



Validation of T stage classification strategy for >2 cm ground-glass opacity non-small cell lung cancer: a retrospective cohort study

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Background: The Lung Cancer Staging Program of the International Association for the Study of Lung Cancer (IASLC) has proposed using solid component size, rather than overall tumor size, for T-staging. However, studies focusing on patients with ground-glass opacity (GGO) lesions with a diameter larger than 2 cm are limited. This study aims to validate the T stage classification strategy recommended by IASLC in this specific and less-studied patient group.

Methods: Patients diagnosed with primary non-small cell lung cancer (NSCLC) who underwent lobectomy between December 2009 and December 2018 were included in this study. Clinical, pathological, and prognostic data were prospectively collected and retrospectively reviewed. Patients were eligible if they were confirmed to have NSCLC, underwent lobectomy, had complete follow-up data, and were not diagnosed with any other malignancies. The propensity score matching (PSM) method was employed to ensure baseline characteristic balance. Two groups of patients matched with the GGO group at baseline were stratified based on overall tumor size (group matched by overall size) and solid component size (group matched by solid component size), respectively. Overall survival (OS) and recurrence-free survival (RFS) were analyzed using the Cox proportional model and Kaplan-Meier method. Follow-up was conducted regularly to assess these outcomes. The T-staging applied was based on the solid component size according to the 8th edition IASLC staging guidelines.

Results: A total of 4,472 NSCLC patients who underwent lobectomy were included in the study (including 4,083 cases of solid lesions and 389 cases of subsolid lesions). The median follow-up time was 75.4 months. Patients in the GGO group had significantly better OS and RFS than those in the solid group [OS: hazard ratio (HR) =0.55, 95% confidence interval (CI): 0.40–0.73, P<0.001; RFS: HR =0.53, 95% CI: 0.42–0.67, P<0.001]. Comparing patients' PSM by overall size, the GGO group still had better OS and RFS (OS: HR =0.60, 95% CI: 0.43–0.85, P=0.004; RFS: HR =0.59, 95% CI: 0.44–0.79, P<0.001). After PSM by solid component size, no significant difference was detected between the GGO group and the group matched by solid component size on OS and RFS (OS: HR =0.89, 95% CI: 0.61–1.28, P=0.52; RFS: HR =0.92, 95% CI: 0.67–1.26, P=0.61). In subgroup analysis, after PSM by solid component size, the results showed no difference in OS and RFS between the restaged patients (c-T1 and c-T2) and the corresponding patients in the solid group (for OS, HR =1.06, 95% CI: 0.61–1.83, P=0.83; HR =1.11, 95% CI: 0.60–2.07, P=0.73, respectively; and RFS, HR =1.17, 95% CI: 0.75–1.82, P=0.49; HR =0.80, 95% CI: 0.48–1.34, P=0.39, respectively).

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Conclusions: The T stage classification strategy proposed by ISALC remains applicable in patients with GGOs larger than 2 cm.

Keywords: Ground-glass opacity (GGO); tumor-node-metastasis stage (TNM stage); solid component size

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Introduction

Non-small cell lung cancer (NSCLC) remains the leading cause of cancer-related mortality, responsible for approximately 1.8 million deaths annually (1). The National Lung Screening Trial in 2011 demonstrated that low-dose computed tomography (CT) screening significantly reduces lung cancer mortality (2). Subsequently, an increasing number of tumors characterized by ground-glass opacities (GGOs) have been detected. Numerous studies have indicated that NSCLC patients with GGOs generally have more favorable prognoses (3-7). Therefore, the presence of GGOs should influence both tumor staging and treatment

decisions (8).

Tumor-node-metastasis (TNM) stage is one of the most important prognostic indicators in NSCLC. A previous study showed that using modified T descriptors, which measure the overall tumor size excluding the GGO component on CT, more accurately predicts the outcomes for patients with early-stage lung cancer (9). The International Association for the Study of Lung Cancer (IASLC) Lung Cancer Staging Program also recommends prioritizing the measurement of the solid component over the overall size for T descriptors (10,11). Moreover, for larger lesions and advanced stages, clinical decisions should consider the solid-to-GGO ratio as it may impact treatment choices and outcomes (12). TNM stage guides the therapeutic approach. For lesions larger than 2 cm in diameter, lobectomy is a better option than sublobectomy (13-15). Additionally, postoperative adjuvant therapy in T2N0M0 (stage IB) patients improves prognosis (16-20). Thus, it is crucial that TNM staging effectively accounts for GGO components to optimize treatment and prognostication in NSCLC.

