

## Predictors for Benign Solitary Pulmonary Nodule in Tuberculosis-Endemic Area

Hojoong Kim, M.D., Soo Jung Kang, M.D., Gee Young Suh, M.D.,  
Man Pyo Chung, M.D., O Jung Kwon, M.D., Chong H. Rhee, M.D.,  
Kyung Jae Jung, M.D.\*, Tae Sung Kim, M.D.\* and Kyung Soo Lee, M.D.\*

*Division of Pulmonary and Critical Care Medicine, Departments of Medicine  
and Radiology\*,  
Samsung Medical Center, Sungkyunkwan University School of Medicine,  
Seoul, Korea*

**Background :** Solitary pulmonary nodule (SPN) may show different presentation in tuberculosis (TB)-endemic countries. The aim of this study was to identify clinical and radiological predictors favoring benign or malignant SPN in TB-endemic region.

**Methods :** Two hundred one SPNs in 201 consecutive Korean patients were included (< 3 cm in diameter, all confirmed by pathology or bacteriology, 93 benign and 108 malignant diseases). For clinical parameters, age, sex, smoking status and amount, and past history of pulmonary tuberculosis and diabetes mellitus were investigated retrospectively. For radiological parameters, size, location, margin characteristics, presence of calcification, pleural tag, surrounding satellite nodule, cavitation, internal low attenuation, open bronchus sign, surrounding ground-glass opacity, enhancement pattern of the SPNs and mediastinal lymph node (LN) enlargement were analyzed on chest CT scans.

**Results :** Patients with a older age ( $60.7 \pm 9.6$  vs  $56.2 \pm 13.1$ ,  $p = 0.008$ ) and more than 40-pack years smoking (27.8% vs 14.0%,  $p = 0.017$ ) were more frequently related with malignant than benign SPN. On chest CT scans, spiculated margin, contrast enhancement more than 20 Hounsfield unit and presence of pleural tag and mediastinal LN enlargement were more frequently observed in malignant than benign SPNs. In contrast to previous studies, satellite lesions (21.5% vs 1.9%,  $p < 0.001$ ) and cavitation (20.4% vs 5.6%,  $p = 0.001$ ) were more frequently seen in benign than malignant SPN. Positive predictive values of benignity were 90.9% and 76.0%, respectively, when satellite lesions and cavitation were found in cases of SPN.

**Conclusion :** Satellite lesions and cavitation on chest CT scan could be useful predictors for benign SPN in TB-endemic areas.

**Key Words :** Pulmonary Coin Lesion, Risk Factors, Malignancy

### INTRODUCTION

Solitary pulmonary nodule (SPN) is defined as a single

---

*Address reprint requests to : O Jung Kwon, M.D.,  
Division of Pulmonary & Critical Care Medicine,  
Department of Medicine, Samsung Medical Center,  
50 Ilwon-dong, Kangnam-ku, Seoul, 135-710, Korea*

round or oval lesion within the lung parenchyma in the absence of adenopathy, atelectasis or pneumonia on plain chest X-ray<sup>1)</sup>. The main concern of SPN is whether it is benign or malignant. According to previous studies, up to 40% of SPN is malignant<sup>2,4)</sup> and 10-15% of lung cancer presents as SPN<sup>5)</sup>. Most malignant SPN is in its early stage and resectable, thus long-term survival can

be expected<sup>5</sup>). On the other hand, if SPN is expected to be benign with high probability, unnecessary work-up or operation could be avoided.

By using computed tomography (CT), previous studies clarified radiological predictors for malignant SPN, such as size > 2 cm, spiculated edge, pleural tag, air bronchogram and enhancement of 20 Hounsfield unit (HU) or more after contrast dye injection<sup>6-12</sup>). The likelihood of benign or malignant SPN, however, may be different in countries where the incidence of tuberculosis and other granulomatous diseases is high.

In South Korea, the national prevalence of pulmonary tuberculosis was 1.0% in 1995<sup>13</sup>) and annual lung cancer incidence was 35 /100,000 in 1998 (GLOBOCAN, International Agency for Research on Cancer 1998). Assuming the mean duration of tuberculosis treatment is 9 months, the annual incidence of pulmonary tuberculosis could be estimated as 1300/100,000, which is about 40 times as frequent as that of lung cancer.

Therefore, predictors for benign or malignant SPN in Korea may be different from those of developed countries where most of the previous studies were performed and the prevalence of pulmonary tuberculosis is much lower than in Korea. The aim of this study was to identify clinical and radiological predictors for benign or malignant SPN in a tuberculosis-endemic area.

