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From focal pulmonary pure ground-glass opacity nodule detected by low-dose computed tomography into invasive lung adenocarcinoma: A growth pattern analysis in the elderly

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Abstract

Background: Elderly patients are under-represented in studies of pure ground-glass opacity (pGGO) nodules; thus, this study analyzed the growth pattern and clinical outcomes of pGGO nodules in the elderly in order to help make treatment decisions.

Methods: We retrospectively reviewed patients aged over 60 years with screening-detected and pathologically confirmed growing focal pGGO nodules.

Results: During the study period, 858 subjects had undergone at least three low-dose computed tomography scans in our center. Twenty patients were treated for growing focal pGGO nodules. The median age at detection was 66 years (range: 60–80). The median time to an increase of at least 2 mm was 348 days (range: 98–1527) and to develop a solid portion, 1141 days (range: 480–3010). Seven patients had surgery for increased nodule size, four had surgery immediately after the solid portion appeared, and nine were treated after a median follow-up of 1153 days (range: 240–2342) since the solid portion developed. The median size of the solid component was 8 mm (2–13) before surgery. No recurrence was observed after a median follow-up of 41 months. Pathology revealed adenocarcinoma in situ in five patients, and minimally invasive or invasive adenocarcinoma in the remainder. The appearance of a solid portion was significantly associated with invasive adenocarcinoma compared to increased size alone (100% vs. 44.4%; $P = 0.005$).

Conclusions: pGGO nodules had an indolent growth pattern and good prognosis in our patient sample, even after the appearance of a solid portion. Therefore, minimally invasive surgery after the development of a solid component may be an option for the elderly.

Introduction

The incidence of lung cancer begins to increase rapidly after the age of 60 years. Screening detection of pulmonary pure ground-glass opacity (pGGO) nodules has increased since the introduction of low-dose computed tomography (LDCT) for lung cancer screening, and has reduced mortality rates.[1] The persistent presence of a pGGO nodule usually suggests a diagnosis of premalignant, minimally invasive, or truly invasive tumor.[2] The Fleischner Society recommendations for subsolid pulmonary nodules suggest that surgical resection should be considered if a pGGO nodule enlarges and/or increases in attenuation. Persistent pGGO nodules > 10 mm should be resected.[3]

Pure GGO nodules are reported to grow slowly, thus uncertainty exists over the appropriate duration of follow-

up imaging. Treatment decisions require balancing the risk of metastatic lung cancer and the potential harms of intervention. For some elderly patients, resection will not be necessary in their lifetime. Thus, appropriate imaging follow-up and surgical opportunities are particularly important. Because of the low incidence and indolent growth pattern of focal pGGO nodules in the screened population,[4] the chronologic evolution of lung cancer that exhibits as pGGO nodules on thin-section CT images detected by LDCT screening requires elucidation. Elderly patients are under-represented in most studies of pGGO nodules; therefore data focusing on the elderly is lacking. This study analyzed the growth pattern and clinical outcomes of screening-detected pGGO nodules in the elderly in order to help make treatment decisions.

Methods

Subjects

We retrospectively reviewed a database of subjects aged over 60 years who had undergone screening involving LDCT scans at the Department of Gerontology, Beijing Hospital, between January 2003 and 2012. The participants selected were in reasonably good health, with a 20 or more pack-year history of smoking tobacco or second-hand tobacco exposure. They had no history of lung cancer.

Among the patients with pulmonary nodules detected by annual low-dose helical CT, patients with histologically diagnosed nodules exhibiting focal pGGO nodules > 5 mm at the largest diameter at the time of the first LDCT and followed-up by thin-section CT for > 3 months, were included. If the nodule size increased or a new solid portion appeared, an assessment of the need for intervention (surgery or transthoracic core needle aspiration) was made. The final follow-up date for survival was June 2016. The ethical committee of Beijing Hospital approved the study.

Computed tomography scan imaging and serial follow-up

A CT scanner (GE Discovery CT750 HD, GE Medical Systems LLC, Waukesha, WI, USA) was used for all examinations. Low-dose helical CT screening was performed at 100 kV, 50 mA. Reconstruction was performed at intervals of 1 mm. If newly developed nodules were identified, thin-section CT examinations were performed at 120 kV, 250 mA. Reconstruction was performed at intervals of 1 mm using a thin-section CT algorithm. Thin-section CT scans were first obtained within three to six months. If no change in the CT findings was observed, the CT examination was repeated annually thereafter. When a mixed GGO lesion was detected, follow-up examinations were repeated every three to six months.

