Novel and Convenient Method to Evaluate the Character of Solitary Pulmonary Nodule-Comparison of Three Mathematical Prediction Models and Further Stratification of Risk Factors

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Abstract

Objective: To study risk factors that affect the evaluation of malignancy in patients with solitary pulmonary nodules (SPN) and verify different predictive models for malignant probability of SPN.

Methods: Retrospectively analyzed 107 cases of SPN with definite post-operative histological diagnosis whom underwent surgical procedures in China-Japan Friendship Hospital from November of 2010 to February of 2013. Age, gender, smoking history, malignancy history of patients, imaging features of the nodule including maximum diameter, position, spiculation, lobulation, calcification and serum level of CEA and Cyfra21-1 were assessed as potential risk factors. Univariate analysis model was used to establish statistical correlation between risk factors and post-operative histological diagnosis. Receiver operating characteristic (ROC) curves were drawn using different predictive models for malignant probability of SPN to get areas under the curves (AUC values), sensitivity, specificity, positive predictive values, negative predictive values for each model, respectively. The predictive effectiveness of each model was statistically assessed subsequently.

Results: In 107 patients, 78 cases were malignant (72.9%), 29 cases were benign (27.1%). Statistical significant difference was found between benign and malignant group in age, maximum diameter, serum level of Cyfra21-1, spiculation, lobulation and calcification of the nodules. The AUC values were 0.786±0.053 (Mayo model), 0.682±0.060 (VA model) and 0.810±0.051 (Peking University People’s Hospital model), respectively.

Conclusions: Serum level of Cyfra21-1, patient’s age, maximum diameter of the nodule, spiculation, lobulation and calcification of the nodule are independent risk factors associated with the malignant probability of SPN. Peking University People’s Hospital model is of high accuracy and clinical value for patients with SPN. Adding serum index (e.g. Cyfra21-1) into the prediction models as a new risk factor and adjusting the weight of age in the models might improve the accuracy of prediction for SPN.

Introduction

Solitary pulmonary nodule (SPN) is defined as a spherical radiographic opacity that measures up to 3 cm in diameter and completely surrounded by lung tissue. The pathological diagnosis of SPN ranges from primary lung cancer or metastases from extrathoracic malignancy to infections, scar formation, and other benign lesions [1]. About 1 of 500 chest X-ray could display a SPN (0.2%), and more than 90% of the SPN was found without intention [2]. Surgical intervention may clarify the histological character of SPN when necessary to set up proper therapeutic strategy, and reduce the mortality associated with lung cancer [3].

Materials and Methods

Ethics Statement

This retrospective study was performed after been approved by the ethics committee of China-Japan Friendship Hospital, and written consent was given by the patients for their information to be stored in the hospital database and used for clinical research.

Clinical Data

From November of 2010 to February of 2013, 107 patients with SPN confirmed by plain/enhanced chest CT scan who underwent surgical procedure in China-Japan Friendship Hospital were reviewed retrospectively. The histological result of each SPN was definite post-operatively. Based on current mathematical prediction models for malignant probability of SPN [4–7], clinical data
including age, gender, smoking history, malignancy history, and imaging characteristics of nodule including the maximum diameter, location, spiculation, lobulation and calcification were considered as risk factors to assess (Table 1). Imaging characteristics were judged independently by two thoracic surgeons and a radiologist while the major opinion was adopted.

Surgical Methods
All the patients obtained definite histological result after surgical resection.
Different surgical procedures were adopted according to the clinical diagnosis, age, heart and pulmonary function of the patients, either to the malignant probability of SPN predicted by prediction models.

1. **Wedge resection.** Linear cut stapler was applied to remove the nodule together with surrounding normal lung tissue that minimum the size of the maximum diameter of SPN. If any malignant component of SPN was explored by the frozen section, anatomical lobectomy and systematic lymphadenectomy would be performed subsequently.

2. **Segmentectomy.** Anatomical or multiple segmentectomy was performed based on the size and location of SPN, in order to keep the distance between the margin of resection and the margin of SPN not less than the maximum diameter of SPN, further steps including systematic lymphadenectomy, lobectomy or termination might be chosen based on the result of frozen section biopsy.

3. **Lobectomy.** Lobectomy might be performed directly after medical informed when the malignant probability of nodule was comparatively high, lymphadenectomy might be chosen based on the result of frozen section biopsy.

