European Journal of Cardio-Thoracic Surgery 55 (2019) 1130–1135
doi:10.1093/ejcts/ezy422 Advance Access publication 18 December 2018

ORIGINAL ARTICLE

Cite this article as: Ding H, Wang H, Zhang P, Song N, Chen L, Jiang G. Prognostic factors of lung adenocarcinoma manifesting as ground glass nodules larger than 3 cm. Eur J Cardiothorac Surg 2019;55:1130–5.

Prognostic factors of lung adenocarcinoma manifesting as ground glass nodules larger than 3 cm

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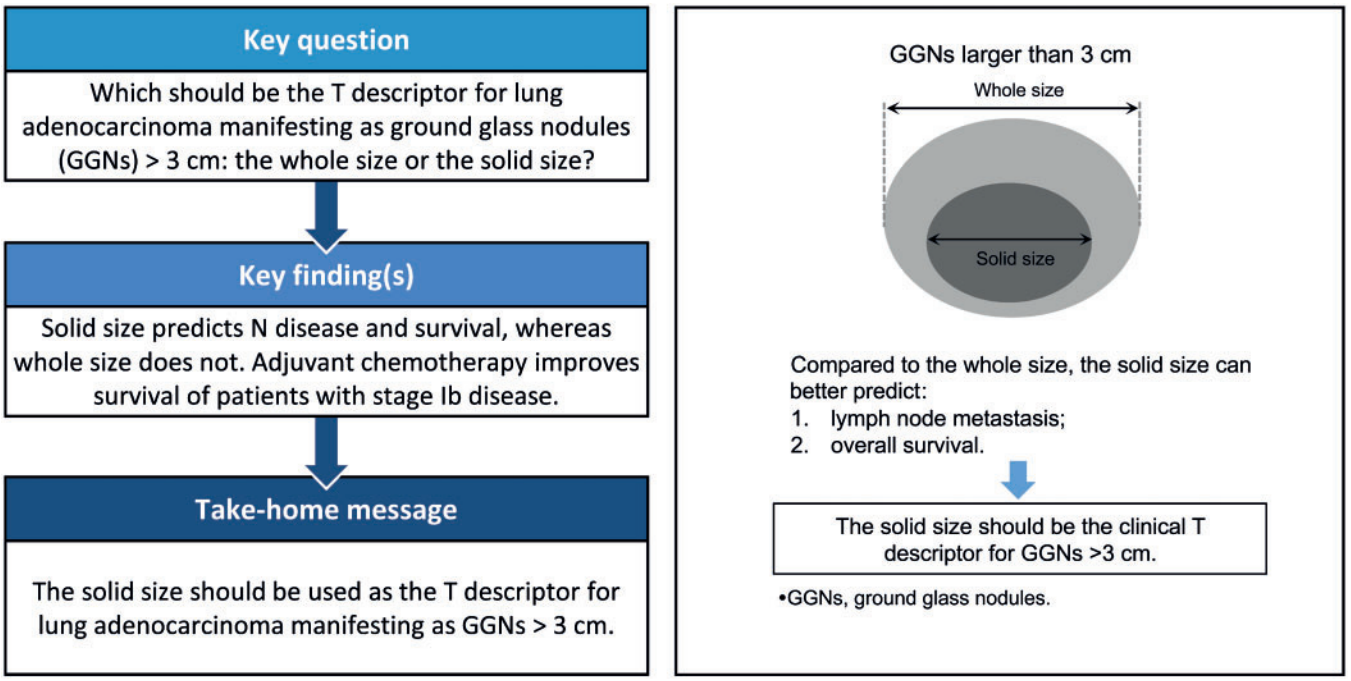
Received 26 July 2018; received in revised form 24 October 2018; accepted 27 October 2018



Abstract

OBJECTIVES: The aim of the study was to investigate prognostic factors of lung adenocarcinomas manifesting as ground glass nodules larger than 3 cm on thin-section computed tomography scans, especially comparing the prognostic role of the whole size and the solid size.