## MATERIALS AND METHODS

### Population

Two hundred and one SPNs (< 3 cm in diameter on plain chest X-ray) in 201 consecutive Korean patients were included from January 1995 to December 1998 at Samsung Medical Center, a tertiary general hospital located in the southern part of Seoul, Korea. Chest CT was taken in all patients. Bronchoscopy (for bronchial washing and forcep biopsy), and/or percutaneous needle aspiration biopsy, and/or open lung biopsy were also performed in all patients. Diagnostic confirmation was made pathologically or bacteriologically.

### Evaluation of Clinical Characteristics

Age, sex, smoking status and amount and past history of pulmonary tuberculosis and diabetes mellitus were investigated retrospectively by reviewing medical records.

### Image Acquisition and Interpretation of CT Scans

All CT scans were obtained with GE HiSpeed

Advantage scanner (General Electric Medical Systems, Milwaukee, WI USA). Initially, high-resolution CT scans were obtained through a nodule with 1.0 mm collimation and at 3-5 mm intervals. After that, helical CT scans were obtained from the level of thoracic inlet to the level of the middle portion of the kidneys with 7 mm collimation and a pitch of one 20 seconds after administration of 100 mL of Iopamiro (Iopamiron 300; Bracco, Milan, Italy). Because CT scans were obtained 20 seconds after the injection of contrast medium, enhanced CT scans through the nodule were usually obtained 35-40 seconds after the injection of contrast medium (first enhanced scans). Additional high-resolution CT scans were obtained through the nodule 4 minutes after the injection of contrast medium (second enhanced scans).

Chest CT scans were evaluated retrospectively by two chest radiologists without prior knowledge of the benign or malignant histology of the nodules. Decisions on the findings were reached by consensus. The longest diameter of SPN was measured at the CT scan where the nodule appeared the largest on transverse scans. The lobe where the SPN was identified was recorded. The location was defined as central when the SPN was observed within one third of the inner lung. Otherwise, it was defined as peripheral. The margin of the nodule was classified as smooth, lobulated and spiculated. If calcification was observed, the pattern was described (central, eccentric, diffuse, stippled, and laminated). Presence or absence of pleural tag, surrounding satellite nodule(s), internal cavitation, necrotic low attenuation, open bronchus sign and surrounding ground-glass opacity were also recorded. The extent of contrast enhancement was measured by comparing the initial unenhanced CT scans with the second enhanced scans. We observed whether the extent of enhancement was more than or less than 20 HU. Mediastinal node was regarded as significantly enlarged when the short axis of the node was more than 10 mm in diameter on CT scans, though LN enlargement was not observed in plain chest X-ray films.

### Statistical analysis

Clinical and CT parameters were analyzed according to the benign or malignant etiology. Chi-square test and Student's *t*-test were used for univariate analysis and logistic regression was used for multivariate analysis.

All values are presented as mean ± standard deviation (SD) unless described otherwise. Statistical difference was considered significant for  $p < 0.05$ .

RESULTS

Etiology of SPN (Table 1)

One hundred and eight malignant SPNs consisted of 69 adenocarcinomas, 20 squamous cell carcinomas, 15 bronchioloalveolar carcinomas, 2 adenosquamous carcinomas and 2 large cell carcinomas. Ninety-three benign SPNs were comprised of 55 tuberculomas, 17 hamartomas, 13 organizing pneumonias, 3 aspergillomas, 1 abscess, 1 hemangiopericytoma, 1 actinomycosis, 1 nodule of pulmonary paragonimiasis and 1 inflammatory pseudotumor.

Table 1. Etiology of solitary pulmonary nodules

Benign	n=93	Malignant	n=108
Tuberculoma	55	Adenocarcinoma	69
Hamartoma	17	Squamous cell carcinoma	20
Organizing pneumonia	13	Bronchioloalveolar carcinoma	15
Aspergilloma	3	Adenosquamous carcinoma	2
Abscess	1	Large cell carcinoma	2
Hemangiopericytoma	1		
Actinomycosis	1		
Paragonimiasis	1		
Inflammatory pseudotumor	1		

Clinical Characteristics (Table 2)

The age of patients with malignant SPN (60.7 ± 9.6 years) was older than that of benign SPN (56.2 ± 13.1 years, *p*=0.008). Most malignant SPNs were seen in patients over 40 years of age (107/108, 99.1%). There were no differences in sex, percentage in past or current smoking and the amount of smoking. However, smokers of more than 40-pack years had malignant (27.8%)

