RESEARCH ARTICLE

CT Findings of Persistent Pure Ground Glass Opacity: Can We Predict the Invasiveness?

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Abstract

Background: To investigate whether CT findings can predict the invasiveness of persistent cancerous pure ground glass opacity (pGGO) by correlating the CT imaging features of persistent pGGO with pathological changes. Materials and Methods: Ninety five patients with persistent pGGOs were included. Three radiologists evaluated the morphologic features of these pGGOs at high resolution CT (HRCT). Binary logistic regression was used to assess the association between CT findings and histopathological classification (pre-invasive and invasive groups). Receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic performance of diameters. Results: A total of 105 pGGOs were identified. Between pre-invasive (atypical adenomatous hyperplasia, AAH, and adenocarcinoma in situ, AIS) and invasive group (minimally invasive adenocarcinoma, MIA and invasive lung adenocarcinomas, ILA), there were significant differences in diameter, spiculation and vessel dilatation ($p<0.05$). No difference was found in air-bronchogram, bubble-lucency, lobulated-margin, pleural indentation or vascular convergence ($p>0.05$). The optimal threshold value of the diameters to predict the invasiveness of pGGO was 12.50mm. Conclusions: HRCT features can predict the invasiveness of persistent pGGO. The pGGO with a diameter more than 12.50mm, presences of spiculation and vessel dilatation are important factors to differentiate invasive adenocarcinoma from pre-invasive cancerous lesions.

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Introduction

Ground glass opacity (GGO) in pulmonary CT imaging is defined as hazy increased attenuation of the lung with preservation of bronchial and vascular margins. GGO is classified as pure GGO (pGGO) and mixed GGO (mGGO), according to whether solid component within the lesion is present or not. Previous research indicated that about 18% of the pGGOs are malignant lesions (Jemal et al., 2010). According to a new classification system proposed in 2011 (Travis et al., 2011), the lung adenocarcinoma includes pre-invasive lesions (atypical adenomatous hyperplasia, AAH, and adenocarcinoma in situ, AIS), minimally invasive adenocarcinoma (MIA) and invasive lung adenocarcinomas(ILA). Persistent pGGOs can represent preinvasive lesions or MIA, occasionally even the invasive adenocarcinomas, but the clinical managements are different (Eisenberg et al., 2010), so it is necessary to predict the invasiveness of persistent pGGO. To date, only a few studies reported the imaging features of persistent pGGOs, but most of them discussed the different features between cancerous lesions and non-cancerous ones, how to distinguish subtype of cancerous lesions has not been determined. In this study, we retrospectively evaluate the HRCT findings of persistent pGGOs and correlate these findings with the histological diagnosis, to investigate whether there were differences between pre- and invasive lesions.

Materials and Methods

Subjects

This retrospective study was approved by the review board of Shandong Cancer Hospital & Institute, China, with patients' informed consent.

We selected patients according to the following criteria: *i)* with lung pGGO; *ii)* the GGO remained for at least 3 months with no or little changes at CT scan; *iii)* underwent surgical resection and proved to be AAH, AIS, MIA, or ILA; After retrospectively reviewed the clinical data between May 2011 and September 2014, 95 patients with a total of 105 persistent pGGOs are included, with 41 women and 54 men (mean age, 55.5y; median, 54y). There were 86 patients with single lesion, 9 patients with

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2 or 3 lesions. The characteristics of the patients are listed in Table 1. Out of the 105 pGGOs, 25 were proved to be AAH by operation and pathology (24%), 18 were AIS (17%), 24 were MIS (22%) and 38 were ILA (36%). All the 105 pGGOs were divided into two groups according to the histopathologic classification: pre-invasive group and invasive group. The pre-invasive group included AAH and AIS, and the invasive group included MIS and ILA.

CT scan program

The lung CT scans were performed with a Brilliance 64 CT and a Brilliance 128 iCT (Philips medical, Eindhoven, Netherlands). The CT scan program was carried out as follows. Scan parameters: 120KV, 200mAs. HRCT reconstruction thickness and increment are all 1mm with the algorithm "sharpYB". The lung window width was 1600HU, and window level was -600HU. All the lesions were scanned without contrast-enhanced.

