European Journal of Cardio-Thoracic Surgery 54 (2018) 1028–1036
doi:10.1093/ejcts/ezy225 Advance Access publication 12 June 2018

ORIGINAL ARTICLE

Cite this article as: Su H, Dai C, She Y, Ren Y, Zhang L, Xie H *et al*. Which T descriptor is more predictive of recurrence after sublobar resection: whole tumour size versus solid component size? Eur J Cardiothorac Surg 2018;54:1028–36.

Which T descriptor is more predictive of recurrence after sublobar resection: whole tumour size versus solid component size?

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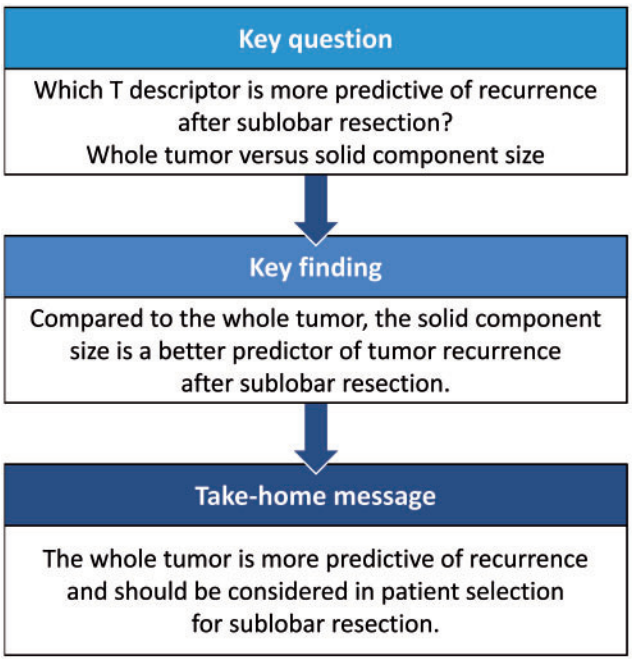
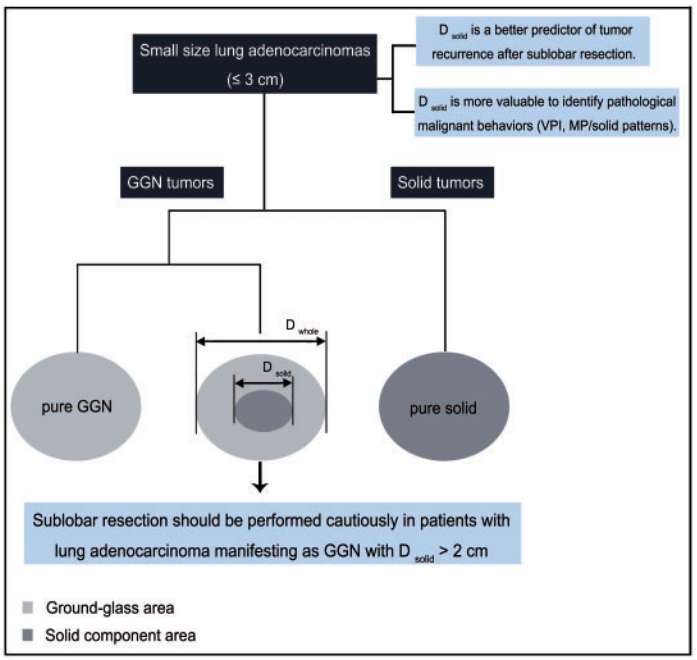
Received 10 January 2018; received in revised form 2 May 2018; accepted 9 May 2018





Abstract

OBJECTIVES: We aimed to assess the predictive value of different T descriptors, including the whole tumour size (D_{whole}) and solid component size (D_{solid}), in patients with clinical Stage IA adenocarcinoma who underwent sublobar resection.

METHODS: According to computed tomography images in the lung window, T descriptors, D_{whole} and D_{solid}, were applied. To evaluate the predictive value of these 2 different descriptors in predicting tumour recurrence and pathological malignant behaviours, Cox hazard regression and a receiver-operating characteristic curve analysis, respectively, were used.

†The first three authors contributed equally to this work.

RESULTS: In total, 247 patients were included. Of these patients, 109 and 138 had ground glass and solid nodules, respectively. When the T descriptor was changed from D_{whole} to D_{solid}, 37 tumours (15%) were downgraded to T1a status from T1b/T1c status. Multivariable Cox analysis showed that D_{solid} was an independent risk factor of worse recurrence-free survival [hazard ratio (HR) 2.36, 95% confidence interval (CI) 1.24–4.47; $P = 0.009$], while D_{whole} was not (HR 1.51, 95% CI 0.79–2.89; $P = 0.215$). In the receiver-operating characteristic analysis, the areas under the curves for D_{whole} and D_{solid} used to identify pathological malignant behaviours were 0.598 and 0.739, respectively.

