The Probability of Malignancy in Solitary Pulmonary Nodules

Application to Small Radiologically Indeterminate Nodules

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Background: A clinical prediction model to identify malignant nodules based on clinical data and radiological characteristics of lung nodules was derived using logistic regression from a random sample of patients (n=419) and tested on data from a separate group of patients (n=210).

Objective: To use multivariate logistic regression to estimate the probability of malignancy in radiologically indeterminate solitary pulmonary nodules (SPNs) in a clinically relevant subset of patients with SPNs that measured between 4 and 30 mm in diameter.

Patients and Methods: A retrospective cohort study at a multispecialty group practice included 629 patients (320 men, 309 women) with newly discovered (between January 1, 1984, and May 1, 1986) 4- to 30-mm radiologically indeterminate SPNs on chest radiography. Patients with a diagnosis of cancer within 5 years prior to the discovery of the nodule were excluded. Clinical data included age, sex, cigarette-smoking status, and history of extrathoracic malignant neoplasm, asbestos exposure, and chronic interstitial or obstructive lung disease; chest radiological data included the diameter, location, edge characteristics (eg, lobulation, spiculation, and shagginess), and other characteristics (eg, cavitation) of the SPNs. Predictors were identified in a random sample of two thirds of the patients and tested in the remaining one third.

Results: Sixty-five percent of the nodules were benign, 23% were malignant, and 12% were indeterminate. Three clinical characteristics (age, cigarette-smoking status, and history of cancer [diagnosis, ≥5 years ago]) and 3 radiological characteristics (diameter, spiculation, and upper lobe location of the SPNs) were independent predictors of malignancy. The area (±SE) under the evaluated receiver operating characteristic curve was 0.8328±0.0226.

Conclusion: Three clinical and 3 radiographic characteristics predicted the malignancy in radiologically indeterminate SPNs.

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A SOLITARY pulmonary nodule (SPN) is usually discovered incidentally on a chest radiograph obtained for some other purpose. Estimates suggest that approximately 150 000 patients have an SPN identified in the United States each year. Because an SPN may be a sign of cancer, virtually all patients undergo a further diagnostic evaluation that may include retrieval and review of any previous chest radiographs, further imaging with conventional tomography or computed tomography (CT), cytologic examination of sputum, bronchoscopy or transthoracic needle aspiration biopsy (TNAB), consultation with a pulmonologist and a surgeon, and, for some patients, a thoracotomy or thoracostomy with resection of the SPN.

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An SPN may be the first sign of malignancy or result from a benign condition (eg, a hamartoma or granuloma).[1] The diagnostic challenge in the evaluation of a patient with an SPN is to establish whether the nodule is benign or malignant. Malignant diseases (primary bronchogenic carcinoma, metastasis to the lung from cancer at another site, and, rarely, carcinoid tumors) are estimated to occur in 20% of patients with SPNs in the population and are reported in 40% of patients with SPNs from surgical series.[1-4] The majority of SPNs, however, result from benign conditions (eg, granulomas [55%] and benign tumors [4%]).[2,3] If the SPN is malignant, the physician should expedite the removal of the nodule and avoid a thoracotomy in patients with surgically incurable lung neoplasms. If the SPN is benign, the physician should avoid a thora-

PATIENTS AND METHODS

Patients with a newly discovered 4- to 30-mm SPN on a conventional chest radiograph between January 1, 1984, and May 1, 1986, were included in this study. An SPN is defined as a solitary, round, or oval lesion in the lung parenchyma on a chest radiograph in the absence of adenopathy, atelectasis, or pneumonia. The nodule was indeterminate radiologically, with no evidence of benign pattern calcification on thin-section CT (collimation, 1-3 mm) or conventional tomography, or both.[2] Benign calcification patterns included target, central, diffuse, and laminated patterns. Patients who were diagnosed as having any cancer within the past 5 years were excluded. No patients with clinical signs of persistent or recurrent malignant neoplasm were included. No patients with a history of primary lung cancer were included. Patients were excluded if they had an SPN present on radiological studies that were performed more than 3 months before their presentation. This allowed the study of the subset of SPNs that had no or minimally established radiological stability at presentation. This also mitigated any bias that was introduced from disproportionate numbers of prevalent nodules. This retrospective cohort study was approved by the institutional review board at the Mayo Clinic, Rochester, Minn.