### Statistical Methods

SPSS17.0 software (2010, IBM, Chicago, US) was used for statistical analysis. The clinical data considered as risk factors associated with the malignant probability of SPN were analyzed by Univariate analysis model. Receiver operating characteristic (ROC) curves were drawn according to different mathematical prediction models. Areas under the ROC curves (AUC values) were calculated subsequently.

MedCalc12.5 software (2013, MedCalc Software Company, Acacialaan, Belgium) was used to compare the AUC values between the three different prediction models. Appropriate cut-off points considering the Youden index were determined and the sensitivity, specificity, positive predictive value, and negative predictive value were calculated.

**Results**

1. Results of Post-operative Histological Diagnosis and Initial Operation Options (Table 2)

2. Results of Univariate Analysis

   There was significant statistical difference with quantitative factors including age, maximal diameter and serum level of Cyfra21-1 between benign and malignant groups (p<0.05) (Table 3).

   There were significant statistical differences with imaging characteristics including spiculation, lobulation and calcification between benign and malignant groups (p<0.05), but no statistical difference with gender, smoking history, malignancy history and location of the nodule (Table 4).

3. Validation and Comparison of Different Mathematical Predictive Models

   According to the published literatures, the following mathematical predictive models were adopted to estimate the malignant probability while x varied by different formulas.

   \[ P = \frac{e^x}{1 + e^x} \]

   As e is the natural logarithm and qualitative factors including smoking history, malignancy history, nodule located on upper lobe, spiculation, lobulation and calcification equals 1 if exist, and 0 otherwise.

   1. Mayo model:

   \[ x = -6.8272 + (0.0391 \times \text{Age}) + (0.7917 \times \text{Smoking history}) + 1.3388 \times \text{Previous cancer history} + (0.1274 \times \text{Diameter}) + (1.0407 \times \text{Spiculation}) + (0.7838 \times \text{Located on upper lobe}) \]

   [4];

   2. VA (Department of Veterans Affairs) model:

   \[ x = -8.404 + (2.061 \times \text{Smoking history}) + (0.779 \times \text{Age}) + (0.112 \times \text{Diameter}) - (0.567 \times \text{Quitting time}) \]

   [5];

   3. Peking University People’s hospital (PKUPH) model:

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**Table 1. Patient Characteristics.**

| Characteristic       | Male     | Female   |      |
|----------------------|----------|----------|------|
| Gender               | 54 (50.5%) | 53 (49.5%) |      |
| Age                  | 58.9±11.73 (24–83) | 56.7±14.3 (21–82) |      |
| Smoking history      | 40 (37.4%)* | 40 (37.4%) |      |
| Malignancy history   | 9 (8.4%)  | 5 (4.7%)  |      |
| Imaging characteristic | 1.93±0.63 (0.5–3.0) | 1.97±0.76 (0.5–3.3) |      |
| Maximal diameter (cm)| 58 (54.2%) | 57 (53.7%) |      |
| Located on Upper lobe| 75 (70.1%) | 73 (68.3%) |      |
| Spiculation          | 96 (89.7%) | 93 (86.8%) |      |
| Lobulation           | 7 (6.5%)  | 6 (5.5%)  |      |

*6 had quitted smoking for 1–20 years.

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Clinical data of 107 patients were applied to test the accuracy of different models. ROC curves were created (Figure 1) and AUC values were calculated (Table 5). MedCalc12.5 software was used to compare AUC values between three models. Mayo model and the Peking University people’s Hospital (PKUPH) model were proved of high accuracy, with no significant difference between each other (p = 0.577). VA model was proved of a significant lower diagnostic accuracy compared with either of other two models (p < 0.05) (Table 6).

According to the ROC curves, suitable cutoff values were selected. Sensitivity, specificity, positive predictive values, negative predictive values of each model were obtained by SPSS subsequently (Table 7).

