The Natural Growth Rate of Growing Malignant Pulmonary Nodules with Ground-Glass Opacity and Association of Clinic Features With It

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Abstract

Objective

The objective of the study was to investigate the volume (VDT) and mass doubling time (MDT) of growing malignant ground-glass opacity(GGO) and explore the relationships between doubling times and clinical-pathological features.

Methods

We collected 37 GGO cases (18 male & 19 female with age between 43- and 82-year-old) between 2016 and 2020 and all of these cases were along with growing malignant pulmonary nodules. The duration of follow-up and the variation in GGOs volume and mass were recorded. The morphologic changes and three-dimensional segmentation of GGO nodules were used to calculate the VDT and MDT based on a modified Schwartz model. The independent sample t-test was used to investigate the relationship between doubling times and their features. Logistic regression was used to evaluate the risk factors of growing malignant GGOs.

Results

The median follow-up time was 725 days (31-1507 days). The averaged VDT and MDT of the GGOs were 973 days and 671 days, respectively. Both VDT and MDT were significantly different among the three different groups of solid components of GGO($p<0.05$). The vacuole sign and lepidic-predominant lung adenocarcinoma (LPA) also made an important role in changing the VDTs and MDTs ($p<0.05$). In addition, the growth of malignant pulmonary nodules was significantly associated with air bronchus sign (OR 6.667; 95% CI of 1.126-39.470; $p=0.037$). Multivariate analysis showed that LPA declined the GGOs growth (odds ratio 0.093, 95% CI of 0.011-0.765, $p = 0.027$).

Conclusions

The solid component of GGOs and vacuole sign were closely associated with the growth rate of GGOs. The GGOs with air bronchus sign was more dangerous in terms of growth rate than other GGO cases. However, the appearance of LPA could inhibit GGO growth. Further studies are still required to verify the obtained results.

Introduction

The popularization utilization of CT screening makes more pulmonary nodules with ground-glass opacity (GGOs) be detected. The Early Lung Cancer Action Project reported that about 63% of these GGOs were malignancy[1]. Many studies [2, 3] observed that persistent subsolid nodules were generally precursors of

cancers of the lung adenocarcinoma spectrum. In general, the differentiation between benign and malignant GGOs is mainly dependent on the size of the solid component[4]. According to the National Comprehensive Cancer Network(NCCN) description on the non-small cell lung cancer[5], pure GGOs and GGOs with solid components require different follow-up intervals. However, most of the GGO patients are anxious during the follow-up duration and finally request surgeons to conduct the surgical program. So, the major concern for patients was whether the nodules grow up and how fast they grow during a fixed follow-up period.

In the past decade, the size measurement of a solid component was generally according to the morphological variations visually observed in the ground-glass nodules (GGNs)[6]. But recently, the growth of a pulmonary nodule was demonstrated as a direct indicator of GNN size and density changes. For some cases, the volume of solid components expands slowly, or some GGOs exhibit necrosis, liquefaction, or cavitation but without changes in the diameter and volume, which make the visual diameter and volume measurements not effective to evaluate the changes in the lesion. Recent studies reported that the volume doubling time (VDT) and mass doubling time (MDT) were effective to reflect the GNN growth and useful for the therapy decision-making[7–11]. But these studies mainly treated the growth rate of GGNs as a biomarker of reflecting the malignant potential of the tumor[12–16], not focusing on the investigation of the relationships between the times (i.e., VDT and MDT) and the clinic features. Some studies are concerned with using VDT/MDT to evaluate the GGO growth. For example, Song et al. Some studies tried to find the risk factors for growth in GGNs[17–19]. But they identified the growth by the diameter. One study[7] has reported that pulmonary nodules with solid components size of $\leq$ 5 mm showed longer VDT and MDT than those with solid components > 5 mm[7]. However, the samples in this study were only consisted of benign nodules, making the results less generalization. The objective of this study was to retrospectively investigate the VDT and MDT of growing malignant GGOs and find out the potential risk factors of clinical features accounting for the growth of GGNs.

Materials And Methods

The sample collection in this retrospective study was agreed upon by our Institutional Review Board, and the informed consent was waived.

