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Comparison of the patient demographics, high resolution computed tomography (HRCT) features of the pulmonary ground-glass opacity (GGO) and its diagnostic value analysis

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Abstract

Background: Pulmonary Ground-Glass Opacity (GGO) on Computed Tomography (CT) is considered a diagnostic feature of lung adenocarcinoma. However, a significant radiological predictive sign remain controversial. We retrospectively analyzed 206 patients with GGO to developing a correlation analysis model between CT images and diagnosis of GGO nodules.

Methods: Histopathologic specimens were obtained from 206 patients (130 women, 76 men; age range 24-77). The clinical data, pathologic findings, and thin section CT features of solid, pGGO and mGGO nodules were compared by using t-test, Fisher's exact test or Univariate logistic regression analysis.

Results: Regarding patient demographics, gender (p=0.016), with smoking history (p=0.002), and nodule size (p=0.002) were significantly different among the three groups. Significant difference in morphologic CT characteristics, e.g., spiculated sign, lobulated sign, vascule sign bubble-lucency sign, or pleural retraction, was found among the solid nodule, pGGO and mGGO groups. However, no significant differences were observed in terms of air-bronchogram sign. pGGO nodules(76.52%) have significantly the highest malignant incident compared to solid (48.48%) and mGGO (73.86%) nodules. The hazard of a malignant lesion was as high as 2.988-fold higher for patients with mGGO compared with who with solid nodules (p=0.036, HR=2.988, Table 4). Similarly, the hazard of a malignant lesion was as high as 2.941-fold higher for patients with pGGO compared with who with solid nodules (p=0.007, HR=2.941, Table 4).

Conclusion: Clinical, pathological, and thin-section CT features of solid, pGGO and mGGO nodules were found to be significantly different. Base on our analysis, patients who were found with a mixed GGO or pure GGO at CT scan were more likely to be diagnosed with the lung cancer.

Keywords: Lung cancer; High resolution computed tomography (HRCT); Patient demographics; Ground-glass opacity (GGO); Pulmonary nodules.

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Introduction

Recently, with the worldwide use of low-dose CT in early lung cancer screening, more and more early lung adenocarcinoma or pre-invasive lesions in the form of GGO are being identified [1,2]. Ground glass opacity (GGO), which is defined as hazy increased opacity of the lung with preservation of bronchial and vascular margin [3,4]. According to the guidelines proposed by the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society (IASLC/ATS/ERS) system, early-stage lung adenocarcinomas can be classified into three histological subtypes namely, pre-invasive lesions (i.e., Adenocarcinoma In Situ (AIS), and A typical Adenomatous Hyperplasia (AAH)), Minimally Invasive Adenocarcinoma (MIA) and Invasive Adenocarcinoma (IAC), which could be observed as a persistent GGO nodule at CT [5,6]. However, besides malignant lesions, some types of benign lesions can also be observed as similar hazy opacity manifestation, such as focal interstitial fibrosis, inflammation, and hemorrhage [7,8]. Radiographic nondeterminacy make GGO a nonspecific finding, and due to the malignant potential and heterogeneous characteristics, GGO nodule diagnosis is a challenging task for radiologists.

Many studies have reported that preoperative CT scan findings are related to pathological features and postoperative prognosis [9-12]. By using quantitative imaging features and machine-learning classifiers, these studies built different models, which aims to determine the pathologic character of GGO nodules effectively in CT scan preoperatively [13]. It is known that some types of image feature in CT scan are supposed to be strongly suggestive of a malignant early lung tumor, for example, spiculated sign, lobulated sign, vascule sign, bubble-lucency sign, air-bronchogram sign and pleural retraction [14]. However, whether these finding can be applied to classify between benign nodules and malignant GGO nodules is still controversial [15-17]. Thus, it is necessary to developing a correlation analysis model between CT images and histopathological subtypes of GGO nodules.

Here, the purpose of our study was to retrospectively analyzed the clinical, pathological, and high resolution CT features of persistent solitary or multiple GGO nodules from 206 post operative patients with pulmonary GGO and to provide some insight into the preoperative GGO diagnosis strategy.