METHODS: We included 195 patients with lung adenocarcinomas manifesting as ground glass nodules larger than 3 cm who underwent surgical resection. We identified clinical factors associated with lymph node metastases by binary logistics regression analysis. Kaplan–Meier analysis was performed to determine the association between the whole size or the solid size and overall survival (OS). Multivariable Cox regression analysis was used to identify prognostic factors of OS.

RESULTS: The median follow-up time was 62 months. The median values of the whole size and the solid size were 3.5 cm and 2.3 cm, respectively. The 3-year and 5-year OS rates were 95.5% and 86.2%, respectively. Patients with lesions <2.3 cm had markedly better OS than those with lesions ≥2.3 cm. No significant differences existed between the survival of patients with lesions <3.5 cm and ≥3.5 cm. Multivariable analysis showed that bigger solid size was significantly associated with the presence of lymph node metastases and inferior OS, whereas larger whole size was not. Adjuvant chemotherapy improved the OS of patients with stage Ib and II–IIIa disease, but not that of patients with stage Ia disease.

CONCLUSIONS: Solid size was a better predictor of lymph node metastases and prognosis than whole size in ground glass nodules larger than 3 cm. Clinical T staging should be based on the solid size rather than on the whole size of these lesions.

Keywords: Ground glass nodules • Whole size • Solid size

INTRODUCTION

The introduction of thin-section computed tomography (CT) and widespread screening has led to the detection of more early-stage lung cancers, especially those manifesting as ground glass nodules (GGNs). Previous studies have demonstrated that most malignant GGNs were proven to be adenocarcinomas or their preinvasive precursors, including adenocarcinoma *in situ* and minimally invasive adenocarcinoma [1, 2]. Currently, a number of published studies reported that GGNs had an indolent course with slow growth rates and low invasiveness [3, 4]. Solitary GGNs less than 3 cm treated with curative resection had a low rate of lymph node metastases and a good long-term survival rate, especially for those whose solid part was less than 80% of the whole lesion in diameter [5]. On pathological examination, the ground glass and solid part on CT findings were correlated with the lepidic growth and invasive component, respectively [6, 7]. Further analysis found that the size of the solid part or the invasive component could better predict the prognosis of lung adenocarcinoma manifesting as GGNs [8, 9]. Based on the preceding results, the International Association for the Study of Lung Cancer proposed that the solid size rather than the whole size of GGNs be used for the clinical T category in the 8th edition staging system for non-mucinous lung adenocarcinomas (≤3 cm) [10]. To ensure uniformity in clinical practice, they recommended that the proposal be extended to all tumours regardless of size. However, data confirming the greater value of the solid part in prognostic prediction are still limited for tumours >3 cm in diameter.

The aim of the study was to investigate prognostic factors of lung adenocarcinomas manifesting as GGNs that were larger than 3 cm on CT scans. We further explored the role of adjuvant chemotherapy in the survival of patients with these tumours.

PATIENTS AND METHODS

From February 2011 to August 2013, a total of 5321 consecutive patients with lung cancer who underwent surgical treatment at Shanghai Pulmonary Hospital (Shanghai, China) were identified in our database. We retrospectively reviewed the CT features of the 2742 patients with a histopathological diagnosis of adenocarcinoma. The inclusion criteria included patients (i) with thin-section CT scans (slice thickness of 1 mm) performed in our hospital 1 month before surgery; (ii) with primary tumours; (iii) who had GGNs identified radiologically that were larger than 3 cm; (iv) who had surgery performed with a curative intent. The exclusion criteria were patients (i) with multiple lesions in the lung; (ii) with metastatic tumours; (iii) who underwent palliative resection or biopsy; (iv) with a history of lung cancer or other tumours; and (v) undergoing neoadjuvant chemotherapy or radiotherapy. Ultimately, we enrolled 195 eligible patients for analysis (Fig. 1).