Patients

From September 2016 to December 2020, we followed up 3500 patients with GGO which was determined via CT scans or at a tertiary hospital in China. The patients with the following characteristics (Fig. 1) will be selected in this study, including (1) GGN was identified by a pathology, (2) pulmonary nodules were regarded as pure GGOs or part-solid GGOs based on the chest CT examination with slice thickness less than 1.25 mm, (3) the GGN was at least twice determined by chest CT scanning with an interval of over 30 days[20], and (4) either the density, volume, or mass of GGN, estimated by the CT embedded software, was increasing, i.e., the GNN was growing. Only the largest size of GGN was recorded if multiple GNNs

were detected from a patiented, these patients also included. The volume and mass of these GGNs can be calculated by CT software. The last value of volume or mass increased ,which was defined as growing GGN.(5)For multiple GGN, only the largest GGN was registered. If part-solid GGN and pure GGO exist in one patient, nodules with largest solid component were selected. The cases with a history of chemotherapy or chemo-radiation therapy before surgery were excluded. Finally, 37 patients were selected, including 18 males and 19 females in this study. Their age ranged from 43 to 82 with a median value of 64-year old and a mean of 62.

CT images acquisition and analysis

All chest CT images were obtained by scanning the lungs from the bottom to the apices with a 4 multi-detector CT scanner (Brilliance 64, Siemens Medical Systems, Forchheim, Germany) whilst the patients were asked to take a deep inspiratory breath. The measurement protocol and slice preparation were performed according to the guideline of the CT provider. The follow-up time, i.e., the period between the two CT scans, ranged from 31 to 1507 days, with a median of 725 days.

The parameters were measured in the lung-tissue windows. One observer (with 5 years working experience in the thoracic CT department) measured the diameter of the GGOs and performed three-dimensional (3D) segmentation using a picture archiving and communication system (Neusoft Medical Systems, Shenyang, China) and a3D reconstruction system (InferRead CT Lung, InferVision, Beijing, China). The VDTs and MDTs of growing nodules from the volume and mass views were calculated using a modified Schwartz formula[21] as follows: VDT (or MDT) = $\log 2 \times T / \log(V_f/V_i)$, where V_f and V_i refer to the final and initial volumes (or masses), respectively, and T is the duration between the two CT scans.[22] The morphological features of the nodules from the follow-up CT scan were also observed, including (1) diameter of GGNs (maximal diameter of the axial section, Fig 2), (2) lobulation sign (the portion of the lesions surface with a wavy or scalloped configuration, Fig 3a), (3) spiculation sign (the presence of strands extending from the nodule margin to the lung parenchyma, but not reaching the pleural surface, Fig 3b), (4) air bronchus sign (air-filled bronchi within the GGNs, Fig 3c), (5) vascular convergence sign (GGNs with dilated, convergent or tortuous supplying vessels, Fig 3d), (6) pleural indentation sign (linear attenuation toward the pleura or the fissure from GGNs, Fig 3e)[14](7) vacuole sign (cystic cavity with diameter < 5mm within GGNs, Fig 3f), (8) based on the size of consolidation and tumor, GGNs were categorized into 3 groups (Fig 3g): ratio of consolidation diameter to tumor diameter (CTR)< 0.25, $0.25 \leq CTR \leq 0.5$, and $CTR \geq 0.5$), The clinical features of the patients included age, sex, smoking history, tumor history of their family members, postoperative pathology, degree of infiltration, and size of pulmonary nodules. Pathological diagnoses of the surgically resected GGNs were also recorded and classified according to the latest 2015 WHO Classification criteria for lung adenocarcinoma[23].

Statistical analysis

The continuous variables were analyzed with the t-test or Mann-Whitney U test while the classified data were analyzed with the chi-square test. The relationships between clinical features and GGO growing rate

were investigated with the univariate and multivariate logistic regression analysis by donating the odds ratio (OR) of 95% confidence interval (CI). All analyses were performed using the SPSS (version 22, International Business Machines Corp.) at a significant level of $p < 0.05$.

Results

A total of 37 patients, including 18 male and 19 female was included in this study, ranging from 43 to 82 years old. Their initial nodule diameters varied between 3 and 26.5 mm, with an average size of 11 mm. Among the 37 cases, 4 of them were at stage 0, 7 at stage of IA1, 17 at the stage of IA2, 5 at the stage of IA3, and 4 at the stage of IB. A fraction of 68% of these cases was diagnosed as LPA (Table 1). In addition, near half of the patients had lobulation sign, 35% of them with spiculation sign. The pleural indentation, air bronchus, vascular convergence, and vacuole signs were also observed in some cases (Table 2).