Although a large number of previous studies have confirmed the better prognosis of GGO lesions compared to equal-sized solid lesions, most recent studies of GGO lesions have been limited to small tumors ≤ 2.0 cm (7,13,14,21-23). The prognostic impact of the GGO component on tumors larger than 2 cm has not been adequately investigated (24). Only a few studies have examined tumors exceeding 3 cm in diameter, and these studies have been limited by small sample sizes, preventing conclusive results regarding the significance of GGO in larger tumors (24,25). Meanwhile, other articles concerning GGOs greater than 2 cm only mention the survival benefits brought about by the GGO component (26,27).

This study aimed to fill this gap by evaluating the effectiveness of the IASLC-recommended T-staging classification specifically for NSCLC patients with GGO-dominant tumors larger than 2 cm in diameter. By comparing the prognostic value of overall tumor size and

Highlight box

Key findings

- This study aimed to validate the T-staging classification strategy recommended by the International Association for the Study of Lung Cancer (IASLC) specifically for non-small cell lung cancer (NSCLC) patients with ground-glass opacity (GGO) lesions greater than 2 cm.

What is known and what is new?

- Although prior studies suggest that NSCLC patients with GGO lesions generally experience better prognoses than those with solid lesions, most research has focused on tumors with a diameter of 2 cm or less, leaving a gap in understanding the impact of larger GGO lesions.
- This study represents a large cohort analysis comparing the prognostic value of overall tumor size and solid component size for T-staging in NSCLC patients with GGO lesions greater than 2 cm. The results reinforce that T-staging based on solid component size, as per the IASLC recommendations, is more accurate in predicting survival outcomes.

What is the implication, and what should change now?

- For NSCLC patients with GGO lesions over 2 cm, using solid component size for T-staging offers a more precise survival prognosis and should guide treatment strategies. This approach supports individualized treatment planning, particularly in surgical and adjuvant therapy decisions for larger GGO tumors.

solid component size as T-staging indicators, we sought to determine an optimal staging approach for this patient subgroup. Our findings could help to establish more precise and individualized treatment strategies for patients with larger GGO lesions, addressing an important clinical need in NSCLC management. We present this article in accordance with the STROBE reporting checklist (available at <https://tldr.amegroups.com/article/view/10.21037/tlcr-24-664/rc>).

Methods

Data source

The Western China Lung Cancer Database (WCLCD) was established in September 2005. Since then, all lung cancer patients who underwent surgery at the Department of Thoracic Surgery, West China Hospital, Sichuan University have been registered in the database. This was a retrospective cohort study with prospectively collected data, designed to evaluate the prognostic impact of GGO size in NSCLC patients with tumors larger than 2 cm. The exclusion criteria were as follows: patients with subsolid lesions having a maximum tumor diameter of 2 cm or less; those undergoing other surgical procedures such as segmental resection, wedge resection, sleeve resection, bilateral surgery, chest wall resection, or other extended resections; those diagnosed with other types of cancer, including small-cell lung cancer and pulmonary metastases; and patients with clinical N1–3 staging or those who were lost to follow-up.

Informed consent and ethical considerations

Informed consent was provided by all study participants prior to data collection, which ensured that their rights and privacy were protected throughout the study. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the Institutional Review Board (IRB) of West China Hospital (No. 2023-1694).

Surgical approach

All patients underwent lobectomy through a thoracic approach, with the entry route determined by tumor characteristics and patient health status. Standard protocols were followed, including intraoperative imaging (e.g., CT or ultrasound) to confirm tumor margins. Postoperatively,

comprehensive lymph node dissection and sampling were mandatory to ensure accurate pathological staging and optimize subsequent treatment planning.

Radiological and clinicopathological evaluation

The preoperative CT scans of all patients were carefully reviewed by the authors (Y.L. and Z.Y.). Each tumor was further assessed using high-resolution CT to determine the consolidation-to-tumor ratio (CTR) for the GGO. The solid component was identified as areas of increased opacity that completely obscured the underlying vascular markers. In contrast, GGOs were defined as areas of slightly homogeneous increased density that did not obscure the underlying vascular markers. Following the Fleischner Society's guidelines (28), the CTR was calculated as the ratio of the maximum diameter of the solid component to the tumor's maximum diameter, based on high-resolution CT imaging. Postoperative pathology included assessments of tumor size, histologic subtype, visceral pleural invasion (VPI), and lymph node involvement according to IASLC and World Health Organization (WHO) guidelines (29).