CONCLUSIONS: The T descriptor, which is represented by D_{solid}, rather than D_{whole}, is a better predictor of tumour recurrence after sublobar resection in clinical Stage IA lung adenocarcinoma. Furthermore, our results provide some clues indicating that sublobar resection should be performed cautiously in patients with lung adenocarcinoma manifesting as ground glass nodule with D_{solid} >2 cm.

Keywords: Sublobar resection • Solid component size • Whole tumour size • Lung adenocarcinoma

INTRODUCTION

Tumour size is not only one of the key elements of tumour, node and metastasis (TNM) staging but is also one of the most important predictors of outcome in lung cancer [1]. In the lung cancer TNM staging system, the T classification is generally based on whole tumour size. However, controversy has arisen on tumour size measurement since the detection rate of ground glass nodules (GGNs) has increased significantly [2]. The fact that patients with larger-sized GGN tumours have favourable prognosis even after sublobar resection indicates that including the ground glass opacity (GGO) area in tumour size possibly overestimates the T status [3–5]. Both radiological and pathological data have been accumulated in support of the view that invasive size is a better prognostic indicator than whole tumour size in lung adenocarcinoma [6].

Nowadays, tumour size is still the key criterion in the recommendation for sublobar resection [7–9]; however, whether whole tumour size or solid component size is applied is a controversial issue in clinical practice [10, 11]. Although both the 8th edition of the TNM staging and Fleischner Society unanimously recommended that a clinical T classification should be determined according to the solid component size without the GGO area, it is often difficult to distinguish the prognosis of patients with GGN tumours from those with solid tumours if they present similar solid component sizes [12, 13]. In addition, this new T classification has not been validated in sublobar resection, and there is little evidence to indicate whether measuring the solid component size is more useful when selecting candidates for sublobar resection.

Hence, the present study aimed to assess and compare the predictive values of the different T descriptors in patients with clinical Stage IA adenocarcinoma who underwent sublobar resection.

MATERIALS AND METHODS

Patient selection

The Shanghai Pulmonary Hospital Institutional Review Board approved this retrospective study. Patients with clinical Stage IA lung adenocarcinoma who underwent sublobar resection from 1 June 2009 to 31 December 2013 were retrospectively reviewed. The exclusion criteria consisted of 3 main parameters: (i) multiple lung adenocarcinomas; (ii) lesions that were pathologically diagnosed as adenocarcinoma *in situ*, minimally invasive adenocarcinoma or benign disease; and (iii) patients with positive lymph node cancer confirmed by intraoperatively frozen pathology.

There were 2 surgical indications of sublobar resection in our institution, including intentional and compromised sublobar resections. For intentional sublobar resection, patients were required to meet all of the following criteria according to previous studies [14, 15]: (i) <3 cm in size with pure-GGN or radiologically non-invasive appearance (consolidation/tumour ratio <0.5), (ii) location within the outer third of the lung parenchyma, (iii) general condition and respiratory function adequate for lobectomy, (iv) patient age ranging from 20 to 79 years and (v) no prior chemotherapy or radiation therapy for any malignant diseases. Compromised sublobar resection was selected for patients who could not tolerate a lobectomy for any of the following reasons: (i) patients with poor pulmonary function (%predicted forced expiratory volume in 1 s ≤ 70%), (ii) patient age ≥80 years and (iii) patients with severe cardiovascular disease. Intraoperative frozen section analysis was used to assess the status of resection margins and lymph nodes. Segmentectomy was followed by systematic lymphadenectomy and wedge resections by lymph node sampling.

Radiological and pathological evaluations

Two reviewers independently re-evaluated all computed tomography (CT) scans. If disagreement occurred in a patient, discussion was necessary before reaching a consensus. GGO was defined as an area of slight homogeneous increase in density that did not obscure the underlying vascular markings [16]. A GGN tumour was defined as a tumour with a GGO component on thin-section CT [17]. All tumours were classified into the GGN or solid group based on the simple presence of a GGO component. D_{whole} was measured as the largest axial diameter of the lesion, and D_{solid} was measured as the largest axial diameter of an area which had increased opacification completely obscuring bronchial and vascular structures on the lung window setting [level, -500 Hounsfield unit (HU); width, 1350 HU].

In our institution, scanning technical characteristics were as follows: tube voltage was 120 kVp, tube current was adjusted automatically, pitch was 0.969, reconstruction thickness was 1.0 mm, and reconstruction interval was 1.0 mm. Further, preoperative chest CT scans were obtained using scanners with 64-detector rows (Somatom Definition AS; Siemens Medical Systems, Erlangen, Germany). Moreover, a total of 235 patients [235 of 247 (95.1%)] underwent contrast material-enhanced CT, except for a few people who are allergic to contrast material. We assessed the pathologically invasive size by the methods proposed in previous study. [18], and the invasive size was measured at ×20 or ×40 magnification on the microscope using a ruler.