Patients with newly discovered SPNs after January 1, 1984, were identified from several sources: (1) patients who had a Mayo Clinic master sheet diagnosis of an SPN or an indeterminate pulmonary nodule, (2) patients who underwent surgical procedures for an SPN at the Mayo Clinic, (3) patients with conventional tomography of an SPN that was performed at the Mayo Clinic, and (4) patients who underwent CT studies of an SPN at the Mayo Clinic.

Data were collected by an experienced nurse abstractor and included the date of birth, sex, ZIP code (for determination of referral distance), smoking status (current or former cigarette smoker, pack-years, interval since the quitting of cigarette smoking for former smokers), and history of extrathoracic malignant neoplasm (>5 years ago), asbestos exposure (determined by the use of CT, chest radiography, or history), and chronic diffuse interstitial or obstructive lung disease.

All chest radiographs, standard tomograms, and CT scans obtained after the discovery of the SPN were reviewed for this study by a radiologist (S.J.S.) for the following information: diameter of the SPN in millimeters (average of diameters if oval or oblong); presence of cavitation; wall thickness of cavitation, if present; presence of an air bronchogram; nodular edge (smooth, shaggy [on <50% or ≥50% of the circumference], or spiculation [<50% or ≥50% of the circumference]); presence of a pleural tail; calcification that did not meet criteria for a benign pattern; satellite lesions (discovered on standard tomography or CT); uncalcified nodules in other lobes (discovered on standard tomography or CT); number and size of any calcified hilar or mediastinal lymph nodes; presence of pulmonary granulomas (bilateral, ipsilateral, or contralateral); enlarged lymph nodes (discovered on a CT scan only); associated pleural effusion (ipsilateral, contralateral, or bilateral); location in the central two thirds of a lung or the peripheral one third of a lung; and location in the lobe of a lung (right upper lobe, right middle lobe, right lower lobe, left upper lobe, lingula, or left lower lobe).

The outcome in each individual patient was determined by 1 of the following methods: (1) radiographic follow-up for 2 years or more (if it resolved or decreased in size, or there was no growth, the nodule was considered to be benign); (2) surgical diagnosis; (3) TNAB positive for malignancy; or (4) bronchoscopic biopsy, washing, or brushing positive for malignancy.

CLASSIFICATION

Benign SPNs

For benign SPNs, there was no change, resolution, or decrease in size on radiological follow-up for at least 2 years, or there was a benign pathologic diagnosis on a surgical

cotomy because benign nodules rarely pose a risk and do not need to be resected.

Clinical and radiological evaluations of patients with SPNs often provide sufficient information to reassure patients that the SPN has resulted from benign disease, or they may alert the physician to the presence of primary lung cancer or disease elsewhere, suggesting metastatic cancer. Nevertheless, after thorough clinical and radiological evaluations, a substantial proportion of SPNs are judged to have an indeterminate risk of malignancy.

To determine if we could improve the outcomes of the diagnosis and treatment of SPNs, we have developed a clinical prediction model to identify malignancy in patients with the most troublesome subset of indeterminate pulmonary nodules, namely, radiologically indeterminate SPNs with a diameter between 4 and 30 mm. Lung masses (diameter, >30 mm), which were included in previous studies, have a high probability of malignancy.[4] In addition, previous studies were based on nodules that were managed with a thoracotomy, and this factor potentially resulted in a bias that excluded patients whose nodules were managed with a TNAB, bronchoscopy, and observation. Finally, previous studies that used the Bayes theorem to evaluate the probability of malignancy in patients with SPNs were limited in that no allowance was made for correlation or interaction between factors; it was a univariate technique.[5-7] For this reason, we used multivariate logistic regression to estimate the probability of malignancy in radiologically indeterminate SPNs in the clinically relevant subset of patients with SPNs that measured between 4 and 30 mm in diameter.

RESULTS

Six hundred twenty-nine patients were identified with newly discovered solitary indeterminate lung nodules. There were 320 men and 309 women. Sixty-five percent of the nodules were benign, 23% were malignant, and 12% remained indeterminate after a thorough chart review, mailed survey, and follow-up telephone survey. The clinical characteristics of the patients with an SPN are

pathology specimen or biopsy tissue (other than biopsy tissue obtained from a TNAB or bronchoscopy).

Malignant SPNs

A malignant pathologic diagnosis was based on tissue obtained from a TNAB, bronchoscopy, thoracoscopy, or thoracotomy.