Clinicodemographic characteristics and pathological results such as age, sex, the location of lesions, the whole size, the solid size, carcinoembryonic antigen (CEA) levels, grade of differentiation, pathological tumour, node and metastasis (TNM) stage, visceral pleural invasion and adjuvant chemotherapy were collected. The lesions were classified into 2 groups according to their location: upper/middle lobe and lower lobe. The whole size and the solid size were measured as we reported previously [11]. The concentration of serum CEA (μg/l) was detected within 1 week before surgery. The differentiation was categorized as well differentiated and moderately/poorly differentiated. All patients were staged according to the American Joint Committee on Cancer, 7th edition, staging system. Chemotherapy done within 8 weeks after surgery was considered adjuvant chemotherapy. It was recommended that all patients have a CT scan of the chest, plus a bone scan and magnetic resonance imaging of the brain, every 6 months for the first 2 years and every 12 months thereafter. We conducted follow-up visits by telephone in the first week of May 2018. Survival status and the date of death were captured. Since a high percentage of patients were followed up postoperatively in local hospitals, the status of recurrence was difficult to identify. Thus, overall survival (OS) was the only end point of interest in this study. OS was defined as the interval between the date of surgery and the last follow-up visit.

The duration of OS was analysed by the Kaplan–Meier method, and differences were determined using the log-rank test. Multivariable logistic regression analysis was used to identify the predictors for lymph node metastasis. Multivariable Cox proportional hazards models were used to assess potential prognostic factors for tumours. Due to the limited number of events, adjustment for the multivariable analysis was performed for the covariates of age, CEA levels, the whole size and the solid size. We chose those 4 covariates from the preoperative factors because they had a high potential effect on lymph node status and survival. All analyses were performed using SPSS 22.0 software (IBM Inc., Armonk, NY, USA) and GraphPad Prism software

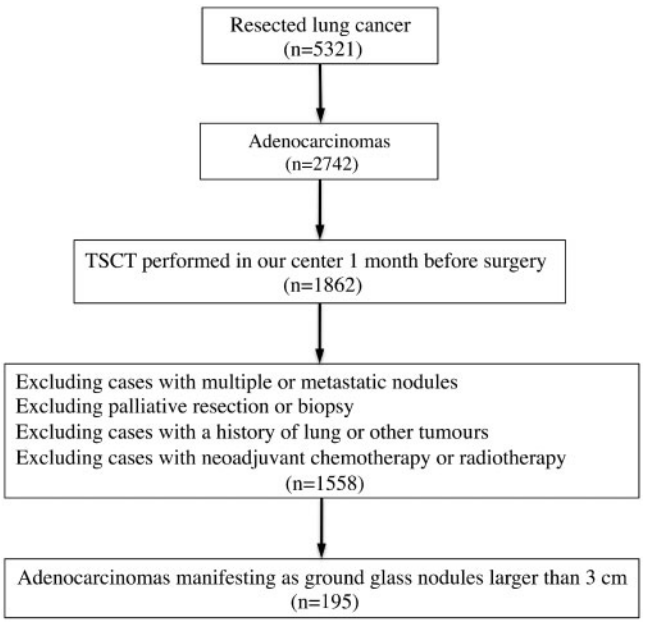


Figure 1: Study group selection criteria ($n = 195$). TSCT: thin-section computed tomography.

(GraphPad Software, La Jolla, CA, USA). No correction for multiple testing was performed in the study. All the statistical tests were 2-sided, and *P*-values of <0.05 were considered statistically significant.

RESULTS

The characteristics of the 195 patients included in our study are summarized in Table 1. The mean age was 60.3 years (range 37–77 years). The majority of the patients were female (61.0%), and most tumours were located in the upper or middle lobe (81.0%). The whole size and solid size are presented in Fig. 2, with a mean value of 3.7 cm and 2.2 cm and a median value of 3.5 cm and 2.3 cm, respectively. All patients underwent lobectomy; 133 patients (68.2%) received adjuvant chemotherapy, all of which were platinum-based regimens. Nine patients were lost to follow-up. The median follow-up time was 62 months (range 7–85 months).