Postoperative follow-up

All patients who underwent sublobar resection were followed up from the date of surgery. In the first 2 years, follow-up

Table 1: Clinicopathological characteristics based on a presence of GGO component

Variables	GGN tumours (n = 109)	Solid tumours (n = 138)	P-value
Age (years), mean ± SD	62.9 ± 12.4	64.7 ± 10.4	0.207
≤65	59 (54)	65 (47)	0.426
>65	50 (46)	73 (53)	
Gender, n (%)			0.077
Male	43 (39)	70 (51)	
Female	66 (61)	68 (49)	
Smoking, n (%)			0.151
Non-smoker	89 (82)	103 (75)	
Current or ex-smoker	20 (18)	35 (25)	
CEA, n (%)			0.046
≤10 ng/ml	105 (96)	1 (88)	
>10 ng/ml	4 (4)	16 (12)	
% predicted FEV_1, n (%)			0.088
≤70%	22 (20)	40 (30)	
>70%	87 (80)	98 (70)	
Tumour location, n (%)			0.581
Upper and middle	71 (65)	95 (69)	
Lower	38 (35)	43 (31)	
Indication of sublobar resection, n (%)			0.011
Intentional sublobar resection	84 (78)	87 (63)	
Not tolerating lobectomy	24 (22)	51 (37)	
Surgery, n (%)			0.060
Wedge resection	62 (57)	91 (66)	
Segmentectomy	47 (43)	47 (34)	
Whole tumour size (mm), mean ± SD	17.5 ± 6.3	18.8 ± 6.2	0.114
Solid component size (mm), mean ± SD	7.9 ± 8.0	18.8 ± 6.2	<0.001
Pathological invasive tumour size (mm), mean ± SD	8.8 ± 7.0	17.7 ± 6.3	<0.001
VATS, n (%)			0.775
No	16 (15)	19 (14)	
Yes	93 (85)	119 (86)	
Postoperative chemotherapy, n (%)			0.003
No	101 (93)	116 (84)	
Yes	8 (7)	22 (16)	
Predominant subtype, n (%)			<0.001
Lepidic	64 (59)	24 (17)	
Acinar/papillary	39 (36)	86 (62)	
Micropapillary/solid	6 (5)	28 (21)	
VPI, n (%)			<0.001
Absent	105 (96)	104 (75)	
Present	4 (4)	34 (25)	
Nodal involvement, n (%)			0.035
N0	106 (97)	122 (89)	
N1	2 (2)	10 (7)	
N2	1 (1)	6 (4)	

CEA: carcinoembryonic antigen; FEV_1: forced expiratory volume in 1 s; GGN: ground glass nodule; GGO: ground glass opacity; SD: standard deviation; VATS: video-assisted thoracoscopic surgery; VPI: visceral pleural invasion.

procedures included a physical examination, chest X-ray and blood examination, including measurements of tumour markers every 3 months and chest CT scans every 6 months. Subsequently, chest X-rays were performed every 6 months and chest CT scans were performed every year. When any symptom or sign of disease recurrence was detected, further examination was performed with brain magnetic resonance imaging and bone scintigraphy. Local recurrence was defined as tumour recurrence in the ipsilateral hemithorax, including the resection margin, ipsilateral lung and pleura or the hilum and mediastinal lymph nodes. Distant recurrence was defined as tumour recurrence in the contralateral hemithorax or extrathoracic organs. Recurrence-free survival (RFS) was defined as the time from surgery until recurrence or death from any cause.

Statistical analysis

All clinical data are shown as mean ± standard deviation and n (%). We used the Pearson χ^2 test to compare categorical variables and the independent sample t-test to compare the continuous variables between different groups. The log-rank test and Cox proportional hazards regression model were applied to evaluate predictive factors for RFS. The receiver-operating characteristic analyses of D_{whole} and D_{solid} were used for the prediction of lymph node metastasis and pathological malignant behaviours. In addition, a logistic regression model was applied to confirm the independent predictive factors of preoperative positive lymph node. All the analyses were performed using SPSS 22.0 (IBM Corporation, Armonk, NY, USA). In the current

study, a 2-sided *P*-value of <0.05 was considered statistically significant.

RESULTS

Overall, 247 patients with clinical Stage IA adenocarcinoma who underwent sublobar resection were recruited into our study, and the mean follow-up time was 52 months. Clinicopathological characteristics of patients are summarized in Table 1. According to the D_{whole} classification, the T stages of tumour distribution are as follows: (i) T1a, *n* = 48 (19.4%); (ii) T1b, *n* = 105 (42.5%); and (iii) T1c, *n* = 94 (38.1%). When applying the D_{solid} classification, the rectified T stages were as follows: (i) T1a, *n* = 85 (34.4%); (ii) T1b, *n* = 95 (38.5%); and (iii) T1c, *n* = 67 (27.1%) (Fig. 1). The total concordance rate of T-stage distributions based on D_{whole} and D_{solid} classification between H. Su and C. Dai were 91.9% and 87.0%, which indicated substantial agreement between the 2 reviewers (Supplementary Material, Table S1). When the 2 distributions classified according to different T descriptors were compared, the proportion of tumours in the T1a status remarkably increased after the reclassification of T1b and T1c statuses. Furthermore, the total concordance rate of T-stage distribution between the radiological (D_{solid}) and pathological ($D_{pathological}$) classifications was 91.5% (Supplementary Material, Table S2).