Undiagnosed SPNs

The SPNs that did not meet either of the previously described criteria were classified as undiagnosed. Patients who underwent radiological follow-up for less than 2 years or who experienced an increase in the size of the nodule (no biopsy) were further evaluated by a chart review; if the outcome was not evident after a chart review, a letter was written to the patient and a telephone follow-up was done, as required.

The date of a definitive diagnosis of an SPN was defined as the date when a thoracotomy or biopsy procedure revealed a specific diagnosis. The date of a definitive diagnosis for patients who were managed by (1) observation with serial chest radiographs or (2) a biopsy procedure and subsequent observation with serial chest radiographs was 2 years after the date of the discovery of the SPN if the final classification was benign disease, or the date of obtaining a tissue diagnosis if the final classification was malignant disease.

DERIVATION OF THE PREDICTION MODEL

Six hundred twenty-nine patients with radiologically indeterminate SPNs were identified. A clinical prediction model to identify malignant SPNs based on clinical data and radiological characteristics of SPNs was derived from a random sample of patients and tested on data from a separate group of patients. A random subset of two thirds of the patients (n=419) was selected to derive the prediction model; the remaining 210 patients made up the validation data set. The outcome or dependent variable was malignancy, and the independent variables (covariates) were the clinical and radiological variables, as described previously. Univariately significant covariates were analyzed for their relationship to the outcome of malignancy by use of stepwise logistic regression with a $P=.05$ level to retain a predictor in the model. Stepwise selection with forward addition of covariates and also with backward elimination of covariates was performed and yielded the same results. Models using alternative coding of the independent variables were evaluated for variables based on clinically relevant criteria; for example, cigarette smoking was analyzed as a categorical variable (ever smoked vs never smoked; as a current smoker, former smoker, or never smoker; and as never smoker, 0-20, 20-40, or >40 pack-years) and as a continuous variable (pack-years). None of these alternative formulations resulted in better prediction than original coding for the variables. Odds ratios (ORs) and 95% confidence intervals (CIs) for univariate and multivariate predictors were identified. The OR is the ratio of the odds of malignancy in those with a predictor and the odds of malignancy in those without a predictor. The clinical prediction model yields an equation that expresses the probability of malignancy as a function of the statistically significant variables from the multivariable logistic regression.

VALIDATION OF THE PREDICTIVE MODEL

The predictive probability model was tested with data from 210 different patients (ie, the validation set). A receiver operating characteristic (ROC) curve was constructed using the predicted probability of malignancy from the logistic regression analysis as a "test" for malignancy. The model was evaluated by comparing the areas under the ROC curve,[8] by comparing calibration curves, and by the goodness-of-fit statistic as described by Lemeshow and Hosmer.[9] Calibration curves are plots of the observed probability of malignancy compared with the predicted probability in each decile of the patients with SPNs in the derivation group ordered by the increasing probability of malignancy.

presented in **Table 1**. The mean age of the patients with benign nodules was 60 years (range, 15-82 years) and with malignant nodules was 65 years (range, 35-87 years). Seventy-nine percent of the benign nodules were granulomas and 7% were hamartomas. The remaining 14% of the benign nodules had numerous diagnoses, including organizing pneumonia, fibrosis, sclerosing hemangioma, and infarction. Diagnoses of malignant nodules included adenocarcinoma (49%), squamous cell carcinoma (29%), large cell carcinoma (8%), small cell carcinoma (4%), and carcinoid tumor of the bronchus (2%). The mode of diagnosis for malignant nodules was thoracotomy (85%), bronchoscopy (11%), and TNAB (4%). The mode of diagnosis for nodules that ultimately proved to be benign was observation (80%), thoracotomy (20%), and TNAB (0.3%).

Radiological characteristics of the SPNs also are given in Table 1. The mean diameter of the benign nodules was 11.6 mm (range, 4-30 mm). The mean diameter of the malignant nodules was 17.8 mm (range, 5-30 mm). Ten benign nodules were cavitated; the mean wall thickness was 5.6 mm. Nine malignant nodules were cavitated; the mean wall thickness was 3.9 mm. The mean age of the patients with indeterminate lung nodules was 65 years (range, 23-91 years). The mean diameter of the indeterminate nodules was 12.3 mm (range, 5-30 mm). Two indeterminate nodules were cavitated; the mean wall thickness was 2 mm.