Imaging analysis

CT findings of the pGGOs, including size, margin, pleural indentation, relations with the vessels, air bronchogram and bubble lucency (Xing et al., 2014) were evaluated. The largest diameters, on behalf of the size of the lesions, were measured, and the margin was classified as smooth, lobulated and spiculated. Lobulated margin was defined when the margin appeared irregular undulation. Spiculation was defined as the stiff strands extending of the margin of the lesion (Jiang et al., 2014). Pleural indentation was considered when there was a linear attenuation heading toward the pleura or the major or minor fissure from a lesion. The relationship between lesions and the vessels included vessel dilatation (dilatation of the vessels travel through the lesion) and vascular convergence. Vessel dilatation was defined according to following criteria: *i)* One or more vessels travelled through a GGO. *ii)* The within GGO portion of at least one of the vessels appeared dilatation. Vascular convergence was defined when Multiple blood vessels gathered toward a GGO. Air bronchogram was considered present when air-filled bronchi were seen within a GGO. Bubble lucency was considered present when small spots of round or ovoid air attenuation were present within a GGO.

The images were reviewed by three chest radiologists (YH, LX and YhL) with over 10 years of lung imaging diagnostic experience. At the beginning of the review, 3 radiologists got together to discuss and be familiar with the criteria of the CT features we need. Every CT imaging feature is the consensus of the former two radiologists (YH and LX). When they can't reach consensus, another radiologist (YhL) will take part in the discussion, and choose one of the idea from YH or LX. All the three radiologists are blinded to the pathologic diagnosis.

Statistical analysis

Statistical analysis was performed with SPSS 17.0 software (IBM Corporation, NY, USA). Kappa value (k) was used to assess inter-observer reliability of CT features assessment, with scores of <0.40, 0.40-0.60, 0.60-0.80 and >0.80 indicating poor agreement, moderate, higher and excellent, respectively. Binary logistic regression was used to assess the association between CT finds and histopathologic diagnosis. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic performance of diameters. Confidence interval of 95% was considered to see the precision of the study. Level of significance was taken at $p < 0.05$.

Results

CT findings of 105 pGGOs and the comparison between the findings and histopathological groups are shown in Table 2. The mean diameter in pre-invasive group was 7.4mm while that in invasive group was 13.6mm. Spiculation presented in 30 pGGOs, 28 of them were invasive lesions, while only 2 were pre-invasive lesions (Figures 1-2). Twenty four pGGOs expressed vessel dilatation (23%), out of these cases, 23 were invasive lesions (n=23, 95%) and 1 was pre-invasive lesion (Figures 1,3). The expression rates of the other CT features were much lower.

For size, the k values of two observations of 3 radiologists were respectively 0.84, 0.76 and 0.78, respectively. The final k value of three observers was 0.79 for size. The other final k values were 0.84 for pleural indentation, 0.77 for vessel dilatation, 0.86 for vascular convergence, 0.85 for air bronchogram and 0.71 for bubble lucency. The agreement between the 3 radiologists is acceptable.

As binary logistic regression analysis indicated, there were no significant differences in air-bronchogram, bubble-lucency, lobulated-margin, pleural indentation and vascular convergence between the pGGOs of two groups. Features with statistically significant included diameter(p=0.001, OR=2.914), spiculated

Table 1. Patient Characteristics

		(N=95)
gender	male	54
	fmale	41
mean age(range)		55.5y(35-80)
with single lesion		86
with two lesions		8
with three lesions		1

Table 2. HRCT Features of pGGOs

	Persistent pure GGOs (n=105)			
	Pre-invasive (n=43, 41%)	Invasive (n=62, 59%)	p	OR
Longest diameter	7.4±2.12	13.6±3.82	0.001	2.914
Pleural indentation	1 (2)	7 (11)	>0.05	-
lobulation	7 (16)	12 (19)	>0.05	-
spiculation	2 (4)	28 (45)	0.001	29
Vessel convergence	2 (4)	16 (25)	>0.05	-
Vessel dilatation	1 (2)	23 (37)	0.01	24
Air bronchogram	7 (16)	14 (22)	>0.05	-
bubble-lucency	7 (16)	13 (20)	>0.05	-

*pGGOs-pure ground glass opacity

Figure 1. A 54-Year-Old Woman with a Persistent Pure Ggo in the Upper Lobe of Right Lung. Axial 1-mm-thickness CT image shows a 9.5-mm-diameter lesion with spiculation and vessel dilatation (black arrow). The vessel is larger than other vessels at the same level (between the two arcs). The histopathological diagnosis was minimally invasive adenocarcinoma (MIA)