Outcomes

Patients underwent regular follow-ups either via telephone visits or in the outpatient department. The long-term survival outcomes were overall survival (OS) and recurrence-free survival (RFS). OS was defined as the interval from surgery to death or the last follow-up, whereas RFS was defined as the time from surgery to the occurrence of recurrence, metastasis, death, or the last follow-up. Follow-up commenced on the day of surgery, with patient status evaluated at regular intervals using chest CT, brain magnetic resonance imaging (MRI) or CT, and upper abdominal CT. Follow-ups occurred every 3 to 6 months during the first 2 years, semiannually for the subsequent 3 years, and annually thereafter. To ensure the accuracy and reliability of the follow-up data, follow-up procedures were standardized, and data quality checks and updates were conducted periodically by independent data monitors. Additional diagnostics, such as bone scans, positron emission tomography (PET)-CT, or biopsies, were conducted as necessary. The latest follow-up was conducted in December 2023.

To assess which indicator is better for evaluating GGO patients, solid component size or overall size, we used propensity score matching (PSM) to compare the two

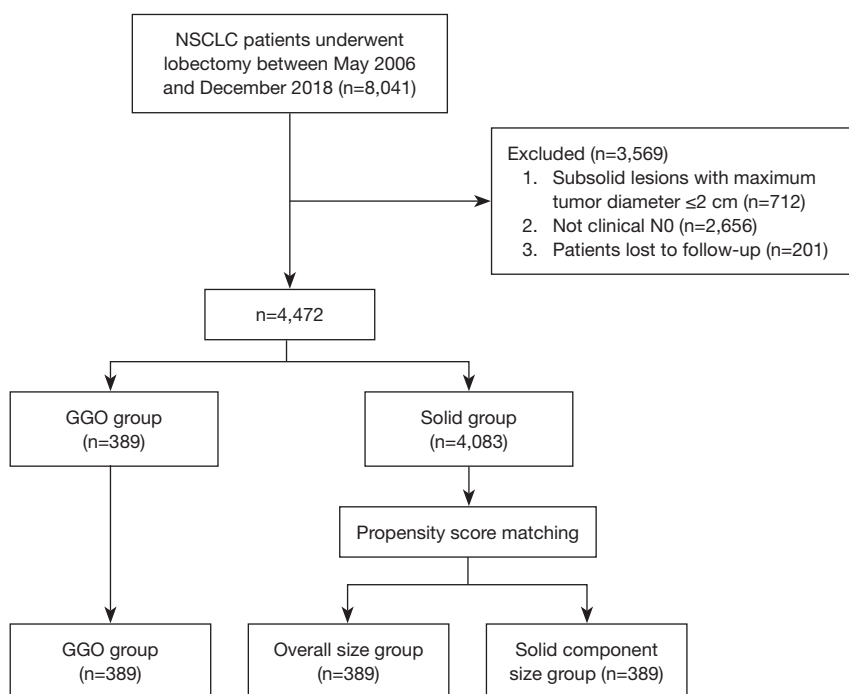


Figure 1 Study patient selection. NSCLC, non-small cell lung cancer; GGO, ground-glass opacity.

groups (group matched by solid component size and group matched by overall size) of patients separately to minimize potential selection bias. Matching indicators included solid component size or overall size (categorical variables based on diameter size: 0–1, 1–2, 2–3 cm, and so on), gender (male, female), age at surgery, smoking history (smoker, non-smoker), Charlson Comorbidity Index (CCI), tumor location (right, left), lymph node dissection (yes, no), histologic type (adenocarcinoma, squamous, adenosquamous carcinoma, and other types of primary NSCLC), p-N status (N0, N1, N2, N3), and adjuvant postoperative therapy (yes, no). The patient inclusion process is shown in *Figure 1*.