Methods

Patients

Two hundred and thirty-five patients with a solitary or multiple GGO of maximum diameter <2 cm on chest CT including HRCT at Department of Thoracic Surgery of The First Affiliated Hospital of Xiamen University between January 2017 and December 2019 were enrolled. All pathology files and clinical information and radiology information system records from patients with pathology findings for at least one GGO nodule are collected, including solid nodules, mixed GGO (mGGO) and pure GGO (pGGO). The majority of patients were identified by low dose CT screening for lung cancer. 29 patients still evaluated by follow-up or lack of information on radiologic-pathologic correlation were excluded from the analysis, which was thus performed on 206 patients (66 solid nodules, 52 pGGOs and 88 mGGOs; 159 solitary GGO and 47 multiple GGO). The demographic and clinical data of patients with GGO nodules were recorded, i.e.: age and sex, smoking history, family history, amount of primary lung nodules.

This study was approved by the institutional review board of the hospitals involved; the requirement for patients' informed consent was waived in this retrospective study.

CT imaging analysis

Chest CT images were obtained on a 256-slice Philips Brilliance iCT Elite FHD machine (PHILIPS) or Somatom Definition Flash dual-source CT scanner (SIEMENS) Images were obtained using a window level of——600 Hounsfield Units (HU), a window width of 1500 HU (lung window), and a level of 30 HU and a width of 400 HU (mediastinal window). Conventional CT images were obtained from the thoracic inlet to the lung base using a 5 mm section thickness and a 5 mm section spacing, and HRCT images were obtained at a section thickness of 1 mm. Two pulmonologists and two radiologists identified GGO sizes and margins, and decided on the presence of a solid portion. GGO lesions were classified as solid nodule, pure GGO (pGGO) or mixed GGO (mGGO) based on the presence of a solid component within a nodule on a HRCT image at a lung window level.

All CT images were reviewed by two chest radiologists, with 8 and 7 years experience of chest CT interpretation, respectively. Both were unaware of clinical information. Decisions on CT findings were reached by consensus. One radiologist measured lesion sizes and solid portions within GGO nodules. The following thin-section CT findings were recorded for each lesion: 1) lesion size, 2) percentage of GGO component, 3) shape (round or oval, polygonal, irregular), 4) margin (smooth, lobulated, spiculated), 5) border (well-defined, ill-defined), and for the 6) presence of air-bronchogram, bubble-lucency, or pleural retraction. Lesion size was defined as longest lesion dimension. Percentage of GGO component was defined as the greatest diameter of the solid portion divided by the greatest diameter of the lesion including the GGO area.

Histopathology and pathologic diagnosis

All of the patient recruited were obtained surgical resection at Department of Thoracic Surgery of The First Affiliated Hospital of Xiamen University after primary diagnosis and preoperative CT scan. Pathologic specimens were obtained by lobectomy in 144, segmentectomy in 18, and wedge resection in 44 nodules. Fresh tissues were immediately snap-frozen and stored at -80 or fixed and embedded in paraffin. Samples were formalin-fixed, paraffin-embedded, and then diagnosed and confirmed by at least two lung cancer pathologists.

Statistical analysis

Comparisons between the imaging and histopathological findings of the pre-invasive lung adenocarcinomas were analyzed using SPSS 20.0 software (SPSS Inc., Chicago, IL, USA). The Chisquare and Fisher tests were used for the comparison analyses. All possible factors including clinical and radiologic characteristics were used with the logistic regression method to make a differential diagnosis between solid, pGGO and mGGO nodules. Two-tailed p-values of less than 0.01 were considered

to indicate statistical significance.

Results

Demographic findings of patients with GGO

Of the 206 patients with pulmonary GGO lesion, 66 had solid nodules, 52 had pGGO and 88 mGGO. Regarding patient demographics, gender (p=0.016), with smoking history (p=0.002), and nodule size (p=0.002) were significantly different among the three groups. According to the results, the patients with pure GGO showed the highest female-to-male ratio (75.0%) and lowest smoked ratio (3.8%). Mean pulmonary GGO nodule diameter showed 12.76 ± 6.87 mm in solid nodule group, 8.24 ± 3.02 mm in pure GGO group and 11.45 ± 6.91 mm in mGGO group. However, because of the heterogeneity of variance, it is unavailable to use one-way ANOVA test. In Table 4, the significant different in pulmonary GGO mean diameter was revealed again under univariate logistic regression analysis.