Univariate analysis of potential clinical and radiological predictors of malignancy is summarized in **Table 2**. For each potential predictor variable, the OR of malignancy, 95% CI around the OR, and P value are shown. In the 419 patients in the derivation data set, age, history of cancer (diagnosis, ≥5 years ago), cigarette-smoking status, and pack-years were the clinical predictors of malignancy. The diameter, spiculation, cavitation, lobulation, and upper lobe location of the SPN were radiological predictors of malignancy. A calcified pulmonary granuloma, a shaggy edge, and the anatomical site of the SPN were not predictors of malignancy. Univariate analysis of these potential predictors from the 210 patients in the validation data set is also presented in Table 2.

Table 1. Clinical Characteristics of Patients With SPN and Radiological Characteristics of SPNs*

Characteristic	SPNs		
	Benign (n=406)	Malignant (n=146)	Indeterminate (n=77)
Clinical			
Mean age, y	60	65	65
Male, %	49	58	49
Current or past smoker, %	61	86	71
Asbestos exposure, No.	1	3	2
Residence >192 km from clinic, %	58	60	86
Pack-years (mean), No.	24	45	32
Pack-years ≥40, %	24	51	36
Other cancer >5 y ago, %	4	10	4
Radiological			
Mean diameter, mm (range)	11.6 (4-30)	17.8 (5-30)	12.3 (5-30)
Cavitation, %	3	6	3
Air bronchogram, %	10	15	6
Nodule edge, %			
Entirely smooth	50	20	44
Spiculation, <50%	2	8	1
Spiculation, ≥50%	2	16	0
Shaggy, <50%	18	16	21
Shaggy, ≥50%	23	27	26
Spiculated and shaggy	4	12	8
Lobulation, %	9	23	14
Pleural tail, %	13	13	17
Calcified nodes, %	4	3	8
Calcified granuloma, %	9	11	14
Location, %			
Central	7	23	9
Peripheral	93	77	91
Upper lobe, %	38	61	43
Location (lobe), %			
RUL	25	36	18
RML	13	8	10
RLL	19	13	13
LUL	13	25	25
Lingula	4	3	8
LLL	25	15	26

SPNs indicates solitary pulmonary nodules; RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; LUL, left upper lobe; and LLL, left lower lobe.

The univariate predictors (Table 2) were used in a logistic regression analysis to derive a prediction model for malignancy using the data from the 419 patients in the derivation data set. Three clinical characteristics (age, cigarette-smoking status, and history of cancer [diagnosis, ≥5 years ago]) and 3 radiological characteristics (diameter, spiculation, and upper lobe location of the SPN) were independent predictors of malignancy (Table 2). This prediction model was tested in the 210 patients, and the results are also given in Table 2. The prediction model was able to distinguish between benign and malignant SPNs (**Figure 1**), and the model was calibrated across a range of probabilities (**Figure 2**). Small changes were observed in the estimates of the OR for some components of the prediction model. Several individual components were not statistically significant at the $P=.05$ level in the smaller validation data set of 210 patients.

Small changes in the OR estimates are often observed when prediction models are tested on different data. Overall, the prediction model appears to be valid as judged by the reproducible ability to distinguish between benign and malignant nodules on different data and the reproducible good calibration throughout a range of the probability of malignancy in different data.

The ROC curves were developed for both the development and evaluation data sets. The area (±SE) under the development ROC curve was 0.8328±0.0226. The area (±SE) under the evaluation ROC curve was 0.8014±0.0360 (Figure 1). A calibration curve for the derivation and validation data sets shows excellent calibration of the prediction model (Figure 2). The goodness-of-fit statistics, as described by Lemeshow-Hosmer,[9] for the derivation ($\chi^2=5.085$; $P=.75$) and validation ($\chi^2=6.221$; $P=.62$) data sets were not statistically significant; these statistical findings indicated an inability to reject the hypothesis that the observed proportion of patients with malignancy was different from the predicted proportion for both the derivation and validation groups.

The clinical prediction model for malignancy in SPNs expresses the probability of malignancy as a function of the 3 clinical and 3 radiographic variables as follows:

$$(1)\ \text{Probability of Malignancy} = e^x/(1+e^x)$$

$$(2)\ x = -6.8272 + (0.0391 \times \text{Age}) + (0.7917 \times \text{Cigarettes}) + (1.3388 \times \text{Cancer}) + (0.1274 \times \text{Diameter}) + (1.0407 \times \text{Spiculation}) + (0.7838 \times \text{upper}),$$

where e is the base of natural logarithms, age is the patient's age in years, cigarettes=1 if the patient is a current or former cigarette smoker (otherwise=0), cancer=1 if the patient has a history of an extrathoracic cancer that was diagnosed more than 5 years ago (otherwise=0), diameter is diameter of the SPN in millimeters, spiculation=1 if the edge of the SPN has spicules (otherwise=0), and upper=1 if the SPN is located in an upper lobe (otherwise=0).