Statistical analysis

All statistical analyses were performed using R (version 4.2.1; R Foundation for Statistical Computing, Vienna, Austria). Quantitative data were expressed as mean \pm standard deviation. Independent samples *t*-tests were used to compare differences between groups. Categorical data were expressed as percentages, and differences between groups were compared using Fisher's exact test or Chi-squared test. Preoperative variables such as solid component size or overall size, gender, age at surgery, smoking history, CCI score, side of surgery, lymph node dissection, histologic

type, p-N status, and adjuvant postoperative therapy were considered covariates for PSM. The PSM process was performed using the nearest method, with the number of patients in each group being 1:1. Kaplan-Meier survival curves were used to describe the OS and RFS before and after PSM in both groups, and survival outcomes were compared using log-rank tests. Additionally, Cox regression models were used to determine independent prognostic factors for these patients, and multicollinearity was assessed using the variance inflation factor (VIF). Only the variables with VIF <10 were selected for modeling (30). All statistical tests were two-sided, with statistical significance set at $P < 0.05$.

Results

Patient characteristics

A total of 8,041 NSCLC patients underwent lobectomy in the Department of Thoracic Surgery, West China Hospital, Sichuan University from December 2009 to December 2018. Of these patients, 3,569 were excluded based on the exclusion criteria, and the remaining 4,472 patients were included in the study (including 4,083 cases of solid lesions and 389 cases of subsolid lesions) (*Figure 1*). The subsequent

PSM identified two groups: the Solid group (389 cases each, group matched by solid component size and group matched by solid component size) and the GGO group (389 cases) based on solid component size or overall size, gender, age at surgery, smoking history, CCI, side of surgery, lymph node dissection, histologic type, p-N status, and adjuvant postoperative therapy.

Unmatched population

Details of patient characteristics are shown in *Table 1*. The GGO group had more female patients but fewer smokers compared to the Solid group. The median follow-up time was 75.4 months. The mean Solid component size of the GGO group was smaller (1.73 ± 1.34 vs. 2.89 ± 1.65 cm, $P < 0.001$). There were statistical differences among the two groups regarding histological type ($P < 0.001$), pathological stage ($P < 0.001$), p-N status ($P < 0.001$), and postoperative adjuvant therapy ($P < 0.001$).

Of the 4,472 patients included in this study, the median follow-up duration was 75.4 months. Patients in the GGO group had significantly better OS and RFS than those in the solid group [the 5-year OS rates were 87.1% in the GGO group, 76.1% in the solid group, hazard ratio (HR) = 0.55, 95% confidence interval (CI): 0.40–0.73, $P < 0.001$; the 5-year RFS rates were 80.7% in the GGO group, 65.4% in the solid group, HR = 0.53, 95% CI: 0.42–0.67, $P < 0.001$] (*Figures S1, S2*).

The descriptions of recurrence sites or metastatic patterns are shown in *Table 2*. Pulmonary metastatic nodules and mediastinal lymph node metastasis were significantly more common in the solid group than in the GGO group ($P = 0.04$ and $P = 0.02$, respectively). For metastatic patterns, brain, lung, and liver metastases were also significantly higher in the solid group ($P < 0.001$, $P = 0.02$, and $P = 0.04$, respectively).

Matched population

After PSM by solid component size or overall size, there were 389 patients in each group. The baseline clinical characteristics and surgical outcomes of PSM-matched patients are listed in *Table 3*. Matched patients were comparable in all data included in the PSM.

Compared to the group matched by overall size, the GGO group had better OS and RFS (the 5-year OS rates were 87.1% in the GGO group, 78.9% in the group matched by overall size, HR = 0.60, 95% CI: 0.43–0.85,

$P = 0.004$; the 5-year RFS rates were 80.7% in the GGO group, 68.5% in group matched by overall size HR = 0.59, 95% CI: 0.44–0.79, $P < 0.001$) (*Figure 2*). However, there was no significant difference between the GGO group and the group matched by solid component size on OS and RFS (the 5-year OS rates were 87.1% in the GGO group, 85.6% in the group matched by solid component size, HR = 0.89, 95% CI: 0.61–1.28, $P = 0.52$; the 5-year RFS rates were 80.7% in the GGO group, 78.3% in the group matched by solid component size, HR = 0.92, 95% CI: 0.67–1.26, $P = 0.61$) (*Figure 2*).

Following multivariable Cox regression analysis of the GGO group and the two matched groups, we identified that the size of the solid component (HR = 1.70, 95% CI: 1.27–2.26, $P < 0.001$), age (HR = 1.02, 95% CI: 1.01–1.04, $P = 0.005$), pathological T stage (HR = 2.53, 95% CI: 1.53–4.17, $P < 0.001$), and pathological N stage (HR = 2.74, 95% CI: 2.06–4.16, $P < 0.001$) were independent prognostic factors for OS (*Table 4*). Overall tumor size did not independently predict OS (HR = 0.77, 95% CI: 0.57–1.04, $P = 0.23$). Additionally, there was no evidence of multicollinearity, with the VIF ranging from 1.04 to 8.63.