The average VDT and MDT were 973 and 671 days, respectively (Table 3). Both VDT and MDT varied significantly among the three groups of components(CTR)< 0.25, $0.25 \leq CTR \leq 0.5$, and $CTR \geq 0.5$) ($p<0.05$). According to the initial diameter (id) of the lesions, the 37 cases were separated into three groups: $id \leq 8mm$, $8mm < id \leq 15mm$, $id > 15mm$. The VDT and MDT were similar among groups in terms of the initial diameter of the lesions. However, the vacuole sign- and LPA-related VDTs and MDTs were significantly different ($p<0.05$). Similar levels of VDT and MDT were found between invasive and non-invasive GGOs and among different stages as well. In addition, VDTs and MDTs had different parents while different characteristics were considered. For the LPA cases, the values of VDT and MDT were larger than those with less solid components.

According to the description in Lindell et al[15], the 37 cases were divided into two groups: fast (VDT/MDT < 400 days) and slow growth rate (VDT/MDT ≥ 400 days). While considering the clinical features as a potential risk factor, we observed that the growth rate of malignant pulmonary nodules was closely associated with air bronchus sign (OR, 6.7; 95% CI, 1.1-39.5; $p=0.037$) and PLA (OR, 0.1; 95% CI, 4.7-32.2; $p=0.018$). The multivariable analysis results showed that LPA seemed an important factor to contribute the growth of malignant pulmonary nodules (Table 5)

Discussion

With the popularization of CT as the first choice for lung cancer screening, GGOs are increasingly identified in time and most of these GGOs were malignant after further diagnosis.[24] Accurate evaluation of the growing rate of malignant GGOs is essential because it determines the selection of surgical methods and the adoption of follow-up strategies. In practice, the follow-up interval and duration of GGOs are determined by the VDT.[24] Specifically, how and when to operate the surgical intervention must be carefully arranged if the VDT value is large in order to avoid overdiagnosis and treatment caused by the premature intervention.[8, 25]

A general of over 400 days of VDT for subsolid pulmonary nodules was reported in published articles.[15–16] However, Hasegawa et al[10] reported an averaged VDT of 813 days for pure GGOs, 457 days for part-solid nodules, and 149 days for solid nodules. This indicates the VDT greatly depending on the case source, historical clinic therapy, type and size of the nodules and pathology. Hasegawa et al[10] reported that mean VDTs were 813 days for pure GGOs (pGGOs), 457 days for part solid nodules (pSNs), and 149 days for solid nodules (SNs). Li et al[11] analyzed follow-up CT of malignant solitary pulmonary nodules and reported that mean VDTs and MDTs are 848 and 655 days for pGGNs, 598 and 462 days for pSNs, and 267 and 230 days for SNs. In our study, the median values of VDT and MDT were 1060 and 800 days for GGOs with CTR<0.25, 507 and 484 days for GGOs with CTR between 0.25 and 0.5, and 522 and 443 days for GGOs with CTR>0.5. Our results showed that the MDT was smaller than the VDT, which is consistent with the published results[10–11]. This indicated a negative correlation between the follow-up period and GGO solid component size, but a positive relationship between growth rate and GGO solid component size.

According to Travis et al. (2011)International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society International Multidisciplinary Classification of Lung Adenocarcinoma[26], invasive adenocarcinoma consists of six subtypes: lepidic predominant, acinar predominant, papillary predominant, micropapillary predominant, solid predominant with mucin production. Variants of invasive adenocarcinoma include invasive mucinous adenocarcinoma, colloid, fetal, and enteric. Preinvasive lesions, including adenocarcinoma in situ (AIS) and minimally invasive adenocarcinoma (MIA), are usually nonmucinous. Different subtypes vary in prognosis, as lepidic-predominant lung adenocarcinoma (LPA) often shows a more advantageous prognosis, while solid and micropapillary-predominant LPA produce worse clinical outcomes.[27–29] LPA typically consists of bland pneumocytic cells growing along the surface of alveolar walls. Hong et al[20] reported that the major histologic subtype of lung adenocarcinoma determinants of the growth rate of lung adenocarcinoma. In our study, GGO cases diagnosed as LPA showed longer VDT and MDT than others, which is helpful to dissect the underlying mechanism of GGO growing.