The RFS curves classified according to the D_{whole} and D_{solid} are shown in Fig. 2. The difference in the 5-year RFS rate of the patients classified according to the D_{solid} classification (T1a, 91.7% vs T1b, 77.8% vs T1c, 58.2%) showed a more defined separation than those of the patients classified according to the D_{whole} classification (T1a, 91.6% vs T1b, 84.7% vs T1c, 61.7%). The difference in recurrence rate between T1a and T1b was significantly different according to the D_{solid} classification (*P* = 0.002), whereas no significant difference was observed between T1a and T1b based on the D_{whole} classification (*P* = 0.275). Table 2 shows the results of the univariable and multivariable Cox regression analyses of RFS, and D_{solid} was an independent risk factor for worse RFS [hazard ratio (HR) 2.36, 95% confidence interval (CI) 1.24–4.47; *P* = 0.009], whereas D_{whole} was not statistically significant (HR 1.51, 95% CI 0.79–2.89; *P* = 0.215).

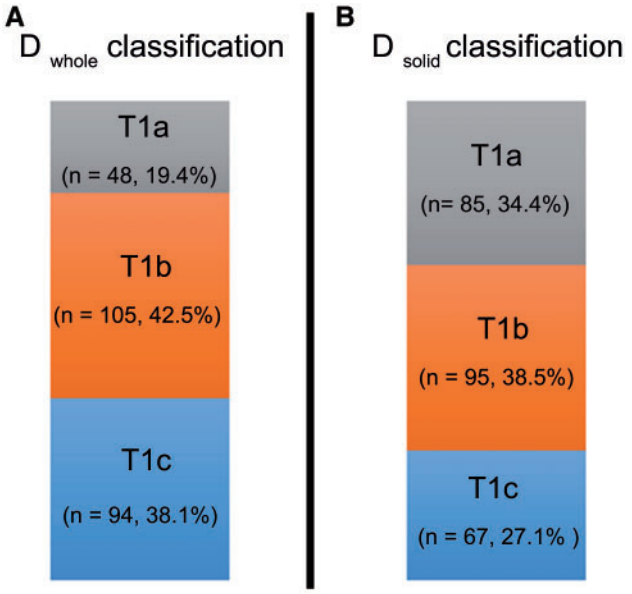


Figure 1: Distributions of T stage according to D_{whole} classification and re-staging by D_{solid} classification. (**A**) D_{whole} classification and (**B**) D_{solid} classification. D_{whole}: whole tumour size; D_{solid}: solid component size.

