curves by pathological grade in 5–10 mm (c), 10–20 mm (d), 20–30 mm (e), and 30–40 mm (f) invasive size. There was significant difference between the G1+2 and G3 groups in those with >5 and ≤20 mm. The 5-year RFS for G1+2 vs. G3 in >5 and ≤10 mm is 96.0% vs. 83.3% (HR = 5.505, 95% CI = 7.156–1850, $p < 0.001$) (c), in >10 and ≤20 mm is 87.8% vs. 67.1% (HR = 2.829, 95% CI = 4.160–43.14, $p < 0.001$) (d), in >20 and ≤30 mm is 74.3% vs. 64.8% (HR = 1.375, 95% CI = 0.515–4.382, $p = 0.456$) (e), and for G2 vs. G3 in >30 and ≤40 mm: 71.9% vs. 54.5% (HR = 2.470, 95% CI = 0.836–7.802, $p = 0.0998$) (f). CI, confidence interval; HR, hazard ratio; RFS, recurrence-free survival

descriptor in TNM stage. In patients with pleural invasion, invasive size <30 mm is not accounted for while categorizing T status and patients can be upstaged by pleural invasion. Therefore, we further evaluated the relationship between T descriptor and pathological grade and found similar results (Figure 4). The proportion of G1 and G3 patients decreased and increased, respectively, as T descriptor advanced (Figure 4(b)). Regarding RFS, classification by T descriptor stratified T1a–T2a cases with significance except for between T1a and T1b. The 5-year RFS for T1a versus T1b was 94.8% versus 89.7% (HR = 1.187, 95% CI = 0.5792–3.953, $p = 0.398$), T1b versus T1c: 89.7% versus 81.7% (HR = 1.747, 95% CI = 1.591–15.10, $p = 0.00563$), and T1c versus T2a: 81.7% versus 58.9% (HR = 2.422, 95% CI = 2.029–8.318, $p < 0.001$) (Figure 4(c)). Among patients with T1a or T1b status, G3 patients had significantly worse RFS than G1+2 patients. The 5-year RFS among T1a patients was 75.0% versus 95.9% (HR = 5.139, 95% CI = 3.301–2578, $p = 0.00775$), while that for T1b patients was 77.9% versus 91.3% (HR = 2.332, 95% CI = 1.195–

TABLE 2 Patient characteristics and comparison according to pathological grade

	G1 ($N = 131$)	G2 ($N = 336$)	G3 ($N = 96$)	p value (G1+2 vs. G3)
Age, years				
Median (interquartile range)	71 (65–76)	69 (63–75)	69 (63–75)	0.519
Sex, *N* (%)				
Male/female	66 (50.4)/65 (49.6)	174 (51.8)/162 (48.2)	65 (67.7)/31 (32.3)	0.00348
Smoking status, *N* (%)				
Never smoked/ex- or current smoker	63 (48.1)/68 (51.9)	165 (49.1)/171 (50.9)	33 (34.4)/63 (65.6)	0.00973
Surgical procedure, *N* (%)				
Lobectomy	71 (54.2)	203 (60.4)	59 (61.5)	0.613
Segmentectomy	45 (34.4)	101 (30.1)	25 (26.0)	0.311
Wedge resection	15 (11.5)	32 (9.5)	12 (12.5)	0.478
Pathological invasive tumor size, *N* (%)				
Median (interquartile range)	8.4 (6–10.75)	16 (11.3–21.1)	20 (13–26.2)	<0.001
>5 and ≤10 mm	92 (70.2)	67 (19.9)	12 (12.5)	<0.001
>10 and ≤20 mm	36 (27.5)	172 (51.2)	47 (49.0)	0.428
>20 and ≤30 mm	3 (2.3)	78 (23.2)	21 (21.9)	0.294
>30 and ≤40 mm	0 (0.0)	19 (5.7)	16 (16.7)	<0.001
T descriptor, *N* (%)				
T1a	88 (67.2)	65 (19.3)	8 (8.3)	<0.001
T1b	31 (23.7)	153 (45.5)	30 (31.3)	0.134
T1c	3 (2.3)	59 (17.6)	13 (13.5)	0.944
T2a	7 (5.3)	47 (14.0)	39 (40.6)	<0.001
T3	2 (1.5)	12 (3.6)	6 (6.3)	0.206
Pleural invasion, *N* (%)				
0/1	123 (93.9)/6 (4.6)/	294 (87.5)/27 (8.0)	62 (64.6)/25 (26.0)	<0.001/<0.001
2/3	1 (0.8)/1 (0.8)	10 (3.0)/5 (1.5)	6 (6.3)/3 (3.1)	0.0885/0.388
Lymphatic invasion, *N* (%)				
Negative/positive	127 (96.9)/4 (3.1)	301 (89.6)/35 (10.4)	64 (66.7)/32 (33.3)	<0.01
Vascular invasion, *N* (%)				
Negative/positive	120 (91.6)/11 (8.4)	282 (83.9)/54 (16.1)	51 (53.1)/45 (46.9)	<0.01
Pulmonary metastasis, *N* (%)				
Negative/positive	130 (99.2)/1 (0.8)	329 (97.9)/7 (2.1)	92 (95.8)/4 (4.2)	0.259
Recurrence, *N* (%)				
Negative/positive	125 (95.4)/6 (4.6)	301 (89.6)/35 (10.4)	75 (78.1)/21 (21.9)	<0.001