Besides, no significant differences were observed in terms of age stratification or the presence of lung cancer family history p=0.051, p=0.323, respectively), or in mode of detection for multiple and solitary GGO nodules (p=0.739) (Table 1).

Table 1:

		Patients(%)	*CT features of pulmonary nodules*			*χ2*	*p* value
			Solid	*pGGO*	*mGGO*		
All		206	66	52	88		
Age	≤40	30	7	15	8	15.440	0.051
	41-50	61	23	15	22		
	51-60	64	21	12	31		
	61-70	44	14	8	23		
	≥71	7	1	2	4		
Gender*	female	130	33	39	58	8.326	0.016
	male	76	33	13	30		
	(Positive rate)*		50.0%	75.0%	65.9%		
Smoking history	Yes	26	16	2	8	12.707	0.002
	No	180	50	50	80		
	(Positive rate)		24.24%	3.8%	9.1%		
Family history	Yes	6	3	0	3	2.259	0.323
	No	200	63	52	85		
Amount	Solitary	159	49	40	70	0.605	0.739
	Multiple	47	17	12	18		
Nodule Size	≤10 mm	128	35	43	50	12.723	0.002
	>10 mm	78	31	9	38		
	Mean diameter (mm)		12.76 ± 6.87	8.24 ± 3.02	11.45 ± 6.91		heterogeneity of variance

Table 2:

		Patients (%)	*CT features of pulmonary nodules*			*χ2*	*p* value
			Solid	*pGGO*	*mGGO*		
All		206	66	52	88		
Spiculated	Yes	134	49	23	62	13.497	0.001
	No	72	17	29	26		
	(Positive rate)*		74.24%	44.23%	70.45%		
Lobulated	Yes	143	50	27	66	10.038	0.007
	No	63	16	25	22		
	(Positive rate)*		75.76%	51.92%	75.00%		
Vascule sign	Yes	182	52	47	83	9.117	0.010
	No	24	14	5	5		
	(Positive rate)*		78.79%	90.38%	94.31%		
Bubble-lucency	Yes	63	11	16	36	10.442	0.005
	No	143	55	36	52		
	(Positive rate)*		16.67%	30.76%	40.91%		
Air-bronchogram	Yes	34	9	5	20	4.658	0.097
	No	172	57	47	68		
	(Positive rate)*		13.63%	9.62%	22.72%		

Pleural retraction	Yes	82	37	11	34	14.878	0.001
	No	124	29	41	54		
	(Positive rate)*		56.06%	20.00%	38.64%		

Table 3:

		Patient	*CT features of pulmonary nodules*			*χ2*	*p* value
			Solid	*pGGO*	*mGGO*		
All		206	66	52	88		
Outcome of Nodules pathology	Benign Lesion	69	34	12	23	14.294	**0.001**
	Malignance	137	32	40	65		
	Malignance rate	66.50%	48.48%	76.92%	73.86%		

Table 4:

	B	*SE*	*Wald*	*df*	*p value*	*Odds Ratio*	*95% CI for Odds Ratio*	
							Lower	*Upper*
Age ≤40			2.393	4	0.664			
41-50	0.504	1.015	0.247	1	0.619	1.656	0.227	12.104
51-60	0.217	0.966	0.051	1	0.822	1.243	0.187	8.248
61-70	0.833	0.965	0.745	1	0.388	2.300	0.347	15.245
≥71	0.744	0.997	0.556	1	0.456	2.103	0.298	14.841
Gender*	-0.789	0.434	3.304	1	0.069	0.454	0.194	1.064
Smoking history	-0.152	0.625	0.059	1	0.808	0.859	0.252	2.927
Family history	-0.435	1.222	0.127	1	0.722	0.647	0.059	7.103
Characteristics Solid			16.270	2	0.000			
pGGO	1.225	0.453	7.297	1	0.007	2.941	1.121	6.715
mGGO	1.095	0.522	4.392	1	0.036	2.988	1.073	8.316
Size	0.088	0.036	6.090	1	0.014	1.092	1.018	1.171
Amount	0.751	0.449	2.806	1	0.094	2.120	0.880	5.108
Spicules of margin	-0.762	0.440	3.008	1	0.083	0.467	0.197	1.104
Lobulated shape	-0.613	0.431	2.023	1	0.155	0.542	0.233	1.261
Vascule sign	-1.247	0.606	4.239	1	0.040	0.287	0.088	0.942
Vacuole sign	0.138	0.429	0.104	1	0.747	1.148	0.495	2.663
Bronchogram sign	-0.539	0.579	0.867	1	0.652	0.583	0.187	1.814
pleural indentation	-0.273	0.422	0.417	1	0.518	0.761	0.333	1.742

*Gender is for females compared to males.