The clinical prediction model is not applicable to patients with a diagnosis of cancer that has been made within the previous 5 years or to patients with previous lung cancer.

The probability of cancer in an SPN is presented in **Table 3** for 9 selected values of the patient's age and the size of an SPN and the combinations of the presence and absence of the categorical predictors (cigarette use, history of extrathoracic malignant neoplasm, and edge spiculation and location of an SPN). These probabilities were calculated using the clinical prediction model. Probabilities for patients of different ages or for SPNs of different sizes can be calculated directly from the equation or estimated from Table 3.

COMMENT

We studied a large number of patients (n=629) with newly discovered, small, and radiologically indeterminate lung nodules. Using multivariate logistic regression analysis, we found 6 variables that were predictors of malignancy: age, cigarette-smoking status, history of cancer, SPN diameter, upper lobe location, and spiculation of the SPN. We developed a clinical prediction model using these

Table 2. Univariate and Multivariate Analyses of Potential and Significant Predictors of Malignancy*

Variable	Derivation Set (n=419) OR	95% CI	P	Validation Set (n=210) OR	95% CI	P
Univariate Analysis—Potential Predictors						
Age, y	1.043	1.020-1.066	<.001	1.031	1.000-1.062	.05
Residence >192 km from clinic	0.831	0.525-1.316	.43	1.161	0.589-2.288	.67
Other cancer	2.889	1.303-6.406	.009	2.035	0.468-8.838	.34
Cigarette smoker	2.507	1.461-4.305	<.001	3.167	1.513-6.630	.002
Pack-years ≥40	2.436	1.525-3.892	<.001	4.859	2.467-9.570	<.001
Pack-years†	1.019	1.011-1.026	<.001	1.015	1.004-1.027	.009
Diameter, mm	1.157	1.113-1.202	<.001	1.135	1.080-1.192	<.001
Spiculation	5.789	3.332-10.057	<.001	5.520	2.423-12.575	<.001
Upper lobe	2.602	1.628-4.157	<.001	2.186	1.142-4.184	.02
Cavitation	3.05	1.078-8.646	.04	1.760	0.297-9.406	.56
Calcified granuloma	1.780	0.914-3.467	.09	0.156	0.020-1.194	.07
Lobulation	2.520	1.432-4.433	.001	2.946	1.093-7.943	.03
Shagginess	1.446	0.916-2.285	.11	1.407	0.740-2.675	.30
Side	1.366	0.864-2.160	.18	0.654	0.343-1.248	.20
Multivariate Analysis—Significant Predictors						
Diameter, mm	1.136	1.088-1.186	<.001	1.131	1.071-1.195	<.001
Age, y	1.040	1.014-1.067	.003	1.011	0.975-1.049	.54
Other cancer	3.815	1.387-10.487	.01	2.376	0.507-11.127	.27
Cigarette smoker	2.207	1.171-4.159	.01	3.128	1.352-7.235	.008
Spiculation	2.831	1.472-5.445	.002	3.170	1.292-7.778	.01
Upper lobe	2.190	1.266-3.789	.005	1.812	0.844-3.891	.13

*OR indicates odds ratio; and CI, confidence interval.
†Continuous variable.

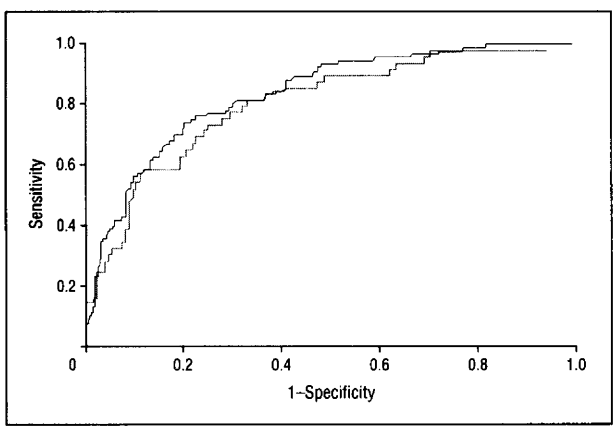

Figure 1. *Receiver operating characteristic curve for clinical prediction model. The model was developed based on data from 419 patients with solitary pulmonary nodules (area±SE, 0.8328±0.0226 [solid curve]) and validated based on data from 210 different patients with solitary pulmonary nodules (area±SE, 0.8014±0.0360 [dashed curve]). The receiver operating characteristic curve displays the true-positive rate (sensitivity) vs the false-positive rate (1−specificity).*