Table 2. Clinical characteristics of patients with solitary pulmonary nodule

	Benign (n=93)	Malignant (n=108)	p-value
Mean age	56.2 ± 13.1	60.7 ± 9.6	0.008
Age ≥ 40	80 (86.0%)	107 (99.1%)	<0.001
Male	57 (61.3%)	62 (57.4%)	0.576
Current or past smoker	47 (50.5%)	48 (44.4%)	0.388
Mean pack years	15.3 ± 19.5	17.0 ± 22.4	0.575
Pack years ≥ 40	13 (14.0%)	30 (27.8%)	0.017
Diabetes mellitus	24 (25.8%)	13 (12.0%)	0.012
Past history of tuberculosis	14 (15.1%)	18 (16.7%)	0.755

more frequently than benign SPNs (14.0%, *p*=0.017). Diabetes was more frequent in patients with benign (25.8%) than malignant SPN (12.0%, *p*=0.012). The frequency of having previous tuberculosis infection was not different between patients with benign (15.1%) and malignant (16.7%) SPN.

CT Characteristics

The mean size of SPN was 22.7 ± 6.0 mm in benign and 23.5 ± 4.8 mm in malignant SPN, respectively. Central location was seen in 21.5% of benign SPNs and in 13.0% of malignant SPNs (*p*=0.107). Lobar distribution was not different between benign and malignant SPNs (Table 3).

Table 3. Size and location of solitary pulmonary nodules

	Benign (n=93)	Malignant (n=108)	p-value
Mean diameter (mm)	22.7 ± 6.0	23.5 ± 4.8	0.289
Central 1/3 location	20 (21.5%)	14 (13.0%)	0.107
RUL	22 (23.7%)	37 (34.3%)	0.100
RML	10 (10.8%)	17 (15.7%)	0.301
RLL	24 (25.8%)	20 (18.5%)	0.213
LUL	20 (21.5%)	19 (17.6%)	0.484
Lingula	3 (3.2%)	5 (4.6%)	0.612
LLL	14 (15.1%)	10 (9.3%)	0.514

In malignant SPNs, spiculated margin, pleural tag, enhancement of 20 HU or more and lymph node enlargement were observed more frequently, compared to those in benign SPNs. On the other hand, satellite lesions (21.5% vs 1.9%, *p* < 0.001) and cavitation (20.4% vs 5.6%, *p*=0.001) were seen more frequently in benign than malignant SPNs (Table 4).

Table 4. CT characteristics of solitary pulmonary nodules

	Benign (n=93)	Malignant (n=108)	p-value
Spiculated margin	35 (37.6%)	68 (63.0%)	<0.001
Lobulated margin	50 (53.8%)	64 (59.3%)	0.645
Pleural tag	32 (34.4%)	71 (65.7%)	<0.001
Calcification	22 (23.7%)	17 (15.7%)	0.226
Contrast enhancement ≥ 20HU	36 (38.7%)	79 (73.1%)	<0.001
Patent bronchus sign	17 (18.3%)	38 (35.2%)	0.059
Node enlargement in CT 8 (8.6%)		32 (29.6%)	<0.001
Cavitation	19 (20.4%)	6 (5.6%)	0.001
Satellite lesion	20 (21.5%)	2 (1.9%)	<0.001

Of 22 patients who had satellite lesion, 18 were patients with tuberculoma. Cavitation was seen in fifteen of 55 patients (27.2%) with tuberculoma (Table 5). The positive predictive value of benignity was 90.9% (20/22) when satellite lesions were found around SPN, and the possibility of malignancy was 98.1% (106/108) when no satellite lesions were observed around SPN in a TB-endemic area (Table 6).

**Table 5. Incidence of satellite lesion and cavitation according to etiology**

Satellite lesion	Cavitation
Tuberculoma 18/55	Tuberculoma 15/55
Organizing pneumonia 1/13	Organizing pneumonia 3/13
Paragonimiasis 1/1	Hamatoma 1/17
Squamous cell carcinoma 1/20	Adenocarcinoma 2/69
Bronchoalveolar carcinoma 1/15	Squamous cell carcinoma 2/20
	Bronchoalveolar carcinoma 1/15
	Large cell carcinoma 1/2

**Table 6. Frequency of satellite lesion in benign and malignant solitary pulmonary nodule**

	Benign (n=93)	Malignant (n=108)	Total (n=201)
Satellite lesion (+)	20	2	22
Satellite lesion (-)	73	106	179

Possibility of a benign SPN when satellite lesion (+)  
= 90.9% (20/22)