31.96, $p = 0.0298$) (Figure 4(d),(e)). Meanwhile, among T1c and T2a patients, there was no significant difference in RFS between G2 and G3 patients due to their small number (Figure 4(f),(g)). For OS, significant difference was found only between T1b and T1c (Supporting Information Figure S2(a)–(e)).

DISCUSSION

Tumor size is the absolute status for predicting malignant potential in several types of solid tumors. In lung cancer, invasive tumor size has been employed to define T descriptor in TNM staging.[7] Pathological features also influence prognosis and their classification has been revised several times, especially in lung adenocarcinoma.[1,2,4] In 2020, an IASLC pathological malignant grading system using the proportion of subhistological components for lung adenocarcinoma was proposed[4] and validated.[8] Although the overlap between growth in tumor size and histological changes was predicted,[9,10] no study has estimated their relationship. As predicted, our results indicated that the proportion of cases with higher malignant grades increased with tumor growth. Nevertheless, some G3 patients were identified in cases with small invasive sizes, and it has been unclear whether higher malignant grade affects prognosis even when the invasive size is small.

We previously showed that pathological status with non- or ≤5 mm invasive size determined prognosis in lung adenocarcinoma. AIS and MIA are free from recurrence and their pathological status is more useful than the whole tumor size in predicting the risk of recurrence.[11] Herein, we