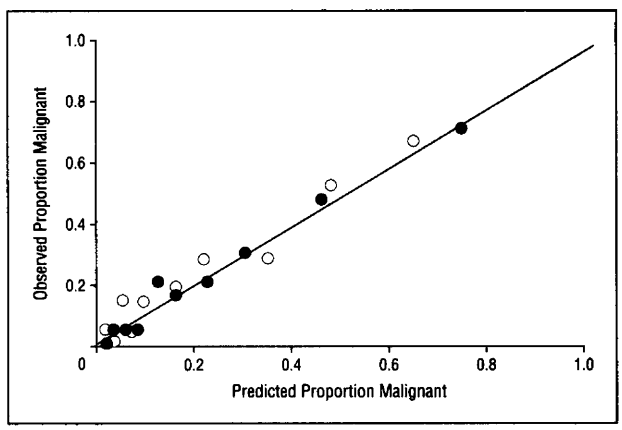

Figure 2. *Calibration curve for the clinical prediction model in 419 patients with solitary pulmonary nodules whose clinical and radiographic data were used to develop the prediction model and in the 210 different patients with solitary pulmonary nodules whose clinical and radiographic data were used to validate the prediction model. Patients were grouped by the decile of the predicted risk of malignancy. The calibration curve displays the observed proportion that was malignant vs the predicted proportion that was malignant for each decile. Solid circles indicate development data; open circles, validation data.*

6 predictors and validated the prediction model on a separate sample of patients.

This study demonstrates that there is diagnostically useful information about the probability of malignancy in the clinical characteristics of patients and the radiographic characteristics of SPNs that are judged to be radiographically indeterminate for malignancy. The probability of malignancy from the probability model can be considered as a diagnostic test, and the trade-off between sensitivity and specificity at various thresholds of the probability of malignancy is given by the ROC curve in Figure 1. The choice of a threshold to use in clinical practice will differ, depending on the clinician's interest in having a high sensitivity or a high specificity. For example, at a threshold of 0.10, the prediction model has a sensitivity of 93% and a specificity of 47%; at a threshold of 0.40, the prediction model has a sensitivity of 51% and a specificity of 90%.

The best strategy for an individual patient with an SPN may depend on the probability that a given nodule is malignant. Clinical and radiological criteria can help to identify the probability of malignancy. Additional fac-

Table 3. Probability of Malignancy*

Cigarettes	Other Cancer	Spiculation	Upper Lobe	P 35 y 10 mm	P 35 y 20 mm	P 35 y 30 mm	P 55 y 10 mm	P 55 y 20 mm	P 55 y 30 mm	P 75 y 10 mm	P 75 y 20 mm	P 75 y 30 mm
0	0	0	0	.02	.05	.16	.03	.11	.30	.07	.21	.48
0	0	0	1	.03	.11	.30	.07	.21	.48	.14	.36	.67
0	0	1	0	.04	.13	.36	.09	.25	.55	.17	.42	.73
0	0	1	1	.09	.25	.55	.17	.43	.73	.31	.62	.85
0	1	0	0	.06	.17	.43	.11	.31	.62	.22	.50	.78
0	1	0	1	.11	.31	.62	.22	.50	.78	.38	.69	.89
0	1	1	0	.14	.37	.68	.26	.56	.82	.44	.74	.91
0	1	1	1	.27	.56	.82	.44	.74	.91	.63	.86	.96
1	0	0	0	.03	.11	.30	.07	.21	.48	.14	.37	.67
1	0	0	1	.07	.21	.49	.14	.37	.67	.26	.56	.82
1	0	1	0	.09	.25	.55	.17	.43	.73	.31	.62	.85
1	0	1	1	.17	.43	.73	.31	.62	.85	.50	.78	.93
1	1	0	0	.11	.31	.62	.22	.50	.78	.38	.69	.89
1	1	0	1	.22	.50	.78	.38	.69	.89	.57	.83	.95
1	1	1	0	.27	.57	.82	.44	.74	.91	.63	.86	.96
1	1	1	1	.44	.74	.91	.64	.86	.96	.79	.93	.98

**For categorical predictors (cigarettes, other cancer, spiculation, and upper lobe), 0 indicates absent; 1, present. For P values, 35, 55, and 75 refer to age of patient; 10, 20, and 30, size of solitary pulmonary nodule.*

tors that enter into the diagnostic approach are the presence of comorbid conditions (eg, chronic obstructive pulmonary disease) that would affect the risk of a thoracotomy, the patient's attitude toward the risk,[10] and the physician's attitudes toward the risk and uncertainty.[11,12] Investigation of these factors that may explain the substantial variation in management decisions for patients with SPNs has been hampered by the unavailability of a validated diagnostic classification rule for the probability of malignancy in the individual patient at the time that decisions about management are made.