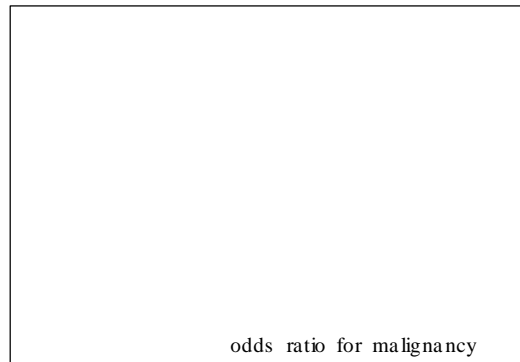
Possibility of a malignant SPN when satellite lesion (-)  
= 98.1% (106/108)

Multivariate analysis of predictors (Figure 1)

LN enlargement and pleural tag on chest CT scans were radiological predictors for malignancy (odds ratio 4.57 and 2.71, confidence interval 1.85- 11.32 and 1.30-5.64, respectively). Smoking more than 40-pack years was a clinical predictor for malignancy (odds ratio 2.23, confidence interval 1.01-5.23).

On the other hand, cavitation and satellite lesion on CT scans were predictors favoring benign rather than malignant SPN (odds ratio for malignancy were 0.24 and 0.079, confidence interval 0.078-0.76 and 0.016-0.38, respectively). Satellite lesion was observed only in 2 of 108 malignant SPNs, whereas it was seen in 20 of 93 benign SPNs (Table 6), showing a high positive predictive value of 90.9% (20/22) for benignity and specificity of 98.1% (106/108) for malignancy. In addition, cavitation of nodule was observed in 5.6% (6/108) of

malignant and 20.4% (19/93) of benign SPNs, presenting a positive predictive value of 76.0% (19/25) for benignity and specificity of 94.4% (102/108) for malignancy (Table 7).



**Figure 1.** Relative risk for malignancy according to the clinical and radiological factors.

**Table 7. Frequency of cavitation in benign and malignant solitary pulmonary nodule**

	Benign (n=93)	Malignant (n=108)	Total (n=201)
Cavitation (+)	19	6	25
Cavitation (-)	74	102	176

Possibility of a benign SPN when cavitation (+)  
= 76.0% (19/25)

Possibility of a malignant SPN when cavitation (-)  
= 94.4% (102/108)

## DISCUSSION

In this study, we found that patients with a older age and more than 40-pack years of smoking history were more frequently related with malignant than benign SPN. In addition, spiculated margin, pleural tag, contrast enhancement more than 20 HU and LN enlargement on CT were more frequently seen in patients with malignant than benign SPNs. On the contrary, satellite lesion and cavitation were more frequently found in patients with benign SPN. Most of these results are consistent with previous studies<sup>5-12</sup>, except satellite lesion and cavitation.

Satellite lesion is usually described as small discrete shadows in the immediate vicinity of the main lesion<sup>14</sup>. A previous study, performed in Germany, showed that satellite lesion was found in 4 of 81 malignant SPN, whereas no satellite lesion was observed in 23 benign SPN<sup>11</sup>. However, satellite lesion could be detected around tuberculoma as frequently as 80% of cases<sup>14</sup>. In our study,

82% (18/22) of satellite lesions were found in patients with tuberculoma and 33% (18/55) of patients with tuberculoma showed satellite lesions on CT (Table 5). Another study showed that satellite lesion was seen in 56% of focal organizing pneumonia<sup>15)</sup>. Since satellite lesion is frequently observed in patients with tuberculoma, and it is also frequently accompanied by organizing pneumonia, presence of satellite lesions around SPN could favor benignity in a TB-endemic area.

In this study, among 108 malignant SPNs, only 2 (2%) showed satellite lesion. On the other hand, satellite lesion was found in 20% (20/93) of benign lesions, including 33% (18/55) of tuberculomas. Therefore, if satellite lesions are found around SPN in a TB-endemic area, the possibility of being a benign SPN (positive predictive value) will be 90.9% (20/22) and if satellite lesion is not found around SPN, the possibility of being a malignant SPN could be 98.1% (106/108, Table 6).

Cavitation, observed in 3.7% (3/81) of malignant and 0% (0/23) of benign SPNs in the German study<sup>9)</sup>, can be frequently observed in tuberculoma. In the current study, of 25 SPNs with cavitation, 15 were tuberculomas, 3 organizing pneumonias and 1 hamartoma. Only 5.6% (6/108) of malignant SPNs showed internal cavitation (Table 5). As in the case of satellite lesion, the significance of cavitation in SPN can depend on the prevalence of TB and other granulomatous diseases.

