ORIGINAL ARTICLE

Long-Term Follow-up of Small Pulmonary Ground-Glass Nodules Stable for 3 Years: Implications of the Proper Follow-up Period and Risk Factors for Subsequent Growth

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ABSTRACT

Introduction: How long persistent and stable ground-glass nodules (GGNs) should be followed is uncertain, although a minimum of 3 years is suggested. Here, we evaluated a group of GGNs that had remained stable for an initial period of 3 years with the aim of determining the proportion of GGNs showing subsequent growth after the initial 3 years and identifying the clinical and radiologic factors associated with subsequent growth.

Methods: We retrospectively analyzed patients who underwent further computed tomography (CT) after the initial 3-year follow-up period showing a persistent and stable GGN (at least 5 years of follow-up from the initial CT).

Results: Between May 2003 and June 2015, 453 GGNs (438 pure GGNs and 15 part-solid GGNs) were found in 218 patients. Of the 218 patients, 14 had 15 GGNs showing subsequent growth after the initial 3 years during the median follow-up period of 6.4 years. For the person-based analysis, the frequency of subsequent growth of GGNs that had been stable during the initial 3 years was 6.7% (14 of 218). For the nodule-based analysis, the frequency was 3.3% (15 of 453). In a multivariate analysis, age 65 years or older (OR = 5.51, $p = 0.012$), history of lung cancer (OR = 6.44, $p = 0.006$), initial size 8 mm or larger (OR = 5.74, $p = 0.008$), presence of a solid component (OR = 16.58, $p = 0.009$), and air bronchogram (OR = 5.83, $p = 0.015$) were independent risk factors for subsequent GGN growth.

Conclusions: For the individuals with GGNs having the aforementioned risk factors, the longer follow-up period is required to confirm subsequent GGN growth.

Keywords: Ground-glass nodule; Follow-up; Growth; Computed tomography

Introduction

With the widespread use of computed tomography (CT) for screening, ground-glass nodules (GGNs) are being increasingly detected. Transient GGNs, which disappear spontaneously, are the manifestation of benign conditions, including inflammation, hemorrhage, and pulmonary infiltrates with eosinophilia.[1] However, persistent GGNs are mostly invasive adenocarcinoma or its preinvasive lesions such as atypical adenomatous hyperplasia and adenocarcinoma in situ.[2] As previous studies investigating the natural course of persistent GGNs have demonstrated their indolent nature,[3–7] how long GGNs should be followed is controversial, especially

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when the GGNs do not meet the indications for surgical resection. A recent study evaluating 108 persistent GGNs reported that all GGNs began to grow within the first 3 years.[3] The authors concluded that GGNs should be followed for at least 3 years. However, several studies have reported that a few GGNs actually showed significant growth after the first 3 years.[4–7]

Considering the mean volume doubling time (VDT) of GGNs, which ranges 769 to 1005 days, the duration of follow-up for GGNs would be extended to more than 3 years.[5,6,8] The most recent National Comprehensive Cancer Network guidelines for lung cancer screening (version 1.2016) recommend annual low-dose CT (LDCT) for 2 years to individuals with GGNs that have been stable and do not meet indications of surgical resection and suggest annual LDCT until the individuals are no longer candidates for definitive treatment.[9] On the other hand, the American College of Chest Physicians guidelines and Fleischner Society guidelines recommend annual surveillance CT for a minimum of 3 years regarding management of those GGNs.[10,11] However, further management for persistent and stable GGNs during the initial 3 years is not specified.

To discuss the proper duration of follow-up for GGNs, it is necessary to know how many GGNs grow after the initial 3 years of observation. Therefore, our study aimed to evaluate the proportion of GGNs showing subsequent growth after the initial 3 years among GGNs that had been stable during the initial 3 years, and to determine clinical and radiologic factors associated with subsequent growth.

Materials and Methods

Patients

Our potential study population included patients who had GGNs confirmed by chest CT scans with a thickness of 1 to 3 mm and were followed up for a minimum of 3 years between May 2003 and June 2015 at Seoul National University Bundang Hospital, Seongnam, Republic of Korea. The following inclusion criteria were used to select patients for the current study: (1) patients who underwent further CT scans after the initial 3-year follow-up period showing a persistent and stable GGN (at least a 5-year follow-up from the initial CT scans) or (2) patients who underwent surgical resection of a GGN after the 3-year persistent and stable follow-up. Exclusion criteria were transient GGNs, resection of GGNs within the initial 3 years, treatment with systemic chemotherapy for concurrent lung cancer in the prior 6 months, loss to follow-up after the initial 3 years, and GGNs with growth during the initial 3 years. The present study was approved by the institutional review board of the Seoul National University Bundang Hospital (B-1508-310-101). The requirement for informed consent was waived.

Radiologic Evaluation

CT scans were obtained using various instruments, including the Brilliance-64, MX-8000 IDT, and iCT 256 (Philips Medical Systems, Cleveland, OH).[12] Image data were reconstructed with a thickness of 1 to 3 mm. Images were obtained using a lung window setting with a level of −600 Hounsfield units (HU) and width of 1500 HU and a mediastinal window setting with a level of 30 HU and width of 400 HU. We reviewed all available CT images of the study patients, and changes in size and characteristics of their GGNs were recorded. The size of a GGN was defined by its maximal diameter on a lung window setting. The definitions of pure GGNs and part-solid GGNs were based on the tumor shadow disappearance rate (TDR), which was classified as follows: solid nodule ($TDR = 0$), part-solid GGN ($0 < TDR < 1$), and pure GGN ($TDR = 1$).[13] The size of a solid component was measured with its maximal diameter on a mediastinal window setting for a part-solid GGN. Growth of a GGN was defined as (1) a 2-mm or greater increase in size of a GGN, (2) a 2-mm or greater increase in the solid component of a part-solid GGN, or (3) an emerging new solid component of any size in a pure GGN.[4] A decrease in size of a GGN was defined as a decrease of 2 mm or more from the size on the initial CT scan. According to the aforementioned definition of growth, a GGN that developed a new solid component and simultaneously decreased in its whole size was classified as a GGN with growth. Other conditions were stated as stable. The criteria involving 2-mm changes in diameter are based on previous literature reporting that an increase in the maximal diameter larger than 1.72 mm is necessary to identify growth of GGNs.[14] GGNs without growth were defined as those GGNs that were stable or decreased in size during the follow-up period. The VDT was calculated for GGNs with growth using the modified Schwartz formula.[15,16] For the person-based analysis, a patient with any GGN showing growth was classified into the growth group. For each GGN, the presence of an air bronchogram, bubble lucency, pleural or fissure retraction, and spiculated margin was evaluated. GGNs were considered peripherally distributed if they were located in the outer two-thirds of the lung according to the CT scans.

Pathologic Diagnosis

Pathologic diagnosis and histologic subtypes of lung cancer were established according to the 2015 World Health Organization classification.[17]

Statistical Analysis

Continuous data are presented as medians (ranges), whereas categorical data are presented as numbers (percentages). The results of comparisons of clinical and