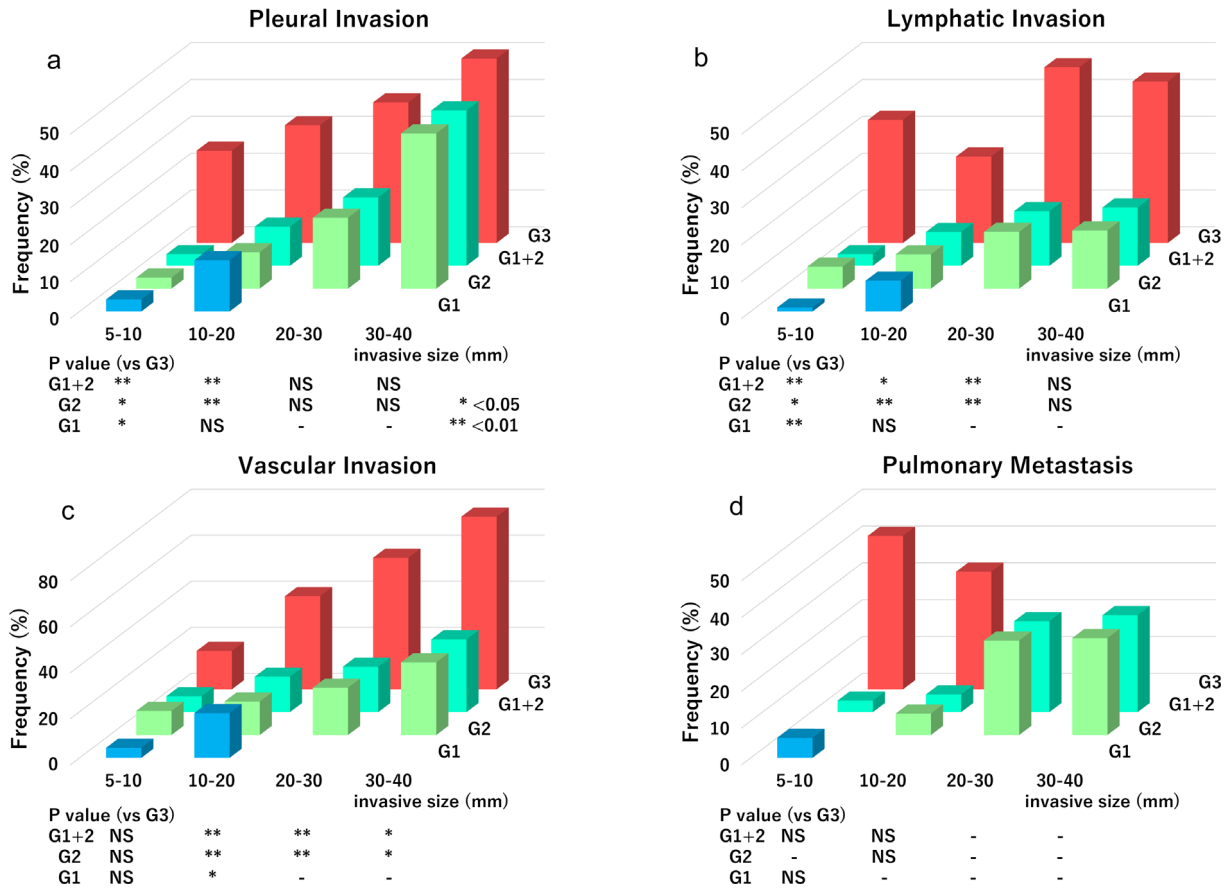

FIGURE 3 Frequency and comparison among G1, G2, G1+2, and G3 patients according to pleural invasion (a), lymphatic invasion (b), vascular invasion (c), or pulmonary metastasis (d). NS, not significant

TABLE 3 Uni- and multivariate analyses for recurrence-free survival

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age	1.074 (1.047–1.101)	<0.001	1.076 (1.051–1.103)	<0.001
Male sex	1.283 (0.860–1.914)	0.222	0.684 (0.379–1.232)	0.206
Ex- or current smoker	1.688 (1.123–2.539)	0.012	1.712 (1.130–2.592)	0.011
Sublobar resection	0.888 (0.589–1.337)	0.569	0.941 (0.605–1.463)	0.786
Invasive size	1.061 (1.038–1.084)	<0.001	1.046 (1.022–1.071)	<0.001
Pathological grade 3	2.931 (1.905–4.511)	<0.001	2.097 (1.320–3.333)	0.002
Pulmonary metastasis	2.528 (0.925–6.906)	0.070	1.521 (0.550–4.209)	0.419

Abbreviations: CI, confidence interval; HR, hazard ratio.