Comparisons of the solid nodule, pGGO and mGGO groups in terms of HRCT features

The results showed that significant difference in morphologic CT characteristics, e.g., spiculated sign, lobulated sign, vascule sign bubble-lucency sign, or pleural retraction, was found among the solid nodule, pGGO and mGGO groups(p=0.001, 0.007, 0.010, 0.005, 0.001, respectively, Table 2). However, no significant differences were observed in terms of air-bronchogram sign (p=0.097, Table 2). Based on our data, solid nodules of 66 patients were more frequently observed to have a spiculated margin, lobulated shape or pleural retraction at thin-section CT scan(positive rate= 74.24%, 75.76%, 56.06, respectively), whereas the mixed GGO nodules were more frequently showed a micrangium vascule sign or bubble-lucency sign in there CT manifestation(positive rate= 94.31%, 40.91%, respectively). Compared to the other two groups, pure GGO nodules showed little specific features at thin-section CT scan, presences of a smooth margin , intact constitute or a nummular shape were more frequently for pGGO nodules. The lowest positive rate of spiculated sign (44.23%), lobulated sign (51.92%), air-bronchogram sign (9.62%) and pleural retraction (20.00%) was detected in pure GGO nodules group.

Pathologic findings of patients with GGO

Pathologic diagnoses of solid, pure GGO and mixed GGO nodules are summarized in Table 3. After postoperative pathologic diagnosis, Atypical Adenomatous Hyperplasia (AAH) or other benign lesion (e.g. inflammation, calcification or tuberculosis) were regarded as benign group, while Adenocarcinoma In Situ (AIS), MIA, IAC or other early stage lung cancer were included in malignant group Of the 206 pulmonary nodules, 137 (66.50%) were diagnosed as lung cancer. From the results, significant difference in the nodule histologic character among solid, pGGO or mGGO groups was detected (p=0.001, Table 3). The percentage of malignant nodules diagnosed of each group is 48.48% (solid), 76.52% (pGGO) and 73.86% (mGGO). The highest malig-

nant rate was observed in pure GGO groups, whereas the solid nodules come out as the most benign radiologic implication.

Univariate logistic regression analysis of patient demographics and radiologic features of patients with GGO

The univariate logistic regression analysis was proceeded to reveal the hazard ratio of the demographics and radiologic features of 206 included pathologic diagnosed patients, the results showed in Table 4. Base on our analysis, patients who were found with a mixed GGO or pure GGO at CT scan were more likely to be diagnosed with the lung cancer. The hazard of a malignant lesion was as high as 2.988-fold higher for patients with mGGO compared with who with solid nodules (p=0.036, HR=2.988, Table 4). Similarly, the hazard of a malignant lesion was as high as 2.941-fold higher for patients with pGGO compared with who with solid nodules (p=0.007, HR=2.941, Table 4). Besides, the result showed that the higher nodules diameters should be regared as another significant risk factor for GGO patients. Along with every 1mm diameters of pulmonary nodules increasing, the hazard of a malignant diagnostic would be increased 9.2% (p=0.014, HR=1.092, Table 4). However, the vascule sign of GGO at CT scan was more likely to be regarded as a benign sign. Compared to the pulmonary nodules without vascule sign, a patient with vascule signed GGO was 0.287-fold lower hazard ratio to diagnosed as malignant lesion. Addionally, There was no significant difference in the age, gender, smoking, family history, presence of solitary or multiple nodules, and other radiologic implications (e.g., spiculated sign, lobulated sign, air-bronchogram sign bubble-lucency sign, or pleural retraction). ($p > 0.05$) (Table 4).