Image review

Computed tomography scans were retrospectively reviewed at a computer workstation for lung cancer dimensions and attenuation by one radiologist. Definitions of pGGO and mixed GGO nodules were based on the tumor shadow disappearance rate (TDR): solid (TDR = 1), mixed (0 < TDR < 1), and pGGO (TDR = 0). GGO volumes were calculated using the equation: volume (v) = $\pi/6$ (ab^2), where "a" was the longest horizontal axis and "b" was the maximum perpendicular diameter. The volume doubling time (VDT) was calculated based on the sizes of the GGO nodules on the initial LDCT scan and the final chest CT scan before surgery. The VDT was calculated according to a modified method of the Schwartz formula.[5] An increased GGO nodule size was defined as an increase of at least 2 mm in the largest diameter from the initial LDCT.

Pathology review

Specimens were retrospectively reviewed for consensus by two pathologists and were classified according to the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society classification of lung adenocarcinoma.[6] Surgical specimens were pathologically staged.

Statistical analysis

Pearson $\chi 2$ and Fisher's exact tests were used for categorical data. Spearman's rank correlation coefficients (rho) were calculated, including two-tailed significance levels for correlation analysis. P values < 0.05 were considered statistically significant. All statistical analyses were performed using SPSS version 13.0 (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

During the study period, 858 patients aged over 60 years had undergone at least three LDCT scans at the Department of Gerontology, Beijing Hospital. A total of 48 patients displayed pGGO lung lesions on LDCT scans. Twenty patients (19 men, 1 woman) had growing focal pGGO nodules during the median follow-up period of 30 months (range: 3–150), at a growth frequency rate of 41% (20/48).

All patients with growing focal pGGO nodules were pathologically validated. The median follow-up period

before intervention was 1417 days (range: 150–4756). Twelve patients were never smokers but had experienced second-hand tobacco exposure; the remaining eight patients were smokers with an average 30 pack-year history of smoking. The median ages when focal pGGO nodules were detected and intervention was performed were 66 (range: 60–80) and 71.5 (range: 62–88) years, respectively. Nineteen patients underwent surgical resection, two of which had a second surgery for new and increased pGGO nodules detected during postoperative follow-up. One patient refused surgery and received transthoracic needle aspiration. Sixteen patients underwent lobectomy and five underwent wedge resection. No perioperative mortality occurred. Overall, 5 (23.8%) patients had at least one postoperative morbid event.

Intervention and histopathological findings for different growth types

Seven patients underwent surgical resection for pGGO nodules of increased size; two underwent a second surgery during postoperative follow-up. Interventions were applied in the remaining 13 patients (12 patients had surgery, 1 patient had transthoracic needle aspiration) until the appearance of a solid portion. Table 1 summarizes the clinicopathologic characteristics of different growth types. The appearance of a solid portion was significantly associated with minimally invasive or invasive adenocarcinoma compared to increased size of pGGO nodules alone (100% vs. 44.4%; $P = 0.005$).

Table 1 Clinicopathologic characteristics of different growth types

Characteristics	No. of cases (%)		*P*
	Increase in size alone ($n = 9$)	Present solid portion ($n = 13$)	
Pathology			0.005
Adenocarcinomas in situ	5 (55.6%)	0 (0)	
Invasive adenocarcinoma	4 (44.4%)	13 (100%)	
Stage			1
I	9 (100%)	12 (92.3%)	
II	0 (0)	1 (7.7%)	
Initial nodule size (mm)			0.723
Median (range)	12 (5–19)	11 (8–23)	
Nodule size before intervention (mm)			0.09
Median (range)	17 (9–22)	17 (13–43)	
Smoking history			<0.01
Smoker	3 (33.3%)	7 (53.8%)	
Never smoker	6 (66.7%)	6 (46.2%)	
Age (years)			0.55
Median (range)	66 (61–73)	65 (60–79)	

In the nine patients who underwent surgery for increased size of pGGO nodules, the median nodule size before surgery was 17 mm (range: 12–22) in five adenocarcinomas in situ and 14 mm (range: 9–20) in four minimally invasive adenocarcinomas. No significant correlation was observed between the size of pGGO nodules and pathological findings ($r = -0.307$, $P = 0.422$).

In the 12 patients who underwent surgery until the appearance of a solid portion, the median size of the solid component before surgery was 8 mm (range: 2–13). The proportion of the solid part was > 50% of the entire tumor in only one patient before surgery, at pathologic stage T1N1M0. None of the remaining patients had regional lymph node metastasis. The median postoperative follow-up period was 41 months (range: 23–134). No recurrences or deaths occurred during the study period. In the patient with invasive adenocarcinoma who received transthoracic needle aspiration, the largest dimension was initially 13 mm and 23 mm before biopsy. The patient was administered definitive radiotherapy, and no recurrence was observed after follow-up of 48 months.

Changes in ground-glass opacity nodules during the follow-up period

The median nodule size at the initial CT scan was 11 mm (range: 5–23) and 17 mm (range: 9–43) before intervention. The median time to an increase of at least 2 mm was 348 days (range: 98–1527), and to develop a solid portion was 1141 (range: 480–3010). The median VDT was 968 days (range: 62–2213). The rate of appearance of a solid portion was similar between nodules with an initial size > 10 mm and ≤ 10 mm (60% vs. 57.1%, respectively; $P = 0.628$). Nodules of an initial size ≤ 10 mm tended to grow faster than the median VDT compared to nodules > 10 mm (71.4% vs. 37.5%, respectively; $P = 0.148$), although this result was not statistically significant.

