



# Pulmonary nodule tracking using chest computed tomography in a histoplasmosis endemic area <sup>☆☆☆, ★, ★★, ☆☆☆</sup>



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## ARTICLE INFO

### Article history:

Received 29 July 2014

Received in revised form 27 October 2014

Accepted 5 November 2014

### Keywords:

Nodule tracking

Incidental pulmonary nodule

Chest computed tomography

Histoplasmosis

## ABSTRACT

**Objective:** In areas with endemic histoplasmosis, incidental pulmonary nodules are common. Rate of malignancy and applicability of current tracking guidelines in these regions remain unclear.

**Methods:** A total of 148 cases of incidental pulmonary nodules tracked with chest computed tomography were reviewed for radiologic characteristics, diagnosis, number, and size.

**Results:** Of the nodules, 87.8% were benign and 12.2% malignant; 30% of nodules >20 mm were malignant. Number of nodules ( $P=.14$ ) and granulomatous disease ( $P=.71$ ) were not related to malignant diagnosis.

**Conclusion:** Malignancy was lower than expected in nodules >20 mm. Appropriate tracking guidelines for incidentally discovered nodules in histoplasmosis endemic regions must be determined.

Published by Elsevier Inc.

## 1. Introduction

An incidental pulmonary nodule is a nodule detected during the course of imaging done for nonscreening purposes in an individual without symptoms concerning for pulmonary malignancy. Incidental radiographic detection of a pulmonary nodule usually necessitates further evaluation with dedicated chest computed tomography (CT). After initial characterization on chest CT, continued tracking of the incidentally discovered nodule has been dictated by factors predicting nodule malignancy such as size, growth rate, and smoking history [1,2]. For nodules greater than 8 mm, the recommended intervention is based on the risk factor of size alone. The rate of malignancy in pulmonary nodules varies widely in the literature, with reported values as high as 40–50% [3,4]. *Histoplasma capsulatum* is a dimorphic fungus endemic to the Ohio River Valley and multiple other regions of the world that can cause pulmonary infection resulting in solitary or multiple

pulmonary nodules on radiographs. The rate of malignancy among pulmonary nodules in endemic areas is not known and is potentially overestimated when predictive models are applied.

To determine the appropriate treatment pathway for an incidentally discovered solitary pulmonary nodule, the physician has a number of prognostic tools to assess the pretest probability of malignancy [1,2]. The ability to accurately predict malignancy avoids unnecessary invasive and potentially harmful procedures in patients with low pretest probability of malignancy. The Fleischner Society guidelines are the current standard for tracking the incidentally discovered pulmonary nodule. These guidelines recommend varied frequency of screening based on patient risk factors as well as nodule size. When a nodule is determined to be greater than 8 mm, further tracking and intervention such as biopsy are based on size without regard to personal risk factors for malignancy. After 2 years of stable size for a solid nodule and 3 years of stable size for a subsolid nodule, the nodule is considered benign and no further screening is warranted. The relationship between nodule size and malignancy in regions with endemic histoplasmosis has not been studied. Case reports and a single retrospective study suggest that traditional recommendations regarding size of nodule and prediction of malignancy may not apply to these regions [5–7].

Multiple pulmonary nodules on chest CT have been associated with malignancy secondary to metastatic disease [8]. In the patient with incidentally discovered multiple pulmonary nodules, Fleischner Society guidelines are often extrapolated to determine an appropriate tracking schedule for the patient. There is a paucity of literature supporting this practice despite the frequency with which multiple pulmonary nodules are detected. In areas of endemic histoplasmosis, the literature indicates that multiple pulmonary nodules can represent evidence of infection

Abbreviations: CT, Computed tomography; PET, Positron emission tomography.  
 ☆ Financial disclosures: The research submitted was not supported by any source of funding.  
 ☆☆☆ Sponsors: The research submitted was not supported by any sponsors.  
 ★ Conflict of interest: No conflicts of interest: Whittney Warren, Ronald Markert, Elizabeth Stewart.  
 ★★ Funding information: The research submitted was not supported by any source of funding.  
 ☆☆☆ Prior presentation: The research submitted has been presented in poster format at the Wright State University Central Research Forum on October 24, 2013, and Dayton Area GME Research Forum on April 24, 2014.  
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rather than metastatic disease [5–7]. Ginsberg et al. observed that nodule size in patients with multiple pulmonary nodules not detected incidentally is an indicator of malignancy with multiple nodules greater than 1 cm being more likely to indicate malignancy [9]. The relationship between number of incidentally detected nodules and malignancy has not been described.

Histoplasmosis is a ubiquitous soil-inhabiting fungus that causes pulmonary infection when microconidia are aerosolized and inhaled into the alveoli [10]. In immunocompetent patients, histoplasmosis is generally an asymptomatic infection that can result in several typical radiographic findings including multiple pulmonary nodules, calcified pulmonary nodules, calcified mediastinal lymph nodes, and splenic calcifications [10,11]. Evidence of granulomatous disease can complicate the management of incidentally discovered pulmonary nodules. Our study sought to determine the rate of malignancy found in incidentally detected pulmonary nodules in a histoplasmosis endemic region, the relationship between malignancy and the number and size of the discovered pulmonary nodules, and if current tracking guidelines should be modified in regions with endemic histoplasmosis.