Discussion

Recently, the use of chest Computed Tomography (CT) for lung-cancer screening and early-stage adenocarcinoma detection has increased, with a subsequent increase in the detection of pulmonary ground-glass opacity [1,2,18]. Several studies have shown that persistent GGO confers a high risk of malignancy, and created considerable interest in the relation between the CT feature of GGO and lung cancer tentative diagnostic [19,20]. For small or faint lung lesions such as one showing GGO on thin-section CT scan, it is not rare for physicians to speculate histological diagnoses before surgery [21]. It also maked a different on patients decision of receiving surgery. Thus, it is necessary to treat such lesions by non-surgical modalities to accurately speculate its histological characteristic. Here, we attempted to elucidate the association of demographic findings, CT features of patients with GGO and its diagnostic.

Based on our data, female was predominated (63.11%) in this study, which may have been associated with a higher lung cancer screening rate compared to men, because GGO cases were almost asymptomatic and were detected by routine screening by low dose chest CT. However, the results showed that the female and non-smoker were significantly more frequently associated with pure GGO nodules. Several studies have reported that gender and smoking history make no difference among pGGO and mGGO groups [22-24]. While another studies reported by Kim T.J. reveals that female sex, nonsmoker, and multiple primary lung cancers were significantly more frequently associated with multiple GGO nodules, whereas they did not make distinction between nodule manifestation on CTs [14]. The difference among conclusions may due to the various paitents cases analyzed. In the present study, we provide partial evidence between demographic findings and presence of pulmonary GGO, an enlarged range of cases would be further analyzed.

Another interest when we undertook this study was to investigate the nodule size of GGO and to identify whether the GGO size could predict benignity or malignancy. As the results showed in Table 1, we firstly observed that pulmonary GGO sizes among solid nodule, pGGO and mGGO were significantly different. Solid nodules groups was found to be the highest mean pulmonary diameter (12.76 ± 6.87mm) compared to others. Furthermore, from our univariate logistic regression analysis results, we had determined that the higher nodules diameters was a significant risk factor for the hazard of a malignant GGO lesion. Addtionally, with every 1 mm diameters of pulmonary nodules increasing, the hazard of a malignant diagnostic would be increased 9.2% (p=0.014, HR=1.092, Table 4). However, in present relevant studies, the value of the size of GGO for the diagnosis of lung cancer has been controversial, and no standard has been confirmed to date [25]. Naidich et al. has suggested that a detected pGGO less than 5 mm in diameter were more likely to be diagnosed with benign, which was similar to the aforementioned results [26]. In other studies, the size of GGO lesions proved to be a significant predictive factor [27,28]. Indeed, we were not able to identify whether the nodule size we found on thin-section CT should be a significantly independent predictive radiologic factor without survival analysis, but we did reveal that the size of GGO lesions should be considered as a key risk factor for preoperative screening patients.

Several conflicting reports have been issued regarding the predilections of malignant pulmonary lesion for mGGO and pGGO [15-17]. However, whether the classification of GGOs can be applied to identify between benign nodules and malignant GGO nodules is still unknown. Thus, in the present study, we developed a univariate logistic regression analysis to reveal the hazard ratio of the radiologic features of 206 GGO patients. Our results have determined that patients found with a mixed GGO or pure GGO at CT scan were more likely to be diagnosed with the lung cancer compared to whom with solid pulmonary nodules. As the control group, solid nodules had the lowest positive rate for the incidence of lung cancer base on our cases. In addition, the hazard of a malignant lesion was as high as 2.988-fold and 2.941-fold higher for patients with mGGO and pGGO groups respectively. Consistent with our results, Moon,YK et al. has reported that the pure GGO on chest computed tomography should be considered as a significant predictive factors for invasive adenocarcinoma [23]. Another studies reported by Oh JY, et al. demonstrated that the malignancy rate for mGGO (30.2%) appeared higher than that of pGGO (19.4%), but the conclusions was without significance unfortunately, which may have been due to their limitted cases of pGGO analyzed [24]. Addiontally, several studies have provided evidence that a hazy increased opacity that appear as part-solid GGO nodules on thin-section CT were more frequently associated with early stage invasive lung adenocarcinoma [29,30], and anatomical resection has been recommended over lobectomy for treating these tumors. However, since it is difficult to differed the part-solid GGO from mixed GGO nodules on CTs, we still considered that clinical surgeons should be on the alert for a mixed GGO nodules appeared on CT scan.