Pathologically positive lymph nodes were found in 26 patients (13.3%), including 8 N1-positive and 18 N2-positive patients. Multivariable logistic analysis revealed that a larger solid size was associated with the presence of nodal disease, whereas the whole size was not. Besides, older age and CEA level ≥10 μg/l were also related to positive lymph nodes (Table 2).

Overall, 24 patients of the entire cohort had died at the last follow-up. The 3-year and 5-year OS rates were 95.5% and 86.2%. Kaplan–Meier analysis revealed that patients in the solid size <2.3 cm group had significantly better 3-year and 5-year OS than those in the solid size ≥2.3 cm group (3-year: 98.8 vs 92.5%, *P* = 0.033; 5-year: 94.8% vs 79.5%, *P* = 0.008). However, there was no marked difference in the survival of patients with lesions with a whole size <3.5 cm and ≥3.5 cm (3-year: 95.3% vs 95.6%, *P* = 1.00; 5-year: 92.9% vs 80.8%, *P* = 0.17) (Fig. 3). Multivariable Cox regression analysis of selected clinical factors revealed that larger solid size and higher CEA level were independently associated with improved survival whereas the larger whole size and older age were not (Table 3).

We examined the effect of adjuvant chemotherapy on OS for patients with pathological stage Ia, Ib and II–IIIa, respectively (Fig. 4). Kaplan–Meier analysis showed that the platinum-based chemotherapy after surgery conferred a survival benefit for patients with stages Ib and II–IIIa (Ib, log-rank *P* < 0.001; II–IIIa, log-rank *P* = 0.015), but not for patients with stage Ia (log-rank *P* = 0.68).

Table 1: Baseline characteristics and pathological details of the enrolled patients (*n* = 195)

Characteristics	Patients (%)/value
Age (years), mean ± SD (range)	60.3 ± 8.3 (37–77)
Sex	
Male	76 (39.0)
Female	119 (61.0)
Location of tumours	
Upper/middle lobe	158 (81.0)
Lower lobe	37 (19.0)
Whole size (cm), mean ± SD	3.7 ± 0.8
Solid size (cm), mean ± SD	2.2 ± 1.0
CEA level	
<10 μg/l	184 (94.4)
≥10 μg/l	11 (5.6)
Grade	
Well differentiated	53 (27.2)
Moderately/poorly differentiated	142 (72.8)
N stage	
N0	169 (86.7)
N1	8 (4.1)
N2	18 (9.2)
Visceral pleural invasion	
No	68 (34.9)
Yes	127 (65.1)
Pathological stage	
I	163 (83.6)
II	12 (6.2)
IIIa	20 (10.2)
Adjuvant chemotherapy	
No	62 (31.8)
Yes	133 (68.2)
Follow-up time (months), median (range)	62 (7–85)

CEA: carcinoembryonic antigen; SD: standard deviation.

DISCUSSION

We demonstrated that the solid size was a better predictor of lymph node metastasis and OS outcome than the whole size for

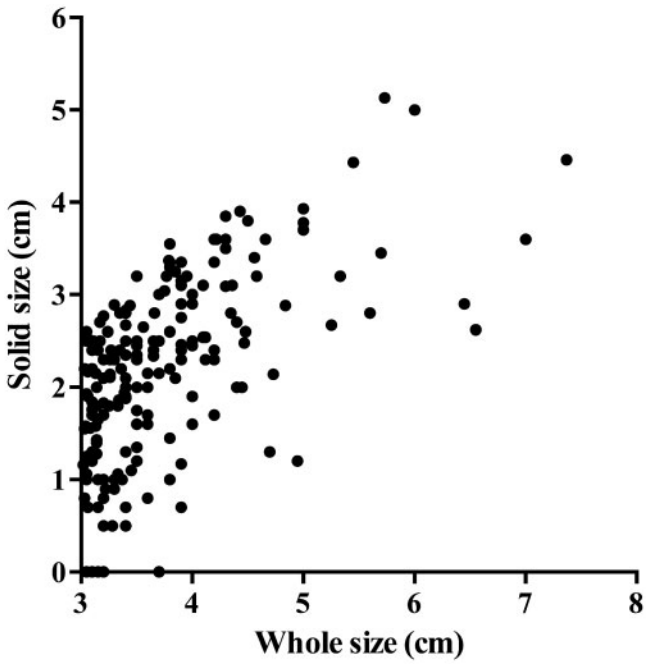


Figure 2: The whole size and solid size of the 195 ground glass nodules larger than 3 cm.