The alveolar inflation or some necrosis tissues were discharged while the alveolar structure was not yet distorted, which is frequently observed in LPA or acinar-predominant adenocarcinoma and regarded as an indication of early invasion.[30] We observed much longer VDT and MDT for GGOs with vacuole sign, indicating that vacuole sign may influence the growth of GGOs. In our study, the results of logistic regression analysis indicated that the air bronchus sign (OR, 6.667, p=0.037) was a factor for speeding up the growth of GGN. Cho et al[31] reported similar results of Cho et al[31]. This means the GGNs may be growing faster with a smaller follow-up time for those CT images containing air bronchus sign than those without the air bronchus sign.

In this study, we used the diameter and volume of the GNNs to calculate the growth rate for determining the risk factors. For pursuing high accuracy, we used the DTs to scale the GGNs growth. However, there are still deficiencies in this study. For example, the experiment and measurement were carried out in a

signal institution with only one retrospective manner. Another shortage of this study was the limited number of GGNs showing growth. This is because most patients with GGNs diameter larger than 15 mm were strongly suggested for surgical procedures, lacking the follow-up observation.

In summary, GGOs had different components. GGOs with air bronchus sign were closely associated with the growth rate of malignant pulmonary nodules. The LPA may be an independent protective factor to explain the fact that most of GGOs grow slowly.

Conclusion

The GGOs with smaller solid components and/or vacuole sign grew much slower than those without solid components, which were well presented in the follow-up intervals. Therefore, VDT and MDT between two CT scans are promising to indicate the growth rate of malignant GGOs. The air bronchus sign is an important factor in accelerating the GGO growth, shorting the follow-up intervals. However, the LPA greatly slowed the GGO growth observed in all cases. More studies are required to further demonstrate the results observed in this study.

Declarations

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Contributions

All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Wenfei Xue. The first draft of the manuscript was written by Guochen Duan and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Conflict of interest

The authors have no relevant financial or non-financial interests to disclose.

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Tables

Table 1. The statistical description of volume (VDT) and mass (MDT) doubling time of different pathological findings.

	n	VDT	MDT
		p value	p value
LPA		0.007	0.003
Yes	9		
No	28		
Stage (TNM)		0.29	0.37
0	4		
IA1	7		
IA2	17		
IA3	5		
IB	4		
Adenocarcinoma		0.64	0.7
AIS	4		
MIA	12		
IAD	21		
Invasive		0.65	0.71
Yes	16		
No	21		

LPA, lepidic-predominant lung adenocarcinoma; AIS, adenocarcinoma in situ; MIA, minimally invasive adenocarcinoma; IAD, invasive adenocarcinoma.

Table 2
The statistical description of volume (VDT) and mass (MDT) doubling time of different component group and morphological features.

Characteristics	n	VDT	MDT
		p value	p value
Component group		0.037	0.032
1(CTR<0.25)	9		
2(CTR0.25-0.5)	16		
3(CTR>0.5)	12		
Lobulation sign		0.76	0.71
No	19		
Yes	18		
Spiculation sign		0.72	0.92
No	24		
Yes	13		
Pleural indentation sign		0.83	0.89
No	27		
Yes	10		
Air bronchus sign		0.48	0.26
No	30		
Yes	7		
Vascular convergence sign		0.63	0.58
No	13		
Yes	24		
Vacuole sign		0.01	0.004
No	19		
Yes	18		
Di (mm)		0.85	0.73
Di≤8	12		

Di, initiate diameter CTR, ratio of consolidation diameter to tumor diameter.

8<Di≤15	19	
Di>15	6	
Di, initiate diameter CTR, ratio of consolidation diameter to tumor diameter.		

Table 3
The statistical description of volume (VDT) and mass (MDT) doubling time of different groups of age, gender and the history of smoking, tumor, and surgical

Characteristics	n	VDT	MDT
		p value	p value
Age(>60years)		0.35	0.12
No	13		
Yes	24		
Gender		0.89	0.95
Female	19		
Male	18		
Smoking history		0.17	0.12
No	25		
Yes	12		
Tumor history		0.89	0.63
No	35		
Yes	2		
Surgical history		0.31	0.36
No	19		
Yes	18		

Table 4
The median and range of volume (VDT) and mass (MDT) doubling time of LPA, component group, and vacuole sign.