Lobulation and spiculation were regarded as specific sign of malignant tumors traditionally. The lobulation and spiculation margin are generated when a portion of the lesion's surface formed a wavy or scalloped configuration and the presence

of stranding extended from the nodule margin into the lung parenchyma [20,31]. In the present study, solid nodules of 66 patients were more frequently observed to have a spiculated margin, lobulated shape, whereas the pGGO nodules showed the lowest positive rate of spiculated sign, and lobulated sign. Interestingly, the results also showed that lobulation and speculation were not significant associated with early stage lung adenocarcinoma. After concideration, we raise a hypothesis that lobulation and spiculation would occur only when the primary lung tumor enters the invasion stage, whereas these two sign were more likely to indicate a benign sign on the early-stage nodules. In fact, the focal fibrous connective tissue proliferates of several benign lesion were frequently regarded as tumor lobulation and speculation, such as interstitial fibrosis, inflammation or even tuberculosis, which are morphological similar. Another studies reported by Xing YF et al revealed that the rate of lobulation and speculation showed no significantly different between AIS and AAH in the mGGO groups, while AIS exhinited higher rate of lobulation and speculation in pGGO group [32]. The results suggested that more data about analyzing morphological different between mGGO and pGGO should be considered in the future studies.

It is widely known that angiogenesis, the formation of new blood vessels, is essential for tumor growth and metastasis [33]. The immature tumor vessels also displays high vascular permeability, thus the tumor tissue is edematous, containing extra vasated plasma components. In addition to edema, the expansion of cancer tissue results in increased interstitial pressure, causing impaired tumor blood flow [34]. Based on our data, the pGGO nodules showed the highest positive rate of vascule sign, compard to other 2 groups. However, the cases in our logistic regression analysis showed that the vascule sign of GGO at CT scan was significantly associated with benign lesion. In our opinion, The opposite results may have due to the inevitable boundedness of bidimensional CT scaning. Differ from vascular sign, the vessel convergence sign of isolated pulmonary nodules may more precisely detect the angiogenesis of malignancy. Two indispensable conditions, the three-dimensional reconstruction and enhanced vessel development, were required for the detection of vessel convergence sign, which may increase the cost of CT imaging. However, several studies have reported that vessel convergence sign were identified as independent predictors of malignant pulmonary focal GGO [35-37], which is suggested to be regarded as a significant sign in future examination. Another possible inevitable limitation of our data may due to the recognition of vascular sign. Different transparency and vague margin of pGGO, mGGO and solid nodules greatly affects the detection and discrimination of vascular signs, which may result in bias of our statistics. Future studies with more tridimensional radiological imaging and with assessment of vessel convergence sign may provide more accurate results.

A recent study reported that patients with invasion lung adenocarcinoma and GGO lesions have a higher incidence of pleural retraction than those with AIS/MIA [38]. In the present study, while pleural retraction could be observed in all groups of patients with GGO, the highest incidence of pleural retraction was observed in solid nodules, and the pGGO and mGGO groups showed a relative low incidence. Even the logistic regression analysis showed no significant association between pleural retraction and malignant lung tumor. The negative results may due to the limited cases collected in studies, however, our results may suggest that people should pay more attention to an unknown pGGO/mGGO nodules without pleural retraction.

Limitations

Several limitations of the present study require consideration. First, a retrospective study design was used. Second, the data was collected from a single institution and the number of cases was relatively limitted. However, all data in this study are recent, since 2017, and bias should be relatively low since management was performed according to the same protocol. Third, the postoperative follow-up was deficient, therefore we were unable to evaluate patient survival or disease recurrence. Last, our study was restricted to surgical patients. More copmprehensive analysis might be proceeded if pathologic analysis of pure-GGO patients who did not undergo surgery was made, which was not practically possible in the present; we still consider our results to be significant.

Conclusion

In conclusion, our present studies demonstrated significant different radiological sign among 206 solid, pGGO and mGGO patients. Based on our data, pGGO nodules have significantly the highest malignant incident compared to solid and mGGO nodules, whereas the solid nodules exhibited the most benign tendency. Compared to solid nodules, mGGO and pGGO were as high as nearly 3-fold higher hazard diagnosed as malignant lesion. In patients with these findings, lobectomy is preferable to limited resection. However, future studies that collect data from larger sample sizes are needed to confirm these findings.

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