Table 2: Multivariable analysis of clinical factors associated with pathological N-positive status among all patients

Characteristics	Odds ratio	95% confidence interval	*P*-value
Age (per 1-year increase)	0.91	0.86–0.96	0.001
CEA level (≥10 μg/l)	6.25	1.45–27.05	0.014
Whole size (per 1-cm increase)	0.61	0.29–1.29	0.19
Solid size (per 1-cm increase)	4.11	1.87–9.00	<0.001

CEA: carcinoembryonic antigen.

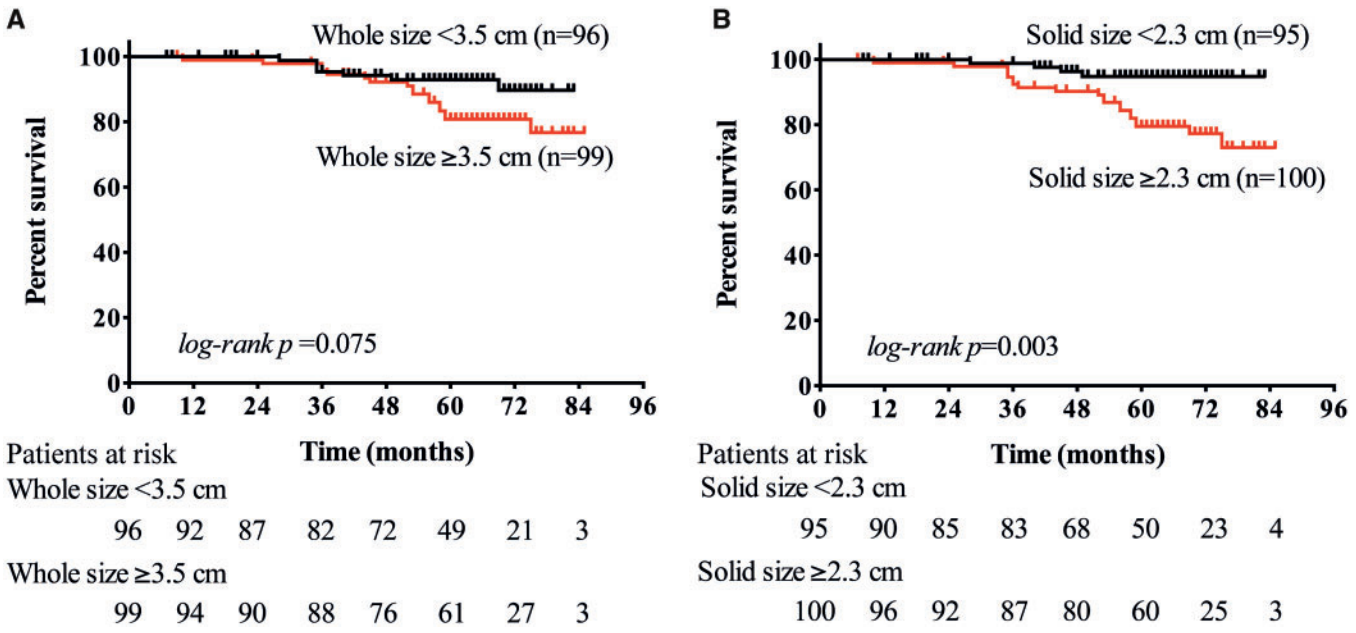


Figure 3: Overall survival of study patients. (**A**) All patients stratified by the whole size; (**B**) all patients stratified by the solid size.