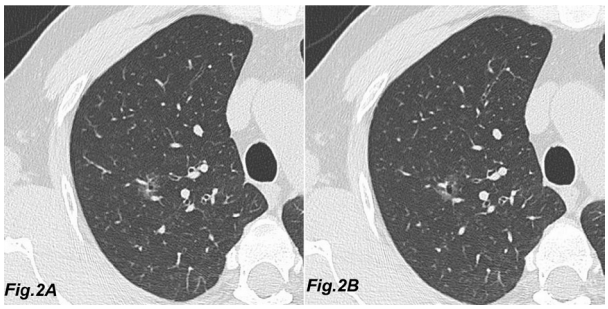

Figure 2A, 2B: A 50-Year-Old Man with Persistent Pure GGO. CT images (thickness=1mm) show a 13.0-mm-diameter lesion with lobulated and spiculated margin (Figure 2A and Figure 2B). Air bronchogram may be seen in the nodule (Figure 2B)

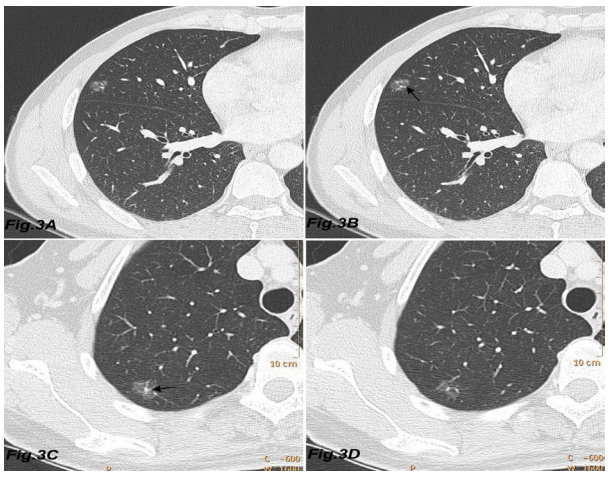

Figure 3A, 3B: A 48 A 48-Year-Old Man with a Persistent Pure GGO. CT images (thickness=1mm) show a 17.1-mm-diameter lesion with vessel dilatation and lobulated margin in the middle lobe of right lung. The vessels across the lesion are mildly enlarged (black arrow). It was proved to be invasive lung adenocarcinoma (ILA) by wedge resection. **Figure. 3C, 3D:** A pure GGO with vessel dilatation (black arrow) was identified in the upper lobe of right lung in a 54-year-old woman. The histopathological diagnosis was invasive adenocarcinoma

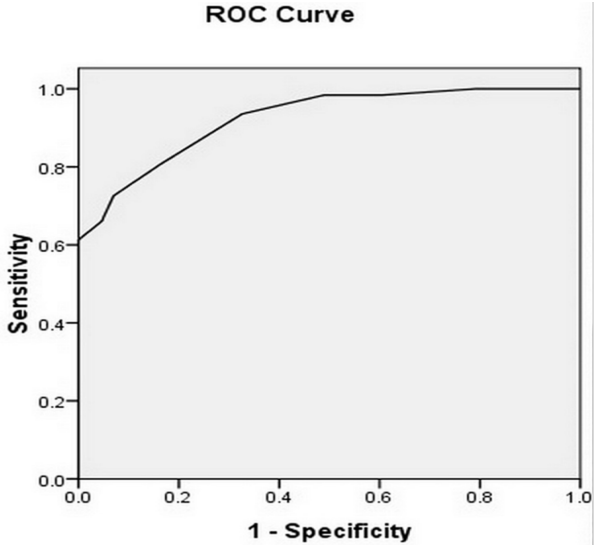

Figure 4. Receiver Operating Characteristic (ROC) Curve of Diameters

margin(p=0.001, OR=29) and vessel dilatation (p=0.016, OR=24). The diameters had the area under the ROC curve of 0.923 (95% confidence interval 0.876 to 0.971). The optimal threshold value of the diameters for positivity was 12.50mm (Figure 4).