Previous studies in which multivariate statistical methods were used to predict the probability of malignancy in an SPN have had methodological limitations and have not been widely accepted in the clinical setting. Rotte and Meiske[13] applied discriminant analysis to 23 clinical and radiographic signs to classify 482 patients with histologically proved SPNs into 3 groups (ie, carcinomas, benign tumors, and tuberculomas). Their overall accuracy was 85%, based on initial findings, and there was an 89% accuracy in a subset of 362 patients for whom follow-up radiographs were performed. The clinical setting from which these patients were selected was not well described, and no attempt was made to identify a more parsimonious set of predictor variables. The trichotomous classification does not reflect the current clinical priority of physicians to distinguish malignant from all nonmalignant SPNs; furthermore, it has not been validated.

Other investigators used a conditional probability matrix that contained information on 44 preoperative clinical, bronchoscopic, and radiological factors in a bayesian algorithm to predict malignancy in 100 patients referred for a thoracotomy. This method produced a 98% sensitivity for malignant SPNs and an 87% specificity in this referral setting with an 85% prevalence of malignant SPNs.[5,6] Similar results were reported in a validation study by the same investigators in 100 patients.[14] All patients had undergone chest radiographs and bronchoscopy, and CT scans of the chest had been performed in most of the patients. If peripheral lesions were noted, a TNAB was attempted. In the validation study, the prevalence of cancer was 82% because all patients were referred for a thoracotomy; the method had a sensitivity of 96% and a specificity of 89% for the diagnosis of malignancy. The results of this study may not be applicable to other settings because of the high prevalence of malignancy and the spectrum of disease in patients referred for a thoracotomy.[15] Nevertheless, the investigators said, "We have not used the test to influence our preoperative management, but such consideration may be warranted."[14]

Two published decision analyses of the management alternatives for patients with an SPN have evaluated the decision among surgery, a biopsy procedure, or observation. Kunstaetter and colleagues[16] used information on patients' age, history of cigarette smoking, and presence of comorbid conditions, along with estimates of the probability of cancer, probability of resectability, biopsy sensitivity, biopsy specificity and morbidity, surgical morbidity and mortality, and life expectancy to identify the expected morbidity-adjusted life-years associated with each management alternative.[16] Thresholds for management choices were demonstrated in 2 examples with expectant management preferred at low probabilities of cancer, biopsy at intermediate probabilities, and surgery at high probabilities of cancer. They expressed concern about the limited size of published series and conflicting data reported by different authors, and they observed that, in 1 of the 2 reported cases, the choice between surgery and biopsy was a "toss-up."

In a more comprehensive analysis that evaluated the alternatives of observation, biopsy and observation, bi-

opsy and surgery, and immediate surgery, the choice between immediate surgery and either biopsy strategy was always a "close call." At low probabilities of cancer, observation was favored because of a slightly longer life expectancy compared with that achieved with a biopsy or immediate surgery, but the differences were small.[17] Thus, based on these analyses, improvements in the management of patients with SPNs are most likely to result from more consistent, accurate, and precise estimates of the probability of cancer to avoid morbidity resulting from a thoracotomy for benign disease and to avoid a theoretical small reduction in life expectancy resulting from delay because of the initial observation for malignant disease.

The actual initial management of patients should be guided by the probability of malignancy. Decisions about the 4 treatment options of observation, biopsy and observation, biopsy and surgery, and immediate surgery are all modified by patients' attitudes toward the risk of procedures and uncertainty if a definitive diagnostic procedure is not initially chosen. At a low probability of cancer, observation would be optimal because surgery could be avoided and there would be little decrease in survival attributable to a delay in curative therapy. At a high probability of malignancy, immediate surgery would be optimal because of the risk of decreased survival due to delay, resulting from observation of a malignant SPN. At intermediate probabilities of malignancy, a biopsy procedure would be preferable to estimate more precisely the risk of malignancy.[16,18]

The strengths of this study include the large number of newly discovered radiologically indeterminate SPNs. The fact that none was larger than 30 mm is a strength in that these are a more challenging diagnostic group of SPNs. In this study, we compared ROC and calibration methods. Finally, the use of an independent set of patients for validation is a strength.