### Table 2. Histological diagnosis and initial operation options.

| Histological diagnosis | No. | Initial operation options |
|------------------------|-----|----------------------------|
|                        |     | Wedge resection | Segmentectomy | Lobectomy |
| Benign                 |     |                 |                |
| Inflammatory lesions   | 7   | 5               | 1              | 1         |
| Tuberculosis           | 8   | 5               | 1              | 2         |
| Aspergillus            | 3   | 2               | 1              | 0         |
| Hamartoma              | 8   | 6               | 2              | 0         |
| Hemangioma             | 3   | 2               | 1              | 0         |
| Total                  | 29  | 20 (69.0%)      | 6 (20.7%)      | 3 (10.3%) |
| Malignant              |     |                 |                |
| Adenocarcinoma         | 53  | 20              | 4              | 29        |
| Squamous cell carcinoma| 13  | 4               | 2              | 7         |
| Small cell lung cancer | 5   | 3               | 0              | 2         |
| Carcinoid              | 1   | 1               | 0              | 0         |
| Lymphoid epithelioma   | 1   | 1               | 0              | 0         |
| Sarcomatoid carcinoma  | 1   | 1               | 0              | 0         |
| Large cell carcinoma   | 1   | 1               | 0              | 0         |
| Metastatic carcinoma   | 3   | 3               | 0              | 0         |
| Total                  | 78  | 34 (43.6%)      | 6 (7.7%)       | 38 (48.7%)|

### Table 3. Univariate analysis of quantitative factors.

|                                | Benign | Malignant | Total | p Value |
|--------------------------------|--------|-----------|-------|---------|
| Age (year)                     | 49.2±11.74 | 62.4±9.56 | 0.000 |
| Maximal diameter (cm)          | 1.63±0.64 | 2.04±0.59 | 0.002 |
| CEA (ng/ml)                    | 2.21±0.99 | 6.72±14.13 | 0.089* |
| Cyfra21-1 (ng/ml)              | 2.18±0.83 | 2.85±1.11 | 0.004 |

*Data of CEA did not achieve the homogeneity of variance, P value of rank-sum test >0.05, indicated no difference between groups. Result may relate to disperse distribution of value of CEA in malignant group, and could be positive after sum of case enlarged.

### Discussion

Estimation of malignant probability for SPN has always been a hotspot that closely related to early diagnosis and treatment of lung cancer. Previous literatures report that age, smoking history and tumor history indicate high malignant risk of SPN [8,9]. Image is usually needed to estimate the malignant probability of SPN, especially chest CT scan. Size and shape of nodule are most common influence factors [10,11]. One specific independent risk factor for the malignant probability of SPN is the maximum diameter of the nodule [1]. Imaging features of SPN including

### Table 4. Univariate analysis of qualitative factors.

|                                | Benign | Malignant | Total | p Value |
|--------------------------------|--------|-----------|-------|---------|
| Gender                         |        |           |       |         |
| Male                           | 17     | 37        | 54    | 0.209   |
| Female                         | 12     | 41        | 53    |         |
| Smoking history                |        |           |       |         |
| No                             | 18     | 49        | 67    | 0.557   |
| Yes                            | 11     | 29        | 40    |         |
| Malignancy history             |        |           |       |         |
| No                             | 28     | 70        | 98    | 0.241   |
| Yes                            | 1      | 8         | 9     |         |
| Located on Upper lobe          |        |           |       |         |
| No                             | 15     | 34        | 49    | 0.297   |
| Yes                            | 14     | 44        | 58    |         |
| Spiculation                    |        |           |       |         |
| No                             | 18     | 14        | 32    | 0.000   |
| Yes                            | 11     | 64        | 75    |         |
| Lobulation                     |        |           |       |         |
| No                             | 10     | 1         | 11    | 0.000   |
| Yes                            | 19     | 77        | 96    |         |
| Calcification                  |        |           |       |         |
| No                             | 24     | 76        | 100   | 0.015   |
| Yes                            | 5      | 2         | 7     |         |

*Data of CEA did not achieve the homogeneity of variance, P value of rank-sum test >0.05, indicated no difference between groups. Result may relate to disperse distribution of value of CEA in malignant group, and could be positive after sum of case enlarged.

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density, margin and calcification are also indicated. Generally high-density solid nodule has low probability of malignancy compared with ground-glass opacity (GGO) [12]. Nodules with rough and irregular margin indicate malignancy, while calcified nodules usually tend to be benign [7,13]. Absence of significant nodule enhancement (< or = 15 HU) on CT scan is a strong predictive factor of benignity [14]. With active surveillance, analysis of the growth rate of nodule would be helpful to narrow the differential diagnosis, doubling time of nodule is between one month and one year would highly suggest malignancy [15]. Nowadays, PET-CT scan is proved to have an established role in the study of pulmonary nodules [16], even the estimating effect of PET-CT for nodules less than 1 cm is still controversial. The latest research also find that plasma miRNAs provide potential circulating biomarkers for noninvasively diagnosing lung cancer among individuals with SPNs [17]. However, the way to improve the level of diagnosis, staging and prognostic assessment of lung cancer with suitable cost-effect ratio is still in researching process for clinicians. Different from advanced expensive examinations and complex time-consuming follow-up mentioned above, mathematical prediction models for malignant probability of SPN provided a novel and convenient way of estimation.