Previously, Swensen and colleagues reported that when contrast enhancement of more than 20 HU was determined as a threshold value favoring malignancy of a nodule, the sensitivity and specificity for malignancy were 98% and 73%, respectively<sup>12)</sup>. Recently, large scale multicenter study showed that, with 15 HU as the threshold, the sensitivity and specificity for malignancy were 98% and 58%, respectively<sup>6)</sup>. In this study, the sensitivity and specificity of malignancy were 73.1% and 61.3%, respectively, with 20 HU as the threshold (Table 4). This study included 15 patients with bronchioloalveolar carcinoma and an additional 15 patients with adenocarcinoma with some component of bronchioloalveolar carcinoma. These 30 patients consisted 27.8% of 108 malignant SPNs. In these particular patients, pulmonary nodules were composed of ground-glass attenuation, therefore, loosely composed tissue showed a lesser degree of enhancement than a solid tumor. This may have led to lower sensitivity and specificity for a sign of malignancy in CT enhancement study.

In conclusion, satellite lesion and cavitation were frequent findings of benign SPN in Korea. Although

satellite lesion and cavitation are still not completely satisfactory in precluding tissue confirmation, they could be useful predictors for benign SPN in a TB-endemic area.

## REFERENCES

1. Khouri NF, Meziane MA, Zerhouni EA, Fishman EK, Siegelman SS. *The solitary pulmonary nodule: assessment, diagnosis and management.* Chest 91:128-133, 1987
2. Burdette WJ, Lillington GA, Richard RJ. *Estimating the probability of malignancy in solitary pulmonary nodules.* Am Rev Respir Dis 134:449-452, 1986
3. Good CA, Wilson TW. *The solitary circumscribed pulmonary nodule. Study of seven hundred and five cases encountered roentgenologically in a period of three and one-half years.* J Am Med Assoc 156:10-24, 1958
4. Steele JD. *The solitary pulmonary nodule: report of cooperative study of resected asymptomatic solitary pulmonary nodules in males.* J Thorac Cardiovasc Surg 46:1-39, 1963
5. Anderson RW, Arentzen CE. *Carcinoma of the lung.* Surg Clin North Am 60:793-814, 1980
6. Furuya K, Murayama S, Soeda H, Murakami J, Ichinose Y, Yabuuchi H, Katsuda Y, Koga M, Masuda K. *New classification of small pulmonary nodules by margin characteristics on high-resolution CT.* Acta Radiol 40:496-504, 1999
7. Gruden JF. *What is the significance of pleural tags.* Am J Roentgenol 164:503-504, 1995
8. Gurney JW. *Determining the likelihood of malignancy in solitary pulmonary nodules with Bayesian analysis. Part I. Theory.* Radiology 186:405-413, 1993
9. Gurney JW, Lyddon DM, McKay JA. *Determining the likelihood of malignancy in solitary pulmonary nodules with Bayesian analysis. Part II. Application.* Radiology 186:415-422, 1993
10. Kii M, Templeton PA, White CS, Cai ZL, Bai YX, Cai YQ. *Evaluation of the air bronchogram sign on CT in solitary pulmonary lesions.* J Comput Assist Tomogr 20:983-986, 1996
11. Seemann MD, Staebler A, Beinert T, Dienemann H, Obst B, Matzko M, Pistitsch C, Reiser MF. *Usefulness of morphological characteristics for the differentiation of benign from malignant solitary pulmonary lesions using HRCT.* Euro Radiol 9:409-417, 1999
12. Swensen SJ, Brown LR, Colby TV, Weaver AL, Midthun DE. *Lung nodule enhancement at CT: prospective findings.* Radiology 201:447-455, 1996
13. Ministry of Health and Welfare, Korean National Tuberculosis Association. *Report on the 7th tuberculosis prevalence survey in Korea.* 1995

14. Fraser RS, Pare JAP, Fraser RG, Pare PD. *Infectious disease of the lung. In: Fraser RS eds. Synopsis of Disease of the Chest. 2nd ed. p.287-391, Philadelphia, Saunders, 1994*
  15. Kohno N, Ikezoe J, Johkoh T, Takeuchi N, Tomiyama N, Kido S, Kondoh H, Arisawa J, Kozuka T. *Focal organizing pneumonia: CT appearance. Radiology 189: 119-123, 1993*
  16. Swensen SJ, Viggiano RW, Midthun DE, Mueller NL, Sherrick A, Yamashita K, Naidich DP, Patz EF, Hartman TE, Muhm JR, Weaver AL. *Lung nodule enhancement at CT: Multicenter study. Radiology 214:73-80, 2000*
-