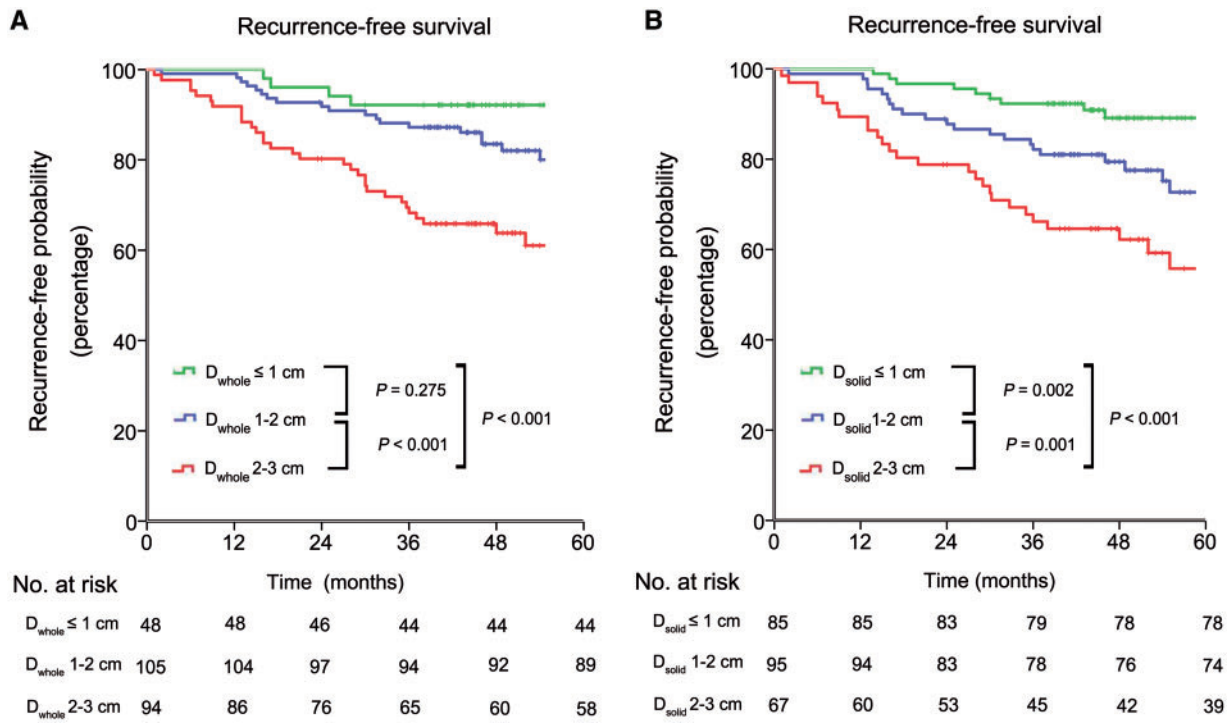


Figure 2: Recurrence-free survival according to different T descriptors in patients with clinical Stage IA adenocarcinoma who underwent sublobar resection. (**A**) D_{whole} classification and (**B**) D_{solid} classification. D_{whole}: whole tumour size; D_{solid}: solid component size.

Table 2: Cox proportional hazards regression model for recurrence-free survival in patients with lung adenocarcinoma underwent sublobar resection

Variables	Recurrence-free survival		
	Univariable analysis	Multivariable analysis	
	P-value	HR (95% CI)	*P*-value
Age (>65 vs ≤65)	0.385		
Gender (male versus female)	0.062		
Smoking (current or ex- versus non-smoker)	0.907		
CEA (>10 ng/ml versus ≤10 ng/ml)	0.201		
% predicted FEV_1 (>70% vs ≤70%)	0.586		
Tumour location (lower versus upper and middle)	0.775		
VPI (present versus absent)	0.101		
Surgery (wedge resection versus segmentectomy)	0.210		
Indication of sublobar resection (intentional versus not tolerating lobectomy)	0.810		
VATS (yes versus no)	0.770		
Whole tumour size (>2 cm vs ≤2 cm)	0.001	1.51 (0.79-2.89)	0.215
Solid component size (>2 cm vs ≤2 cm)	<0.001	2.36 (1.24-4.47)	0.009

CEA: carcinoembryonic antigen; CI: confidence interval; FEV_1: forced expiratory volume in 1 s; HR: hazard ratio; VATS: video-assisted thoracoscopic surgery; VPI: visceral pleural invasion.