Independent risk factors should be assessed before formulating the mathematical predictive model for the malignant probability of SPN. Based on previous literatures [7,11], variables that may affect the evaluation of the malignant probability of SPN were analyzed with univariate analysis model in this study. Age of patient, maximum diameter of the nodule and imaging features including spiculation, lobulation and calcification were confirmed again as independent risk factors in our cohort. Furthermore, serum levels of CEA (carcinoembryonic antigen) and Cyfra21-1 (cytokeratin fragment 21-1) of the malignant group were found higher than those of the benign group in this study. The difference of Cyfra21-1 between the two groups was statistical significant (p<0.05), indicating that serum level of Cyfra21-1 might be a new independent risk factor in evaluating the malignant probability of SPN.

Mayo model, VA model and PKUPH model are the three most frequently cited models during our review of literatures [5,7,8]. Six independent risk factors including age, smoking history, history of extrapulmonary tumors, maximum diameter and location of the nodule, as well as spiculation were confirmed in Mayo model. With good sensitivity and specificity [4], Mayo model as a model

Table 5. Comparison of different models on AUC value.*

| Models       | AUC value | Standard Error | 95% CI Lower | 95% CI Upper |
|--------------|-----------|----------------|--------------|--------------|
| Mayo model   | 0.786     | 0.053          | 0.683        | 0.889        |
| VA model     | 0.682     | 0.060          | 0.565        | 0.799        |
| PKUPH model  | 0.810     | 0.051          | 0.710        | 0.909        |

*AUC is in the range of 0.5 to 1.0. When AUC>0.5, more close to 1, higher diagnostic accuracy the model indicates. AUC in the range of 0.5~0.7, the model has lower accuracy, 0.7~0.9, has a certain extent of accuracy, >0.9, indicates high accuracy. When AUC<0.5, the method shows no diagnostic value. When AUC<0.5, it does not fit the real situation.

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Table 6. Comparison of AUC values between different models.

|              | Mayo-VA | PKUPH-VA | PKUPH-Mayo |
|--------------|---------|----------|------------|
| Difference   | 0.104   | 0.128    | 0.024      |
| Z statistic  | 2.504   | 2.764    | 0.558      |
| P value      | 0.012   | 0.006    | 0.577      |

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Table 7. Comparison of predicting performance between different models.

| Models       | Cutoff value | Sensitivity | Specificity | positive predictive value | negative predictive value |
|--------------|--------------|-------------|-------------|---------------------------|---------------------------|
| Mayo model   | 0.039        | 62/78(79.5%)| 19/29(65.5%)| 62/72(86.1%)              | 19/35(54.3%)              |
| VA model     | 0.036        | 52/78(66.7%)| 16/29(55.2%)| 52/65(80.0%)              | 16/42(38.1%)              |
| PKUPH model  | 0.471        | 65/78(83.3%)| 22/29(75.9%)| 65/72(90.3%)              | 22/35(62.5%)              |

In summary, PKUPH model was found to have the highest diagnostic accuracy among the three verified and compared mathematical prediction models in this study. The tendency of improving the accuracy of prediction model by adding serum index (e.g., Cyfra21-1) and adjusting the weight of age needs future prospective study. The mathematical prediction model could help to evaluate the character of SPN and set up more accurate diagnostic and therapeutic strategies.

Conclusion

In summary, PKUPH model was found to have the highest diagnostic accuracy within the three verified and compared mathematical prediction models in this study. The tendency of improving the accuracy of prediction model by adding serum index (e.g., Cyfra21-1) and adjusting the weight of age needs future prospective study. The mathematical prediction model could help to evaluate the character of SPN and set up more accurate diagnostic and therapeutic strategies.

Author Contributions

Conceived and designed the experiments: CL. Performed the experiments: FX. CL. Analyzed the data: FX. CL. Contributed reagents/materials/analysis tools: DL. YG BS ZS YT. Wrote the paper: FX.