Nine patients did not undergo an intervention immediately after a solid portion appeared, but were continually followed-up by imaging. The tumor growth rate before and after the appearance of a solid component can be observed. The median time from the appearance of a solid portion to intervention was 1153 days (range: 240–2342). The median VDT was 1276 (range: 784–1855) and 800 (range: 409–2790) days before and after a solid portion developed, respectively. The nodules tended to grow faster after a solid portion had developed.

Discussion

Persistent pGGO nodules prove to be benign in up to 20% of cases.[7] The concept of multi-step progression from atypical adenomatous hyperplasia to adenocarcinoma in situ to

invasive adenocarcinoma has been proposed.[8] Therefore, close monitoring is appropriate to prevent unnecessary surgery and to identify lesions that prove to be adenocarcinomas manifesting as pGGO nodules at an early stage.

The median/mean age of patients in previous studies of GGO nodules is < 60 years, thus elderly patients are underrepresented.[9–11] Treatment recommendations obtained from previous studies enroll predominantly younger patients, thus limiting the extension of such data to elderly patients in routine clinical practice. An increased likelihood of treatment-related toxicities exists, with the higher prevalence of comorbid conditions in the elderly. Therefore, it is necessary to estimate the risk of metastatic lung cancer and life expectancy of the elderly before intervention is performed. Our study focuses on elderly patients with screening detected focal pGGO nodules in real clinical practice. Most patients were not initially administered aggressive treatment. Our growth pattern analysis of long-term imaging follow-up could help to guide treatment strategies in the elderly.

The frequency of pGGO growth in our study sample was 41%. The proportion of pGGO nodule growth is 10% in younger patients without a history of lung cancer.[9] In patients with a history of lung cancer, the pGGO growth rate could be as high as 58%.[12] In our study, the median VDT of pGGO nodules was 968 days, and the median time for a pGGO nodule to develop a solid portion was 1141 days. In previous studies including younger patients, the median VDT of pGGO nodules was 769–831 days.[5,9] The frequency of pGGO growth appears to be higher in elderly patients without a history of lung cancer, although the growth of pGGO nodules could be considered more indolent in the elderly. Nodules tended to grow faster after the appearance of a solid portion. However, mixed GGO nodules exhibit a considerably slower growth rate than other screening-detected solid nodules, with a VDT within 200 days.[4] Therefore, observation of pGGO nodules in the elderly is reasonable, especially in those at high risk for surgery.

In our study, the appearance of a solid portion rather than enlargement of a pGGO nodule was significantly associated with minimally invasive or invasive adenocarcinoma. Therefore, follow-up until the appearance of a solid component may be an option for management of pGGO in the elderly. A portion of the patients in our study continued imaging follow-up after a solid portion had developed. The time to intervention ranged from eight months to six years after the development of a solid portion, and none of these patients developed distal metastasis. In a national lung screening trial of stage I cases, the average size of the solid component of part-solid nodules was 9.2 mm before surgery.[13] Our data also supports the follow-up of part-solid nodules with solid components of < 10 mm to assess growth before an invasive diagnostic workup is suggested.

Screening-detected pGGO lung nodules may include heterogeneous populations of both clinically indolent and invasive tumors. In the current study, the time to an increase of at least 2 mm ranged from 98 to 1527 days. The first imaging follow-up should be performed within six months. The optimal follow-up duration for a pGGO nodule in the elderly has yet to be determined. In our study, the median time for a pGGO nodule to develop a solid portion was three years, thus we suggest follow-up of at least three years.

In the current study, additional GGO nodules developed during follow-up in two (10%) patients. GGO nodules could be multi-focal in different lobes. Therefore, minimally invasive surgery with the intent to preserve lung volume is warranted. According to a previous study, adenocarcinomas < 2 cm with GGO components of > 50% were free of regional lymph node metastasis and vessel invasion, and all of the patients in the study are alive without recurrence.[14] In our study, patients with GGO predominant nodules were also free of regional lymph node metastasis. Given the favorable prognoses of patients with pGGO or GGO predominant nodules, wedge resection is recommended as a safe and minimally invasive method instead of lobectomy.[15] Baumann *et al.* reported that stereotactic body radiotherapy could achieve a local tumor control rate of > 90% with limited toxicity in medically inoperable early-stage non-small cell lung cancer patients.[16] Therefore, radiotherapy with curative intent is justified in medically inoperable or high-risk elderly patients.

In conclusion, pGGO nodules show an indolent growth pattern and a good prognosis in the elderly, even after the appearance of a solid portion. Therefore, minimally invasive surgery after the appearance of a solid component may be an option for the elderly.

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Disclosure

No authors report any conflict of interest.

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