Table 3: Multivariable Cox regression analysis for overall survival: clinical factors before surgery

Characteristics	Hazard ratio	95% confidence interval	*P*-value
Age (per 1-year increase)	1.00	0.95–1.05	0.95
CEA level (≥10 μg/l)	3.99	1.33–11.97	0.014
Whole size (per 1-cm increase)	1.34	0.84–2.14	0.22
Solid size (per 1-cm increase)	1.89	1.05–3.41	0.035

CEA: carcinoembryonic antigen.

lung adenocarcinomas that presented as GGNs larger than 3 cm in diameter. Among those lesions, adjuvant chemotherapy improved the survival of patients with pathological stage Ib or II–IIIa disease.

According to the international classification of lung adenocarcinoma released by the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society in 2011, adenocarcinoma *in situ* was defined as a solitary adenocarcinoma with pure lepidic growth and minimally invasive adenocarcinoma as those with a predominantly lepidic pattern and ≤5 mm invasion on pathological examination [6]. Both adenocarcinoma *in situ* and minimally invasive adenocarcinoma were considered preinvasive lesions because patients who had them had 100% 5-year disease-free survival once the lesions were completely resected. Pathologically, the lepidic growth components were found to correspond to the ground glass opacities (GGOs) on CT scans [6, 7]. Besides, solid tumours were more likely to exhibit malignant behaviours such as lymphatic, vascular and pleural invasion and inferior disease-free survival than GGNs even though both had the same solid size on the preoperative thin-section CT [12]. The presence of even a minor GGO component (<25%) conferred OS benefit for patients with GGNs less than 3 cm [13]. Based on the preceding considerations, the solid part and its size were now recommended as referenced parameters in the staging and management of GGNs ≤3 cm [10, 14]. Although the guidelines advocated applying the rule for GGNs larger than 3 cm, few studies have focused on verifying this concept for these lesions.

Nakamura *et al.* [15] retrospectively reviewed 113 cases with clinical T2aN0M0 lung cancer from 2005 to 2011. They enrolled 25 patients with GGNs showing a consolidation/total tumour size ratio (C/T) of ≤0.5 and 88 patients with GGNs showing a C/T ratio of >0.5, more than half of which were solid lesions without any GGO components. The 2 groups were balanced in terms of age, sex and total tumour size. The GGO-dominant group displayed lower pathological invasiveness such as lymphatic, vascular and pleural invasion or lymph node metastasis and a higher 5-year OS rate than the solid-dominant group (96% vs 71%). This study demonstrated that the appearance of a ground glass component suggested a favourable prognosis after surgery for solitary GGNs larger than 3 cm. Suzuki *et al.* [16] first reported the clinical features of GGNs exceeding 3 cm in diameter in 160 patients who underwent complete resection from 2002 to 2012. The lesions were categorized into 3 groups according to the C/T ratio: <0.25 (type A), 0.25 to 0.5 (type B) and >0.5 (type C). Type A and type B tumours showed no lymph node metastases. After a median follow-up time of 68 months, 31% of patients with type C tumours had recurrences whereas no patients with type A and type B tumours had recurrences. Patients with type C lesions had the worst 5-year overall and disease-free survival rates, followed by those with type B lesions. The results of these 2 studies indicated that GGNs >3 cm in size, especially those with a C/T ratio <0.5, had a much better survival outcome than their counterparts with larger or entirely solid opacities. However, both research groups collected eligible patients over a long period and never directly compared the prognostic significance of the solid size and the whole size for large GGNs. The impact of the C/T ratio on prognosis did not indicate that the solid size was a better indicator of long-term survival than the whole size or that the solid size should be used as the T descriptor in clinical staging. With a