Subgroup analysis

We subsequently reassessed clinical T-staging (9th edition TNM stage) for 389 patients in the GGO group according to the solid component size and matched these patients in the solid group. The results showed no difference in OS and RFS between the restaged patients (T1 and T2, since there were only five T3 patients, we did not match for T3) and the corresponding patients in the Solid group (for OS, HR = 1.06, 95% CI: 0.61–1.83, $P = 0.83$; HR = 1.11, 95% CI: 0.60–2.07, $P = 0.73$, respectively and RFS, HR = 1.17, 95% CI: 0.75–1.82, $P = 0.49$; HR = 0.80, 95% CI: 0.48–1.34, $P = 0.39$, respectively) (*Figure 3*).

Discussion

Based on our findings, staging recommendations of IASLC are valid for GGO tumors larger than 2 cm, and solid component size should be used instead of overall size as an indicator for TNM staging. New clinical TNM staging that takes into account the GGO component may provide more accurate survival prediction and treatment guidance for patients with lung cancer tumors over 2 cm in diameter. With numerous studies confirming that patients with GGO have better survival rates, the IASLC recommended a

Table 1 Characteristics of patients with the GGO and solid lesions before matching

Characteristics	GGO group (n=389)	Solid group (n=4,083)	P value
Age (years)	59.28±9.53	58.26±10.27	0.06
Sex			0.001
Male	171 (44.0)	2,170 (53.1)	
Female	218 (56.0)	1,913 (46.9)	
Tumor size (cm)	3.04±0.94	2.89±1.65	0.08
Solid component size (cm)	1.73±1.34	2.89±1.65	<0.001
Smoking			<0.001
Smoker	105 (27.0)	1,699 (41.6)	
Non-smoker	284 (72.0)	2,384 (58.4)	
Location			0.008
Right	262 (67.4)	2,465 (60.4)	
Left	127 (32.6)	1,618 (39.6)	
CCI score			0.10
0	313 (80.5)	3,211 (78.6)	
1	66 (17.0)	633 (15.5)	
2	8 (2.1)	205 (5.0)	
3	2 (0.5)	33 (0.8)	
4	0	1 (0.0)	
Lymph node dissection			0.05
Yes	383 (98.5)	3,939 (96.5)	
No	6 (1.5)	144 (3.5)	
P-stage			<0.001
1	344 (88.4)	2,797 (68.5)	
2	23 (5.9)	652 (16.0)	
3	22 (5.7)	634 (15.5)	
P-N status			<0.001
0	359 (92.3)	3,100 (75.9)	
1	10 (2.6)	445 (10.9)	
2	20 (5.1)	535 (13.1)	
3	0	3 (0.1)	
Histology			<0.001
Adenocarcinoma	328 (84.3)	3,019 (73.9)	
Adenosquamous carcinoma	9 (2.3)	115 (2.8)	
Other	37 (9.5)	255 (6.2)	
Squamous carcinoma	15 (3.9)	694 (17.0)	
Post-therapy			<0.001
Yes	91 (23.4)	1,577 (38.6)	
No	298 (76.6)	2,506 (61.4)	

Data are presented as mean ± SD or n (%). GGO, ground-glass opacity; CCI, Charlson Comorbidity Index; SD, standard deviation.

Table 2 Solid group *vs.* GGO group descriptions of recur sites or metastatic patterns

Descriptions of recur sites or metastatic patterns	Solid group (n=4,144)	GGO group (n=389)	P value
Recur sites	315 (7.6)	13 (3.3)	0.003
Pulmonary metastatic nodules	170 (4.1)	7 (1.8)	0.04
Mediastinal lymph node metastasis	67 (1.6)	0 (0.0)	0.02
Pleural cavity implantation (including pleural nodules and malignant pleural effusion)	60 (1.4)	5 (1.3)	0.97
Residual recurrence	53 (1.3)	2 (0.5)	0.28
Other	36 (0.9)	1 (0.3)	0.32
Metastatic patterns	1,103 (26.6)	49 (12.6)	<0.001
Brain	449 (10.8)	13 (3.3)	<0.001
Bone	402 (9.7)	26 (6.7)	0.06
Lung	266 (6.4)	13 (3.3)	0.02
Liver	136 (3.3)	5 (1.3)	0.04
Adrenal gland	44 (1.1)	3 (0.8)	0.78
Cervical lymph nodes	40 (1.0)	3 (0.8)	0.92
Others	209 (5.0)	11 (2.8)	0.07