Discussion

Large number of lung pGGOs were detected by HRCT, and some of them were proved to be early adenocarcinoma or precancerous lesions (Kim et al., 2007; Jemal et al., 2010). For persistent lesions, the possibility of malignant increased (Garfield et al., 2006). It is difficult and controversial to identify and manage these persistent pGGOs. In present study, we used HRCT to evaluate the characteristics of the 105 pGGOs, and analysed the association to their histopathology types. In a previous study of 39 patients with persistent pGGOs, 23 cases were cancerous lesions, include 21 preinvasive lesions (91%) and 2 invasive lesions (9%) (Cho et al., 2013). In our study, most of the cases were invasive lesions (n=62, 59%). All the patients included underwent operation, the tendentious selection of the operator may explain the difference. However, there is no doubt that some of these persistent pGGOs are invasive adenocarcinomas. So before choose the management methods, the assessment and prognosis of the lesions is very necessary.

Size is an important factor for predicting invasiveness of the lesion. A previous study showed that diameter of the persistent pGGO ≥10mm can differentiate pre-invasive lesion from invasive ones, and 16.4mm is the best cut off value to differentiate MIA from ILA (Lim et al., 2013). Another study showed that most of the pure GGOs less than 5mm were AAH (Naidich et al., 2013). In current study, all of the 8 pure GGOs less than and equal to 5mm were proven to be AAH, this is similar to the results. For the 40 lesions range from 6mm to 10mm, 14 were invasive adenocarcinoma (n=14, 35%). The cut off value of diameter between pre- and invasive groups is 12.5mm. The best cut off value is still controversial.

Some researchers considered that a single pure GGO of 10mm or less in diameter should be followed up using HRCT until it reaches 15mm (Lee et al., 2014). But our study showed some small pure GGO (diameter<10mm) could be invasive adenocarcinoma, especially it displays other malignant characteristics.

The diameters of vessel segments travel through lesions are mildly enlarged, we call that "vessel dilatation". In our study, 23 invasive lesions indicated this feature. To date, few studies have evaluated this imaging characteristic for pure GGO. But we consider it as an important indicator to predict the invasiveness. When the lesion evolve into invasive adenocarcinoma, its oxygen consumption generally increased, and that can influence the supplying vessel, make vessel permeability increased, and vessel diameter enlarged. The progress of invasiveness need more blood supply, and bring about vascular changes. Xing et al. (2014) also found the change of vessel diameter and some other vascular morphological changes, such as the branches of the vessels within the lesion increased. More influence factors to the vessel diameter need to be researched.

Xing et al. (2014) reported that pure GGO could present with lobulation and spiculation, and AIS typically expressed more of the characteristics than AAH. In current study, we also find the phenomenon, the invasive-group express more spiculation. Differences between two groups are statistically significant. Out of the 30 pure GGOs with spiculation, 28 were proven to be MIS or ILA (n=28, 30%). Spiculation is a sign of malignant tumor, it represents invasiveness. This imaging feature suggests malignant transformation to invasive adenocarcinoma (Lee et al., 2011), is the highest predictive value for invasion.

According to some previous studies (Oda et al., 2008; Lim et al., 2013), the presence of air bronchogram was more frequently observed in invasive adenocarcinomas than pre-invasive ones (3% for pre-invasive, 39% for invasive). In our study, there was no significant difference in air bronchogram finds between pre- and invasive groups (16%, 22%, p>0.05). There were also no significant differences in the presences of bubble-lucency, lobulated-margin, pleural indentation and vascular convergence between the two groups. We find that the frequencies of occurrence of these imaging characteristics were relatively low, the pure ground glass opacity usually express less imaging features than mixed ones or solid lesions. In that case, differences in sample selection and sample size will often affect the results of statistics. So future research need to base upon larger sample study.

There are several limitations in our study. First, all the patients underwent surgical operation, the sample selection were influenced by selection criteria of the operators, this might caused selection bias. Second, we have not evaluated the density of the lesion, because some of the pure GGOs were small, and there were vessels, air and bronchium within the lesion, the radiologists considered it was difficult to precisely measure the density of every lesion. Third, we didn't evaluate intra-observer variability.

In conclusion, HRCT can predict the invasiveness of persistent pure GGO. Larger size of persistent pure GGO and presences of spiculation and vessel dilatation are important factors to differentiate invasive cancerous lesions from pre-invasive ones. The knowledge of this study can be used for clinical diagnosis and patient management.

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