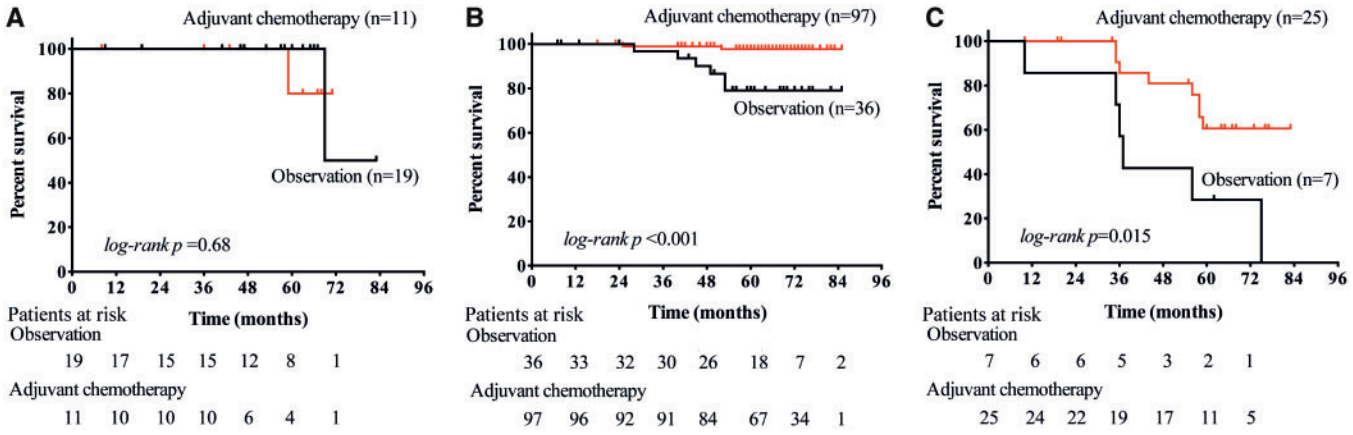


Figure 4: Effects of adjuvant chemotherapy on overall survival for patients with (**A**) stage Ia, (**B**) stage Ib and (**C**) stage II–IIIa non-small-cell lung cancer.

larger sample, both univariable and multivariable analyses of our study suggested that the solid size was significantly related to lymph node metastasis and long-term survival for GGNs >3 cm after curative surgery, but the whole size was not (data of univariable analysis not shown). Our results differed from those of similar studies for GGNs smaller than 3 cm, which revealed that the whole size was correlated with the long-term outcomes in the univariable analysis [17, 18]. We speculated that, compared with GGNs less than 3 cm, the larger variation of the solid size in GGNs >3 cm greatly confounded the impact of the whole size on survival and resulted in a marginal significance.

The effect of adjuvant chemotherapy on survival varied by different stages of resected non-small-cell lung cancer (NSCLC). The survival advantage of adjuvant chemotherapy against observation for completely resected stage II–IIIa NSCLC had been identified by several randomized trials, and it is currently recognized as a standard treatment [19–21]. However, the utility of postoperative chemotherapy was controversial in stage I NSCLC, especially in stage Ib disease. Although little evidence documented the benefit of adjuvant chemotherapy for the total cohort of patients with stage Ib disease, some subgroups with high risks, such as those with poorly differentiated tumours, vascular invasion, tumours >4 cm and visceral pleural invasion, may have improved survival from that treatment [22–24]. Our study demonstrated that, for GGNs with a whole size of at least 3 cm, adjuvant chemotherapy improved the survival of patients with pathological stage Ib and II–IIIa disease but not those with stage Ia disease. The presence of GGO may affect the impact of adjuvant chemotherapy, especially for GGNs larger than 3 cm, which have a large GGO component. However, we were unable to further investigate the subgroups, such as those with a pathological size >4 cm vs ≤4 cm, among patients with stage Ib disease because of the limited number of cases. Further studies are warranted to identify subgroups benefitting from adjuvant chemotherapy for these tumours.

Our study has a unique strength. Although the new TNM staging system has recommended that the solid size should be the T descriptor for GGNs more than 3 cm, few studies have explored the rationality of this recommendation. We compared the prognostic value of the whole size and the solid size directly and confirmed, for the first time, the superiority of the solid size. However, the retrospective nature of the study could also result in selection bias, which would be reduced by prospective studies.

CONCLUSION

In conclusion, the results of our study suggested that the solid size could better predict lymph node metastasis and long-term survival than the whole size in GGNs exceeding 3 cm. Namely, clinical T staging should be based on the solid size rather than on the whole size for those lesions.

Conflict of interest: none declared.

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