Data are presented as n (%). Recur sites: refers to the anatomical or histological locations where NSCLC recurs after initial treatment; Others include the mediastinum, kidneys, pleura, lymph nodes, rectum, systemic metastases, etc. GGO, ground-glass opacity; NSCLC, non-small cell lung cancer.

significant change in the definition of clinical T descriptors, using only the size of the solid component as a descriptor (3,4,10). Our study confirmed that in patients with GGO >2 cm, the solid component size is a better predictor of outcomes compared to the overall size. Our findings validate the previous IASLC staging recommendations for GGO tumors larger than 2 cm and suggest that the solid component size should be used instead of the overall size in TNM staging.

In our study, significant differences in OS and RFS were observed between the group matched by overall size and the GGO group, whereas no differences in OS and RFS were noted between the group matched by solid component size and the GGO group. This observation is consistent with previous studies showing that even a small percentage of GGO components is associated with a better prognosis compared to solid lesions (24,25). These findings support the hypothesis of a linear multistep progression in which a precursor lesion evolves into adenocarcinoma *in situ* and subsequently into invasive adenocarcinoma, particularly in cases of lung adenocarcinomas (LUADs) with a radiographic GGO component (24,31). A recent

study indicated that adenocarcinoma *in situ*/minimally invasive adenocarcinoma and GGO-like LUAD exhibit a lower frequency of oncogene mutations and reduced activity in cell proliferation-related pathways compared to solid LUAD lesions (32). Notably, in our unmatched baseline, the GGO group had fewer lymph node metastases than the solid group (7.7% *vs.* 24.1%), a lower proportion of VPI (11.8% *vs.* 27.0%), and a higher proportion of LUAD (84.3% *vs.* 73.9%). These results are consistent with previous studies and may affect prognosis (24,33–36). However, using PSM to balance variables such as histologic type, pathological N status, and adjuvant postoperative therapy resulted in more balanced matched groups. Consequently, our findings offer greater applicability to postoperative tumor staging and subsequent treatment options. There was still no difference in the T1 and T2 stage subgroups using the same matching method. We hypothesize that the indolent nature of the GGO component underlies this phenomenon, suggesting that the GGO component does not significantly impact tumor progression.

This study validates the IASLC recommendation that for patients with GGO >2 cm, the solid component size should

Table 3 Characteristics of patients after PSM

Characteristics	For overall size			For solid component size		
	GGO group (n=389)	Group matched by overall size (n=389)	P value	GGO group (n=389)	Group matched by solid component size (n=389)	P value
Age (years)	59.28±9.53	59.58±10.02	0.68	59.28±9.53	60.14±9.49	0.21
Sex			0.83			0.72
Male	171 (44.0)	167 (42.9)		171 (44.0)	165 (42.4)	
Female	218 (56.0)	222 (57.1)		218 (56.0)	224 (57.6)	
Smoking			0.94			0.81
Smoker	105 (27.0)	103 (26.5)		105 (27.0)	109 (28.0)	
Non-smoker	284 (73.0)	286 (73.5)		284 (73.0)	280 (72.0)	
Location			0.64			1
Right	262 (67.4)	269 (69.2)		262 (67.4)	261 (67.1)	
Left	127 (32.6)	120 (30.8)		127 (32.6)	128 (32.9)	
CCI score			0.78			0.26
0	313 (80.5)	318 (81.7)		313 (80.5)	324 (83.3)	
1	66 (17.0)	66 (17.0)		66 (17.0)	50 (12.9)	
2	8 (2.1)	5 (1.3)		8 (2.1)	14 (3.6)	
3	2 (0.5)	0 (0.0)		2 (0.5)	1 (0.3)	
4	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Overall size (cm)	3.04±0.94	3.21±1.35	0.05	3.04±0.94	1.88±1.16	<0.001
Solid component size (cm)	1.73±1.34	3.21±1.35	<0.001	1.73±1.34	1.88±1.16	0.09
Lymph node dissection			0.50			0.50
Yes	383 (98.5)	386 (99.2)		383 (98.5)	379 (97.4)	
No	6 (1.5)	3 (0.8)		6 (1.5)	10 (2.6)	
P-stage			0.33			0.61
0	359 (92.3)	355 (91.3)		359 (92.3)	348 (89.5)	
1	10 (2.6)	12 (3.1)		10 (2.6)	16 (4.1)	
2	20 (5.1)	22 (5.7)		20 (5.1)	25 (6.4)	
3	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Histology			0.86			0.42
Adenocarcinoma	328 (84.3)	332 (85.3)		328 (84.3)	332 (85.3)	
Adenosquamous carcinoma	9 (2.3)	11 (2.8)		9 (2.3)	12 (3.1)	
Other	37 (9.5)	31 (8.0)		37 (9.5)	26 (6.7)	
Squamous carcinoma	15 (3.9)	15 (3.9)		15 (3.9)	19 (4.9)	
Post-therapy			0.73			0.44
Yes	91 (23.4)	86 (22.1)		91 (23.4)	81 (20.8)	
No	298 (76.6)	303 (77.9)		298 (76.6)	308 (79.2)	