	N (%)	VDT (days)		MDT (days)	
		Median	Range	Median	Range
LPA					
Yes	9 (24.32%)	603.25	292.94-8333.97	654.4	224.68-3088.52
No	28 (75.68%)	439.42	196.07-714.07	350.18	190.64-589.28
Component group					
1	9 (24.32%)	1060.38	466.13-8333.97	799.92	428.25-3088.52
2	16 (43.24%)	506.77	292.95-1931.00	483.7	224.69-855.78
3	12 (32.44%)	522.44	196.07-1438.11	442.8	190.64-1444.89
Vacuole sign					
No	19 (51.35%)	478.69	196.07-1201.72	428.25	190.64-820.39
Yes	18 (48.65%)	772.23	292.94-8333.97	696.58	224-3088.52
LPA, lepidic-predominant lung adenocarcinoma					

Table 5. Effect of univariate and multivariate variables in patients with growing GGO

Variables	univariate			multivariate		
	OR	95%CI	p	OR	95%CI	p
Age	1.071	0.969-1.183	0.178			
size	1.071	0.951-1.206	0.258	1.070	0.924-1.239	0.364
gender	1.442	0.319-6.529	0.635			
Smoking	0.514	0.089-2.963	0.457			
surgical	0.442	0.319-6.529	0.635			
Tumor history	7.741	0.608-97.846	0.115			
lobulation	1.442	0.319-6.529	0.635			
spikulation	2.639	0.568-12.254	0.215			
aoxian	0.857	0.143-5.130	0.866			
brochio	6.667	1.126-39.470	0.037	4.428	0.591-33.188	0.148
vascular	0.947	0.192-4.677	0.947			
vacuo	0.214	0.038-1.222	0.083			
component	1.314	0.208-8.319	0.772	1.070	0.924-1.293	0.364
PLA	0.136	0.026-0.713	0.018	0.093	0.011-0.765	0.027