show that pathological status influences prognosis in cases with small invasive sizes, as AIS and MIA have. The results of the current study indicate that G3 status, even with small invasive size, should be given special attention due to its high malignant potential, which is, in turn, because of the high frequency of pleural, lymphatic, or vascular invasion. These findings are in line with previous literature. Lymphatic and vascular invasion are associated with a higher risk of recurrence in lung cancer,[12–14] and the existence of micropapillary or solid components is related to worse prognosis even though they are not predominant components.[15–17] Thus, the usefulness of the grading system did not change in patients with small invasive sizes. Namely, patients with at least 20% of micropapillary or solid components (G3 status) showed poor RFS, despite having a small invasive size, owing to the high frequency of pleural, lymphatic, or vascular invasion. The impact of the grading system on OS was similar, but the significance was smaller compared to that on RFS (Supporting Information Figures S1(c),(d) and S2(b)–(e)). This might be due to the small number of patients or the prolonged post-recurrence survival by tyrosine kinase inhibitors[18–20] or immune-checkpoint inhibitors.

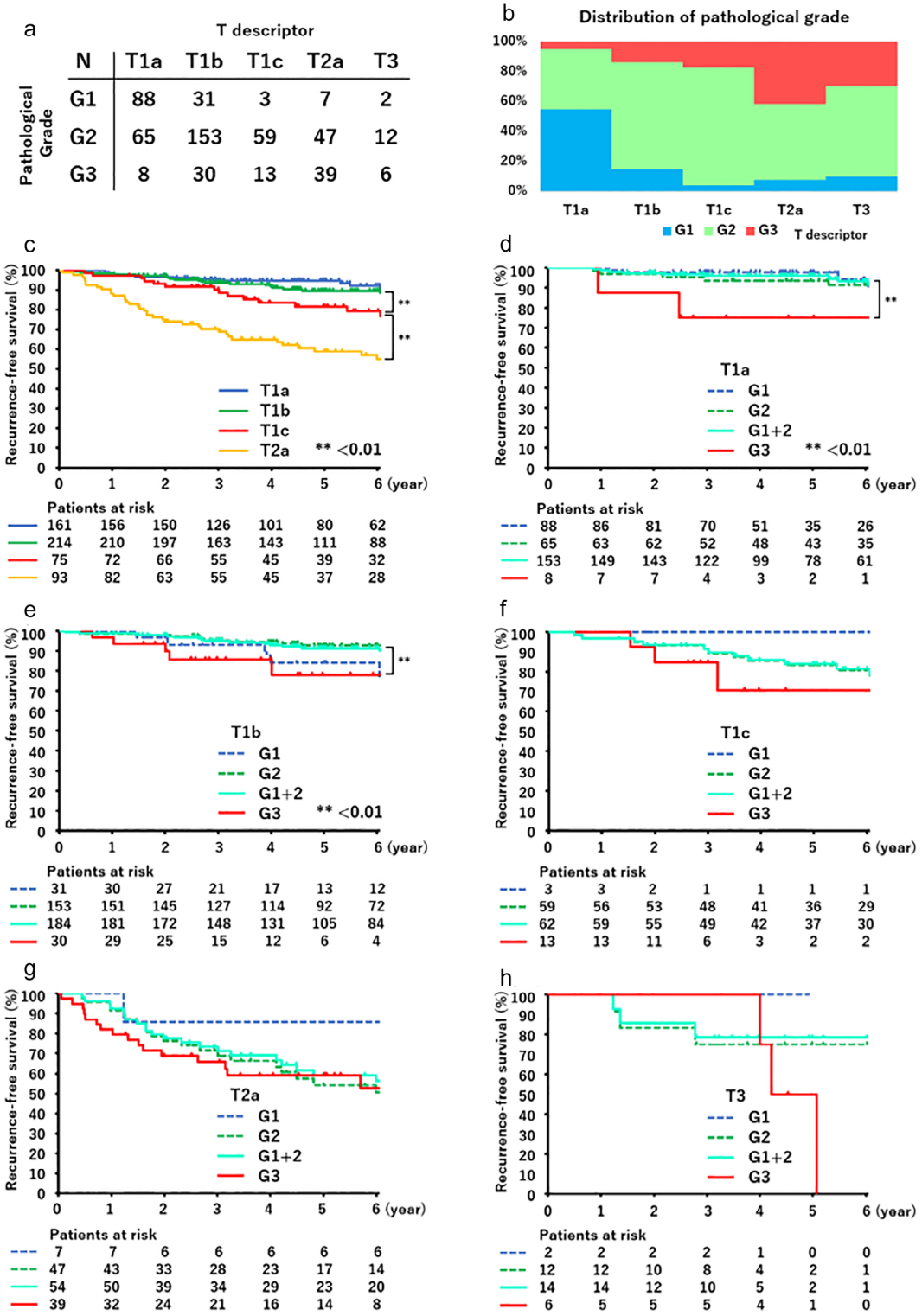

FIGURE 4 Distribution of the 563 patients according to T descriptor and pathological malignant grade (a). Bar graph indicating the percentage of each pathological grade according to T descriptor (b). RFS curves by T descriptor (c) or pathological grade (d). RFS curves by T1a (d), T1b (e), T1c (f), T2a (g), or T3 (h). There was a significant difference between the G1+2 and G3 cohort inT1a and T1b. The 5-year RFS for G1+2 vs. G3 in T1a is 95.9% vs. 75.0% (HR = 5.139, 95% CI = 3.301–2578, $p = 0.00775$) (d), the 5-year RFS for G1+2 vs. G3 in T1b is 91.3% vs. 77.9% (HR = 2.332, 95% CI = 1.195–31.96, $p = 0.0298$) (e), the 5-year RFS for G1+2 vs. G3 in T1c is 83.8% vs. 70.5% (HR = 1.777, 95% CI = 0.434–10.52, $p = 0.350$) (f), G1+2 vs. G3 in T2a: 59.2% vs. 59.2% (HR = 1.340, 95% CI = 0.6995–2.967, $p = 0.322$) (g), and G1+2 vs. G3 in T3: 78.6% vs. 50.0% (HR = 2.018, 95% CI = 0.391–12.07, $p = 0.376$) (h). CI, confidence interval; HR, hazard ratio; RFS, recurrence-free survival