Data are presented as mean ± SD or n (%). PSM, propensity score matching; GGO, ground-glass opacity; CCI, Charlson Comorbidity Index; SD, standard deviation.

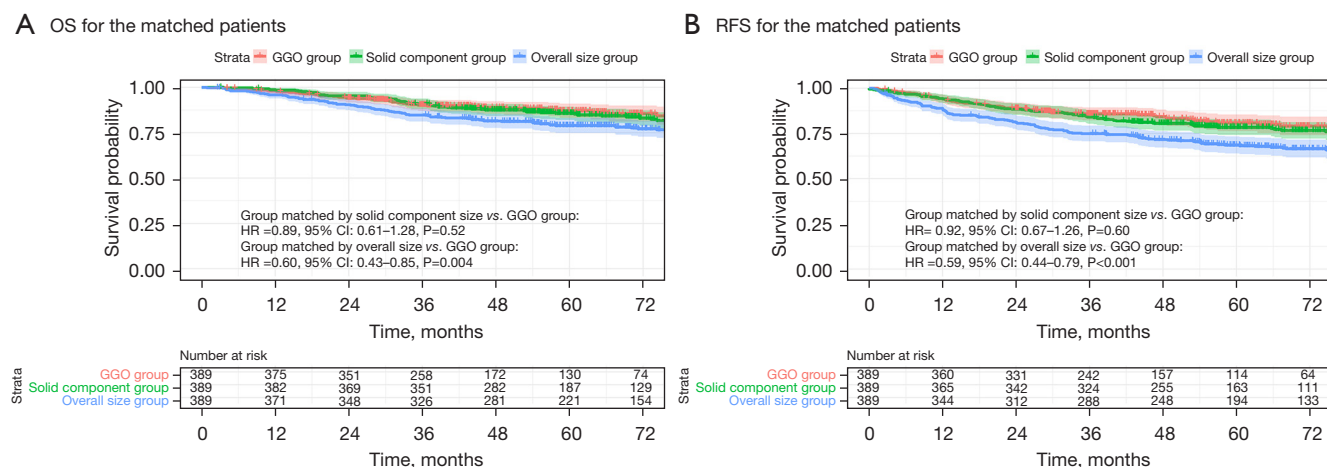


Figure 2 Kaplan-Meier survival curves of OS and RFS for the matched patients. (A) OS for the matched patients. (B) RFS for the matched patients. OS, overall survival; GGO, ground-glass opacity; HR, hazard ratio; CI, confidence interval; RFS, recurrence-free survival.

Table 4 Independent predictors of OS

Predictors of survival	HR	Lower 95%	Upper 95%	P value
Age at surgery	1.02	1.01	1.04	0.005
Gender (ref = male)	1.15	0.78	1.68	0.29
Tumor size	0.77	0.57	1.04	0.23
Solid component size	1.70	1.27	2.26	<0.001
Smoking history (ref = non-smoker)	1.32	0.88	1.98	0.24
CCI (ref >1)	0.79	0.56	1.12	0.18
Location (ref = right side)	0.83	0.63	1.09	0.15
Lymph node dissection (ref = no)	0.53	0.24	1.15	0.17
pT stage (ref = T1)	2.53	1.53	4.17	<0.001
pN stage (ref = N0)	2.74	2.06	4.16	<0.001
Histology (ref = adenocarcinoma)	1.03	0.73	1.46	0.87
Post-therapy (ref = no)	0.79	0.57	1.10	0.16