Figures

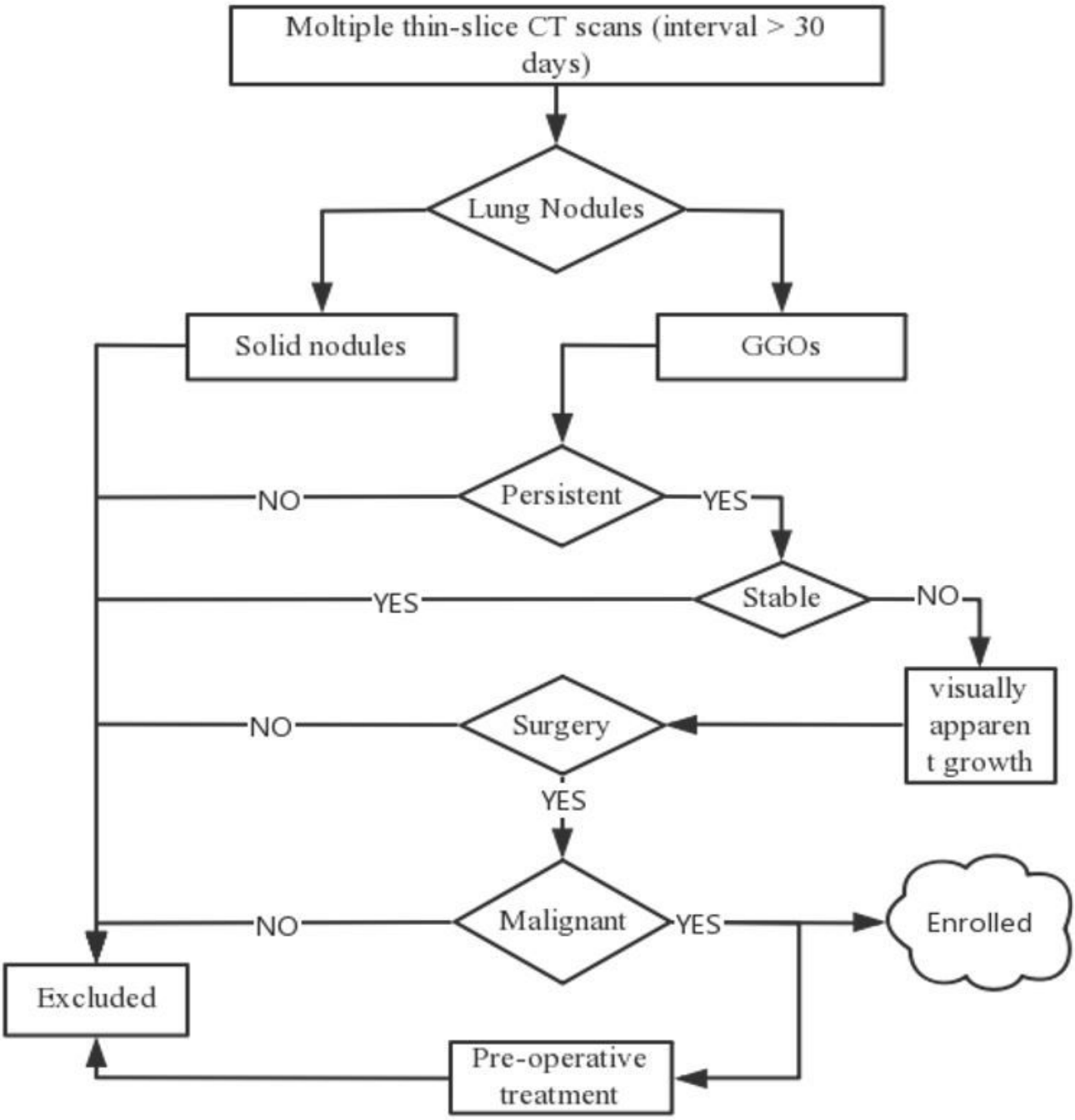

Figure 1

Patient inclusion criteria

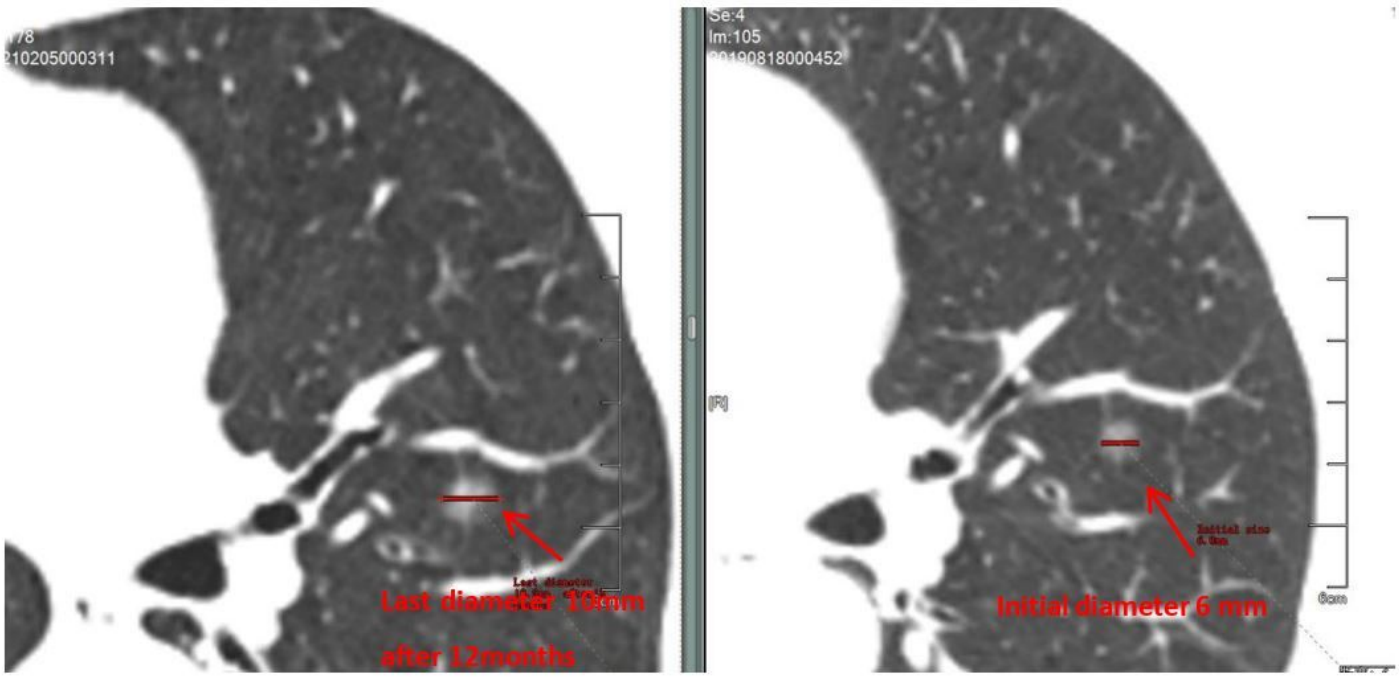

Figure 2

The size change of a GGO from the initial to the final period of 12 months during this study