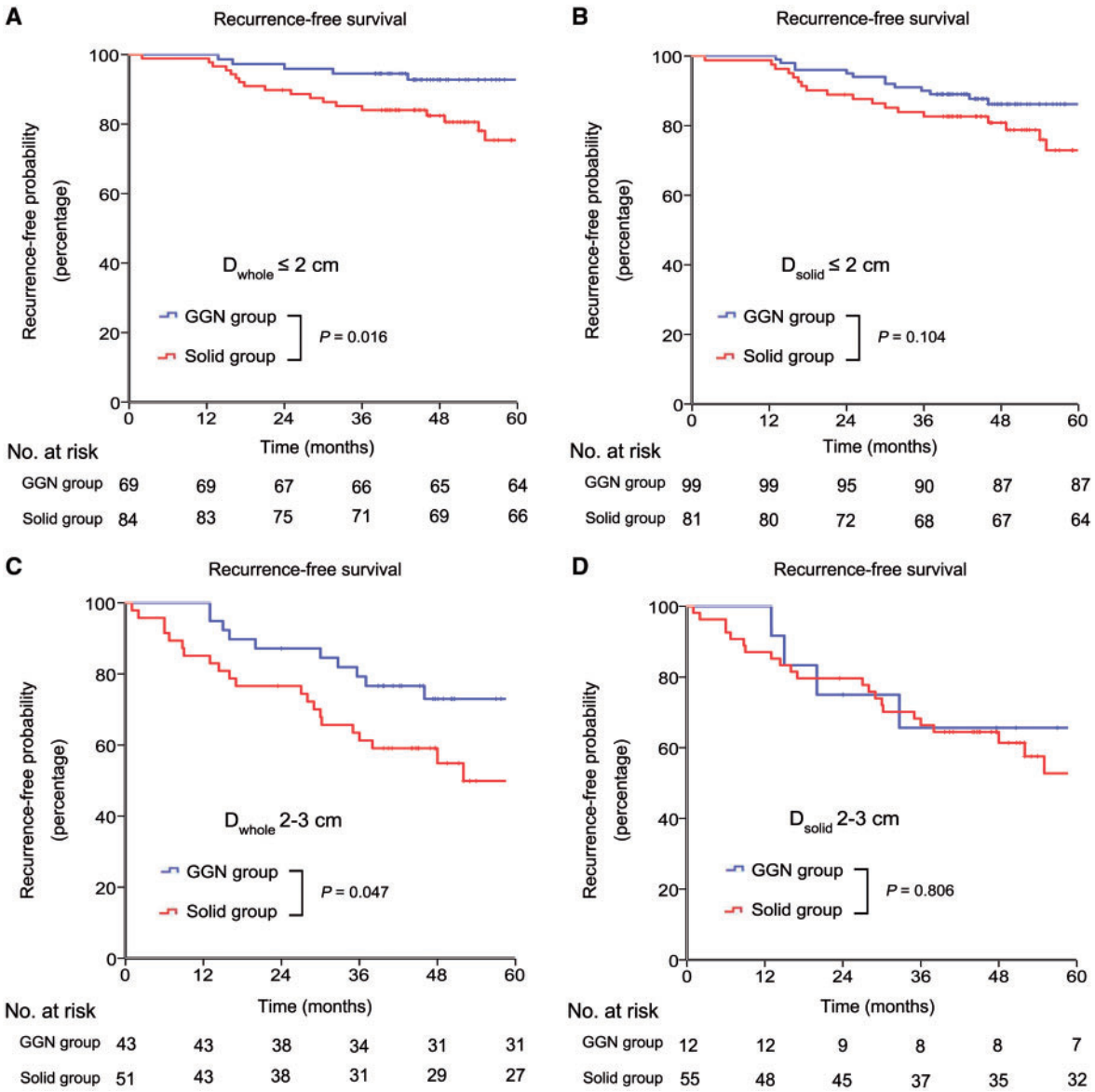


Figure 3: Recurrence-free survival of GGN tumours and solid tumours according to different T descriptors. (**A**, **C**) D_{whole} classification and (**B**, **D**) D_{solid} classification. D_{whole}: whole tumour size; D_{solid}: solid component size; GGN: ground glass nodule.

When the GGN and solid tumour groups were analysed separately, the results were similar. The RFS curves for GGN tumours according to the D_{whole} and D_{solid} classifications are shown in Supplementary Material, Fig. S1. The differences in the recurrence rates of patients classified using the D_{solid} classification were significantly different ($P = 0.001$); however, the recurrence rates were not significantly different when using the D_{whole} classification ($P = 0.078$). In the Cox proportional hazards regression models for GGN tumours, D_{solid} was an independent risk factor of worse RFS (HR 4.28, 95% CI 1.25–14.65; $P = 0.012$), whereas D_{whole} was not (Supplementary Material, Table S3). The RFS curves for solid tumours according to D_{solid} classifications are shown in Supplementary Material, Fig. S2. As to multivariable Cox analysis, D_{solid} was an independent risk factor of poor RFS (HR 2.05, 95% CI 1.25–3.37; $P = 0.005$) (Supplementary Material, Table S4).

To analyse the predictive value of D_{solid} and D_{whole} on different topics, we further conducted multivariable Cox analyses in different subgroups, including intentional versus compromised sublobar resection, wedge versus segment resection and nodal sampling versus lymphadenectomy. When subgroups were analysed according to the topics separately, the results showed that D_{solid} was an independent risk factor of worse RFS in all subgroups except in the compromised sublobar resection subgroup, while D_{whole} was not in all subgroups of our study (Supplementary Material, Table S5).