Limitations of this research include its retrospective nature, the potential presence of referral bias, and our inability to determine the diagnosis in 12% of the patients studied. To evaluate potential referral bias, we included the distance from the patient's home to the Mayo Clinic as a covariate in our analysis and found that it was not important. To evaluate the potential impact of patients with undiagnosed SPNs, we analyzed the predictors of malignant SPNs with benign SPNs and undiagnosed SPNs combined, and we analyzed the predictors of benign SPNs with malignant SPNs and undiagnosed SPNs combined. These analyses yielded similar results, so we do not believe that our inability to follow up all of the patients produced a bias in our findings.

If our predictive probability model using multivariate analysis is sufficiently accurate, it could be used as a clinical aid to help separate benign from malignant SPNs. The following important benefits could be accrued: (1) surgery for early stage (T1) bronchogenic carcinomas could be expedited without the risk of the tumor metastasizing during a period of observation, (2) expensive and invasive bronchoscopy and TNAB procedures could be used more appropriately, and (3) the expense and risk of surgery for benign SPNs could be decreased.

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REFERENCES

1. Khouri NF, Meziane MA, Zerhouni EA, Fishman EK. The solitary pulmonary nodule: assessment, diagnosis, and management. *Chest.* 1987;91:128-133.
2. Swensen SJ, Jett JR, Payne WS, Viggiano RW, Pairolero PC, Trastek VF. An integrated approach to evaluation of the solitary pulmonary nodule. *Mayo Clin Proc.* 1990;65:173-186.
3. Lillington GA. Systematic diagnostic approach to pulmonary nodules. In: Fishman AP, ed. *Pulmonary Diseases and Disorders.* 2nd ed. New York, NY: McGraw-Hill Book Co; 1988;3:1945-1954.
4. Midthun DE, Swensen SJ, Jett JR. Clinical strategies for solitary pulmonary nodule. *Annu Rev Med.* 1992;43:195-208.
5. Edwards FH, Schaefer PS, Callahan S, Graeber GM, Albus RA. Bayesian statistical theory in the preoperative diagnosis of pulmonary lesions. *Chest.* 1987; 92:888-891.
6. Edwards FH, Graeber GM. The theorem of Bayes as a clinical research tool. *Surg Gynecol Obstet.* 1987;165:127-129.
7. Wasson JH, Sox HC, Neff RK, Goldman L. Clinical prediction rules: applications and methodological standards. *N Engl J Med.* 1985;313:793-799.
8. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology.* 1982;143:29-36.
9. Lemeshow S, Hosmer DW Jr. A review of goodness of fit statistics for use in the development of logistic regression models. *Am J Epidemiol.* 1982;115:92-106.
10. McNeil BJ, Weichselbaum R, Pauker SG. Fallacy of the five-year survival in lung cancer. *N Engl J Med.* 1978;299:1397-1401.
11. Nightingale SD. Risk preference and laboratory use. *Med Decis Making.* 1987; 7:168-172.
12. Nightingale SD, Grant M. Risk preference and decision making in critical care situations. *Chest.* 1988;93:684-687.
13. Rotte KH, Meiske W. Results of computer-aided diagnosis of peripheral bronchial carcinoma. *Radiology.* 1977;125:583-586.
14. Edwards FH, Schaefer PS, Cohen AJ, et al. Use of artificial intelligence for the preoperative diagnosis of pulmonary lesions. *Ann Thorac Surg.* 1989;48:556-559.
15. Ransohoff DF, Feinstein AR. Problems of spectrum and bias in evaluating the efficacy of diagnostic tests. *N Engl J Med.* 1978;299:926-930.
16. Kunstaetter R, Wolkove N, Kreisman H, Cohen C, Frank H. The solitary pulmonary nodule: decision analysis. *Med Decis Making.* 1985;5:61-75.
17. Cummings SR, Lillington GA, Richard RJ. Estimating the probability of malignancy in solitary pulmonary nodules: a bayesian approach. *Am Rev Respir Dis.* 1986;134:449-452.
18. Cummings SR, Lillington GA, Richard RJ. Managing solitary pulmonary nodules: the choice of strategy is a 'close call.' *Am Rev Respir Dis.* 1986;134: 453-460.