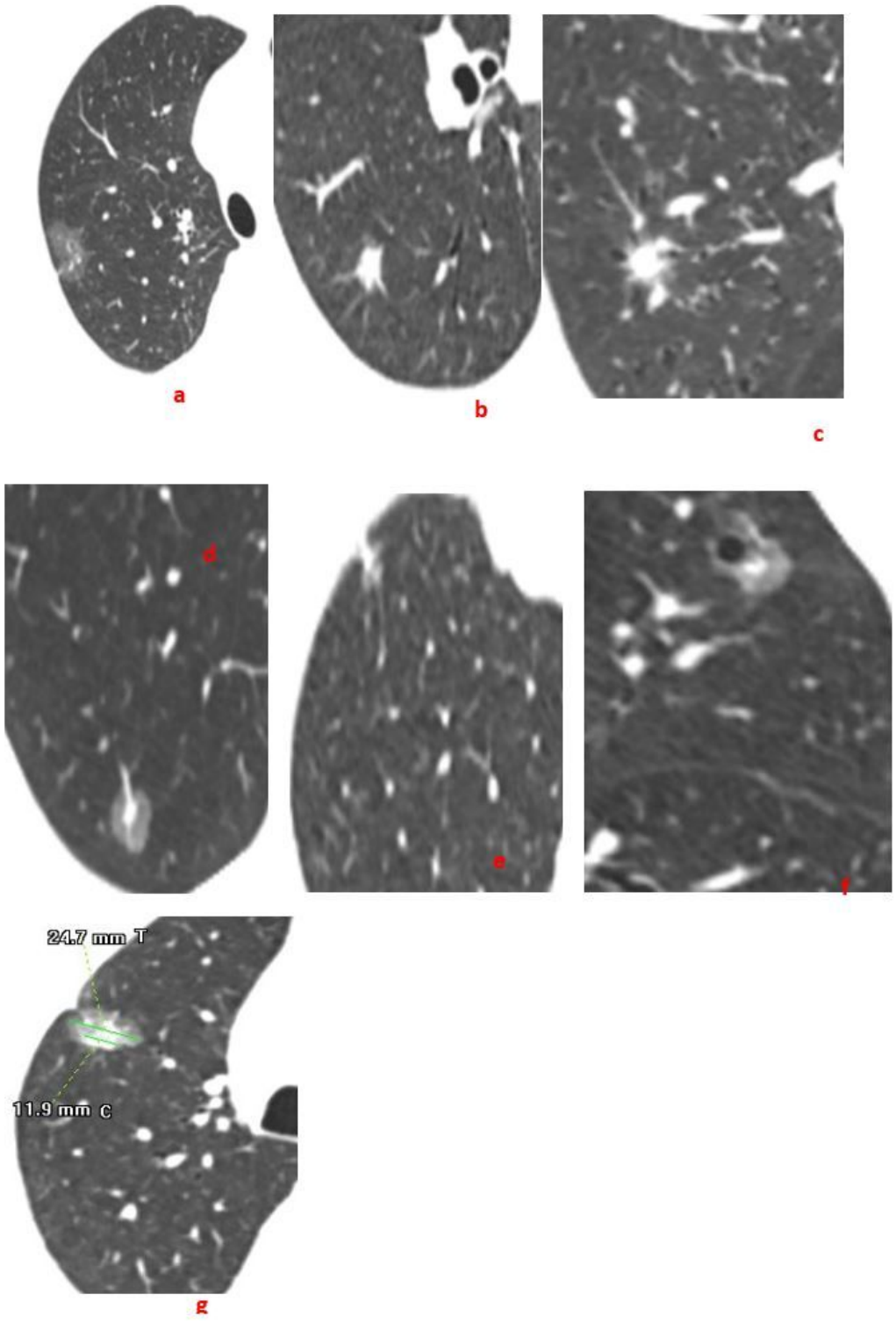

Figure 3

(a) Lobulation sign **(b)**spiculation sign, **(c)**air bronchus sign **(d)**vascular convergence sign,**(e)**Pleural indentation sign**(f)** vacuole sign**(g)**The maximum diameter of consolidation in tumor (C) and the greatest diameter of the whole tumor including GGO (T)