Lower 95%, lower bound of the 95% CI; upper 95%, upper bound of the 95% CI. OS, overall survival; HR, hazard ratio; CCI, Charlson Comorbidity Index; CI, confidence interval.

be used instead of the overall size. Our findings provide updated data to support this recommendation and improve the choice of surgical approach and postoperative treatment for GGO >2 cm. In multivariate Cox regression analyses, we verified that the solid component size differentiated patient survival more significantly than the overall size. Other significant factors included age and postoperative T stage and N stage. Notably, in our study cohort, adjuvant therapy did not result in better survival outcomes for the

GGO group. In subgroup analysis, adjuvant therapy was also not significant for patients in the T2 GGO group after modified staging (Figure S3). The use of adjuvant therapy in patients with GGO >2 cm needs further consideration.

The limitations of this study should also be acknowledged. We acknowledge that there is a significant disproportion in the number of patients between the two groups, which potentially could have influenced the generalizability of our findings. To address this, we applied

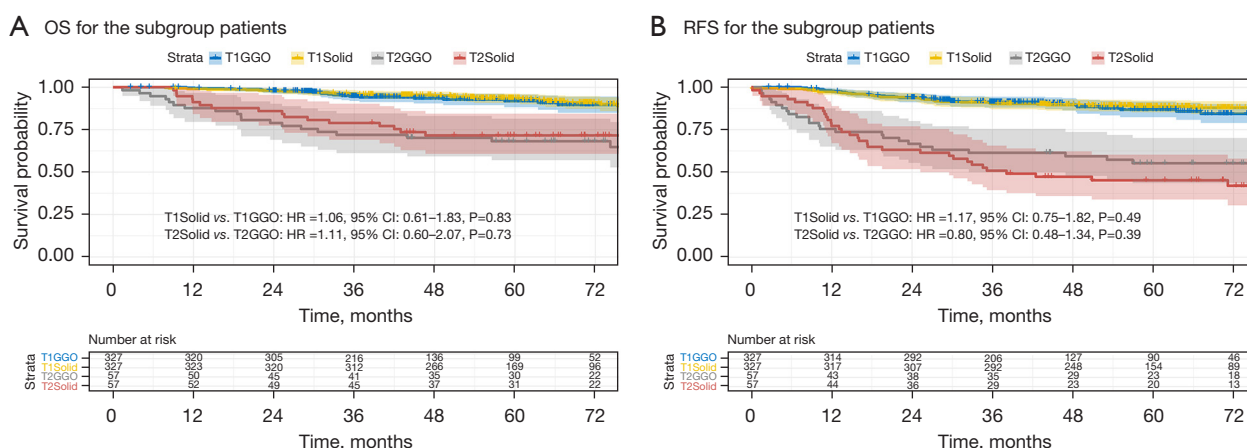


Figure 3 Kaplan-Meier survival curves of OS and RFS in different subgroups of patients. (A) OS for the subgroup patients. (B) RFS for the subgroup patients. OS, overall survival; GGO, ground-glass opacity; HR, hazard ratio; CI, confidence interval; RFS, recurrence-free survival.

PSM to balance key variables such as gender distribution, smoking history, and tumor size, thus controlling for these factors in our analysis. However, although PSM effectively minimizes bias for observed variables, it cannot completely eliminate residual bias, especially from unmeasured confounding factors that may also impact survival outcomes. Additionally, the retrospective nature of the study, though based on prospectively collected data, may have introduced inherent observational bias. Another limitation lies in the relatively long study period [2009–2018], during which treatment practices and staging criteria may have evolved, potentially influencing the interpretation of outcomes. Future studies with more balanced cohorts and adjustments for potential unobserved confounders are recommended to validate our findings and further refine T-staging criteria for NSCLC patients with larger GGO lesions.

Conclusions

Based on our findings, the IASLC staging recommendations are valid for GGO tumors larger than 2 cm in diameter, and the solid component size should be used instead of the overall size as an indicator for TNM staging. New clinical TNM staging that considers the GGO component may provide more accurate survival prediction and treatment guidance for patients with lung cancer over 2 cm.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at <https://tclr.amegroups.com/article/view/10.21037/tclr-24-664/rc>

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://tclr.amegroups.com/article/view/10.21037/tclr-24-664/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. Informed consent was obtained from all study participants prior to data collection. The study was conducted in accordance with the

Declaration of Helsinki (as revised in 2013). The use of the data for this study was approved by the Institutional Review Board (IRB) of West China Hospital (No. 2023-1694).

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