References

1. Wahidi MM, Govert JA, Goudar RK, Gould MK, McCrory DC (2007) Evidence for the treatment of patients with pulmonary nodules: when is it lung cancer?: ACCP evidence-based clinical practice guidelines (2nd edition). Chest 132: 948–1078.

2. Tan BB, Flaherty KR, Kazerooni EA, Iannettoni MD (2003) The solitary pulmonary nodule. Chest 123: 895–968.

3. Nair A, Hansell DM (2011) European and North American lung cancer screening experience and implications for pulmonary nodule management. Eur Radiol 21: 2445–2454.
4. Swensen SJ, Silverstein MD, Blotow DM, Schleck CD, Edell ES (1997) The probability of malignancy in solitary pulmonary nodules. Application to small radiologically indeterminate nodules. Arch Intern Med 157: 849–855.
5. Gould MK, Ananth L, Barnett PG (2007) A clinical model to estimate the pretest probability of lung cancer in patients with solitary pulmonary nodules. Chest 131: 838–848.
6. Li Y, Chen KZ, Sui XZ, Bu L, Zhou ZL, et al. (2011) [Establishment of a mathematical prediction model to evaluate the probability of malignancy or benign in patients with solitary pulmonary nodules]. Beijing Da Xue Xue Bao 43: 450–454.
7. Li Y, Wang J (2012) A mathematical model for predicting malignancy of solitary pulmonary nodules. World J Surg 36: 830–835.
8. Schultz EM, Sanders GD, Trotter PR, Patz EF, Jr., Silvestri GA, et al. (2008) Validation of two models to estimate the probability of malignancy in patients with solitary pulmonary nodules. Thorax 63: 335–341.
9. Mery CM, Pappas AN, Bueno R, Mentzer SJ, Lukacik JM, et al. (2004) Relationship between a history of antecedent cancer and the probability of malignancy for a solitary pulmonary nodule. Chest 125: 2173–2181.
10. Mikita K, Saito H, Sakuma Y, Kondo T, Honda T, et al. (2012) Growth rate of lung cancer recognized as small solid nodule on initial CT findings. Eur J Radiol 81: e540–553.
11. Gould MK, Fletcher J, Iannettoni MD, Lynch WR, Midhaan DE, et al. (2007) Evaluation of patients with pulmonary nodules: when is it lung cancer?. ACCP evidence-based clinical practice guidelines (2nd edition). Chest 132: 1008–1308.
12. Takashima S, Sone S, Li F, Marayama Y, Hasegawa M, et al. (2003) Small solitary pulmonary nodules (< or = 1 cm) detected at population-based CT screening for lung cancer: Reliable high-resolution CT features of benign lesions. AJR Am J Roentgenol 180: 955–964.
13. Yonemori K, Tatsumi U, Uno H, Yonemori Y, Tsuta K, et al. (2007) Development and validation of diagnostic prediction model for solitary pulmonary nodules. Respirology 12: 856–862.
14. Swensen SJ, Viggiano RW, Midhaan DE, Muller NL, Sherrick A, et al. (2000) Lung nodule enhancement at CT: multicenter study. Radiology 214: 73–80.
15. Albert RH, Russell JJ (2009) Evaluation of the solitary pulmonary nodule. Am Fam Physician 80: 827–831.
16. Ambrosini V, Nicolini S, Caroli P, Nanni C, Massaro A, et al. (2012) PET/CT imaging in different types of lung cancer: an overview. Eur J Radiol 81: 1001–1007.
17. Shen J, Liu Z, Todd NW, Zhang H, Liao J, et al. (2011) Diagnosis of lung cancer in individuals with solitary pulmonary nodules by plasma microRNA biomarkers. BMC Cancer 11: 374.
18. Vines P, Hoek G, Krzyzanowski M, Vigna-Taglianti F, Veglia F, et al. (2006) Air pollution and risk of lung cancer in a prospective study in Europe. Int J Cancer 119: 169–174.
19. Dela Cruz CS, Tanoue LT, Matthay RA (2011) Lung cancer: epidemiology, etiology, and prevention. Clin Chest Med 32: 605–644.
20. Kupert E, Anderson M, Liu Y, Succop P, Levin L, et al. (2011) Plasma secretory phospholipase A2-IlA as a potential biomarker for lung cancer in patients with solitary pulmonary nodules. BMC Cancer 11: 519.