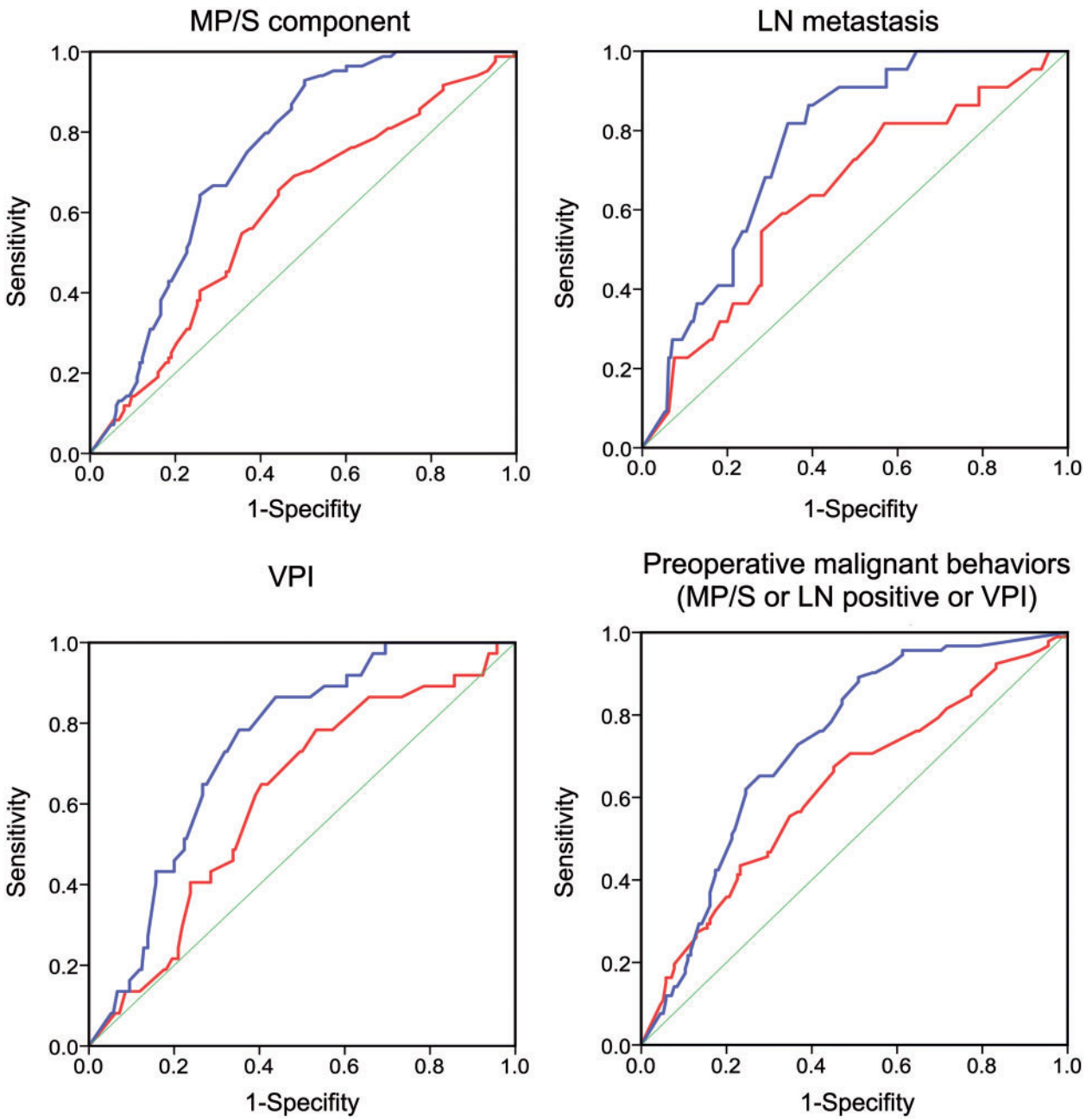


Figure 4: Receiver-operating characteristic curves of whole and solid tumour sizes used for predicting pathological malignant behaviours. LN: lymph node; MP: micropapillary; S: solid; VPI: visceral pleural invasion.

Table 3: Receiver-operative characteristic AUC values of the whole and solid component sizes to predict preoperative pathological malignant behaviours

Variable	Whole tumour size		Solid component size	
	AUC (95% CI)	*P*-value	AUC (95% CI)	*P*-value
VPI	0.618 (0.525–0.710)	0.022	0.742 (0.671–0.814)	<0.001
LN metastasis	0.699 (0.592–0.807)	0.003	0.785 (0.704–0.866)	<0.001
MP/S components	0.617 (0.542–0.692)	0.002	0.756 (0.696–0.816)	<0.001
Malignant behaviours (MP/S/VPI/LN+)	0.598 (0.523–0.672)	0.012	0.739 (0.679–0.799)	<0.001

AUC: area under the curve; CI: confidence interval; LN: lymph node; MP: micropapillary; S: solid; VPI: visceral pleural invasion.

GGN tumours with D_{whole} ≤2 cm showed better RFS than solid tumours (5-year RFS: 93.2% vs 79.5%, $P = 0.016$); however, those with D_{solid} ≤2 cm did not show significant differences compared to solid tumours (5-year RFS: 87.8% vs 79.5%, $P = 0.104$) (Fig. 3A and B). Similarly, GGN tumours with 2–3 cm D_{whole} showed better RFS than solid tumours (5-year RFS: 71.8% vs 53.2%, $P = 0.047$); however, those with 2–3 cm D_{solid} did not show significant differences compared to solid tumours (5-year RFS: 58.3% vs 57.4%, $P = 0.806$) (Fig. 3C and D).

Figure 4 and Table 3 show receiver-operating characteristic curves and area under the curve of the D_{whole} and D_{solid} used for predicting preoperative positive lymph node and pathological malignant behaviours. The present study demonstrated that D_{solid} was more effective in predicting preoperative lymph node positive and malignant behaviours, such as micropapillary or/and solid patterns and visceral pleural invasion. Further multivariable logistic regression analysis revealed that the D_{solid} (odds ratio 2.62, 95% CI 1.07–7.00; $P = 0.026$) was an independent predictive factor for preoperative positive lymph node (Table 4).

Table 4: Logistic regression model for preoperative positive lymph node in patients with clinical Stage IA lung adenocarcinoma underwent sublobar resection

Variables	Multivariable	
	OR (95% CI)	*P*-value
CEA (high versus >normal)	1.26 (0.26–2.07)	0.771
VPI (present versus absent)	1.93 (0.68–5.43)	0.215
Solid tumour size (>2 cm vs ≤2 cm)	2.62 (1.07–7.00)	0.026
Whole tumour size (>2 cm vs ≤2 cm)	1.15 (0.41–3.19)	0.794

CEA: carcinoembryonic antigen; CI: confidence interval; OR: odds ratio; VPI: visceral pleural invasion.