In TNM staging, invasive tumor size is usually represented by T descriptor, which also considers pleural invasiveness. We also confirmed the overlap between pathological grade and T descriptor, and the high malignant behavior of G3 did not change in patients with early T descriptors. RFS was worse in G3 patients with pT1a–1b disease that was not accompanied by pleural invasion (Figure 4(d),(e)). After excluding cases with lymphatic or vascular invasion, RFS in G3 patients remained worse than that in G1+2 patients. The 5-year RFS for G1+2 versus G3 was 94.5% versus 75.6% (HR = 3.292, 95% CI = 5.916–423.9, $p < 0.001$; data not shown). This suggests that the high malignant potential of G3 stems not only from pleural, lymphatic, and/or vascular invasion, but also probably from G3 status itself. Among patients with >20 and ≤40 mm invasive size or pT1c–2a patients, RFS did not significantly differ according to the malignant grade (G1+2 vs. G3). This might also be because of the small number of cases. However, estimating the impact of G3 status in >20 and ≤40 mm or pT1c–2a patients might be less meaningful because of their overlapping. We found a higher proportion of G3 patients among those with larger invasive sizes or more advanced T descriptors. Therefore, estimating the G3 status is more akin to evaluating the malignant potential of tumors with larger invasive size or more advanced T descriptor itself. The notable result in the present study is that patients with G3 status showed poor prognosis despite having a small invasive size of ≤20 mm.

Our study had some limitations. This was a retrospective and single-center study. After classification by invasive size and pathological grade, the number of patients in each category was unbalanced. Future studies should include a larger and equally distributed sample size to further evaluate the prognostic impact and relationship between invasive size and pathological grade.

In conclusion, the pathological invasive tumor size and malignant grade overlap in invasive adenocarcinoma of the lung. Invasive adenocarcinoma with pathological G3 status is more likely to involve pleural, lymphatic, and/or vascular invasion and has significantly worse RFS than G1/G2 status, even when the invasive size is ≤20 mm.

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CONFLICT OF INTEREST

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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