## 2. Methods

The Wright-Patterson Medical Center nodule-tracking database was reviewed for patients enrolled between May 2010 and April 2011. The nodule-tracking database was created to facilitate tracking and to generate patient reminders for follow-up chest CT. One hundred and forty eight patient charts and applicable reports of chest CT scans read by a

board certified radiologist were reviewed. Only patients with incidentally discovered pulmonary nodules were included in the study. Patients with imaging done as a result of symptoms concerning for malignancy such as weight loss or hemoptysis were excluded from the study as nodules detected in this population would be considered nonincidental. Patients with known pulmonary malignancy were excluded from the study (Fig. 1).

Demographic characteristics (sex and age) and history of smoking were obtained from chart review. Radiologic characteristics (size of largest nodule, number of nodules, presence of typical findings of granulomatous disease, and location of nodule) were obtained from chest CT scans and radiology reports. Granulomatous disease was recorded if the patient had chest CT evidence of completely calcified nodules, mediastinal node calcification, and splenic calcifications. Diagnosis of the largest nodule tracked was recorded from pathology reports and chart review. A nodule was determined to be benign after 2 years of tracking with stable or decreased size if the nodule was solid. Subsolid nodules were determined to be benign after 3 years of tracking with stable or decreased size. Criteria for determining benign disease were based on recommendations from the Fleischner Society [12,13]. Malignancy was determined based on pathology reports from biopsy. All biopsy reports demonstrated primary pulmonary malignancy. In one case, biopsy was not done, and malignancy was presumed based on rapid growth and supportive findings on positron emission tomography (PET) scan. Pulmonary nodules were categorized by number (single vs. multiple) and size (<4 mm, 4–6 mm, 7–8 mm, 9–20 mm, and >20 mm). Size categorization was derived from the Fleischner's guideline recommendations for nodule tracking.

The mean and standard deviation are reported as continuous variables. However, when comparing the benign and malignant groups on number of nodules and nodule size, medians are reported since these two variables were not normally distributed. Counts and percents are reported for categorical variables. The nonparametric Mann–Whitney test was used to compare differences between the benign group and malignant group on number of nodules and nodule size. The chi square test was used to compare the two groups on categorical variables. Inferences were made at the 0.05 level of significance with no corrections for multiple comparisons. Analyses were conducted using IBM SPSS Statistics 21.0 (IBM, Armonk, NY).

This study was conducted in accordance with the amended Declaration of Helsinki. Local institutional review boards or independent ethics committees approved the protocol. The local institutional review board determined that written patient consent was not required (institutional review board, #FWP20130013H).

## 3. Results

The mean age of the 148 patients was 65 years, and the sample was equally divided by gender (Table 1). A significant proportion of patients had a history of smoking.

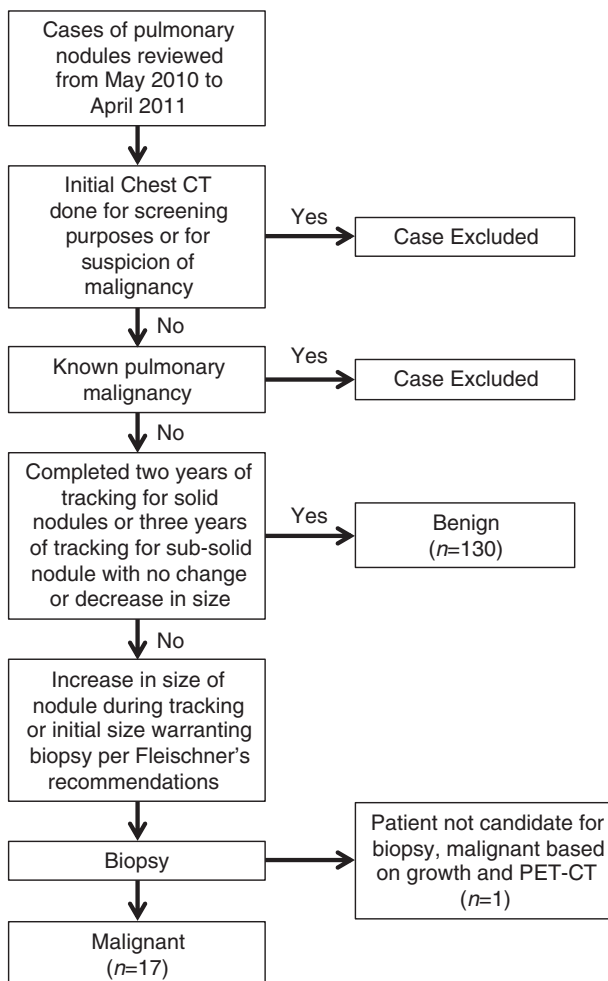
The mean nodule size was 11 mm (Table 2). The mean number of nodules was 4.0 with 87% of patients having more than one nodule. Nearly half of patients had typical findings of granulomatous disease.

**Table 1**

Characteristics of 148 patients from the Wright-Patterson Medical Center nodule-tracking database

Characteristic	
Age (years) (mean±S.D.)	65.2±13.6
Gender	
Male	72 (48.6%) <sup>a</sup>
Female	76 (51.4%)
Smoking history	
Yes	84 (56.8%)
No	64 (43.2%)

<sup>a</sup> Percentage.



**Fig. 1.** Algorithm for study inclusion and final diagnosis.

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