DISCUSSION

Compared to lobectomy, sublobar resection has several advantages, including preservation of pulmonary function, improved postoperative complications and increased potential for a second resection with a subsequent primary tumour [19]. Moreover, a previous study has demonstrated that the well-selected use of sublobar resection can offer comparable survival to lobectomy [20]. Small-sized lung cancers often contain a GGO component on CT scans, which result in conflicting evidence for tumour size measurement.

The predictive value of tumour size has been verified in many publications, including large databases similar to those assembled by the Surveillance, Epidemiology and End Results (SEER) database registry and the International Association for the Study of Lung Cancer (IASLC) [21, 22]. Previous studies have evaluated and compared the prognostic significance of the solid tumour size with that of whole tumour size [10, 23]. They found that solid tumour size provides more valuable information for predicting invasiveness and prognosis. Moreover, Tsutani *et al.* [24] demonstrated that pathological invasive component size, rather than whole tumour size, is more significantly associated with malignant behaviours.

In the present study, GGN tumours with D_{whole} ≤2 cm showed better RFS than solid tumours; however, those with D_{solid} ≤2 cm did not. In other words, it is highly possible that T status is usually overestimated due to the GGO component in subsolid nodules according to the D_{whole} classification. GGN tumours had similar malignancies compared to solid tumours if they present the same solid component size. Hence, GGN tumours, even those with larger whole tumour size, may be appropriate for sublobar resection as long as their solid component size meets the sublobar resection criteria.

For GGN tumours, multivariate analyses demonstrated that the solid component size rather than whole tumour size was an independent risk factor for poor RFS. This result can be explained by the fact that the solid component of GGO tumours closely correlated with the invasive component on pathology, and the invasive components of an adenocarcinoma are determinants in the prognosis of these patients [25]. Although D_{whole} is not an independent risk factor for RFS in multivariable Cox regression analysis, the upper limit of the corresponding 95% CI is up to 2.89. It means that a patient with a higher D_{whole} might have a 3-fold risk compared to a patient with the same D_{solid}. Future multicentre prospective studies with larger sample sizes may address this issue.

In our study, it was more effective to use D_{solid} instead of D_{whole} for predicting preoperative pathological malignant behaviour, which is consistent with a previous study [26]. These findings indicate that the D_{solid}, but not the D_{whole}, accurately reflects tumour malignancy. Concerning the association between the tumour diameter and positive lymph node, we should take into account N-stage migration. Even for small-

sized lung cancers, lymph node metastasis can be found in about 15% of lung cancers [27].

Theoretically, GGO on CT scans usually corresponds to the lepidic component on pathology, while solid components frequently indicate invasive components. Investigators have found that there was a significant correlation between the solid component size on CT and the invasive component size on pathology in lung adenocarcinomas manifesting as subsolid nodules [28, 29]. Moreover, previous studies confirmed that the invasive tumour size without the lepidic pattern was an important predictor of the outcome in Stage I lung adenocarcinoma [18, 30]. Hence, the solid component size on preoperative CT scans can predict pathological invasive size, which is very helpful for surgical decision making.

Limitations

We must acknowledge some limitations of our study. First, because of the nature of this retrospective study, performance bias and selection bias were inevitable. For example, it may not be feasible to perform sublobar resection because of some anatomical limitations on GGNs near the lung hilum. Second, there are some GGN tumours with several solid components that can pose a particular challenge, as there is no consensus on how these solid lesions should be measured, and we measured only the single largest focus of invasion and did not measure the remaining foci. Finally, positron emission tomography–CT (PET-CT) was quite expensive, and it is not covered by medical insurance in China; thus, few patients in this study had a PET-CT examination. Further multicentre studies with larger patient cohorts may address these limitations.

CONCLUSION

In conclusion, the T descriptor D_{solid} is a better predictor of tumour recurrence than D_{whole} after sublobar resection in clinical Stage IA lung adenocarcinoma. We provided preliminary evidence that D_{solid} rather than D_{whole} should be considered when selecting candidates for sublobar resection. Furthermore, our results provide some clues that sublobar resection should be performed cautiously in patients with lung adenocarcinoma manifesting as GGN with D_{solid} >2 cm, and lobectomy might be the first choice.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *EJCTS* online.

Funding

This work was supported by the projects from Shanghai Hospital Development Center [SHDC12015116]; Science and Technology Commission of Shanghai Municipality [15411968400, 14411962600]; Health and Family Planning Commission of Shanghai Municipality [2013ZYJB0003, 20154Y0097]; and Shanghai Pujiang Program [15PJD034].

Conflict of interest: none declared.

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