Factors affecting the diagnostic yield of flexible bronchoscopy without guidance in pulmonary nodules or masses

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ABSTRACT

Introduction: In day-to-day bronchoscopic practice, no guidance is available to pinpoint the precise location of pulmonary nodules or masses, especially in developing countries. This results in a large number of non-diagnostic testings. The present study aimed to determine the predictors of diagnostic yield in bronchoscopy without guidance and develop a model to predict the decision to perform this procedure.

Methods: A retrospective study was conducted on 330 patients with pulmonary nodules or masses without any sign of atelectasis on chest radiographs, who underwent diagnostic bronchoscopy without guidance between June 2004 and May 2008. The patient characteristics, as well as radiological and bronchoscopic findings were included in the analysis of factors affecting the diagnostic yield.

Results: The overall diagnostic yield of bronchoscopy was 55.8 percent. The tumour size, endobronchial visibility and the characteristics of endobronchial abnormalities were predictors of higher diagnostic yield. The prediction model was developed from the data that can be recognised before bronchoscopy. Bronchoscopy provided the diagnosis in 66.4 percent of the patients who had a tumour size of 4 cm or larger.

Conclusion: The diagnostic yield of bronchoscopy without guidance was influenced by the size of the lesion, the endobronchial visibility and the characteristics of endobronchial abnormalities. Computed tomography (CT) of the chest should be performed to evaluate airway involvement. If the lesion is less than 4 cm in diameter and there is a negative CT illustration of airway involvement, flexible bronchoscopy with guidance should be considered.

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INTRODUCTION

The diagnosis of pulmonary nodules or masses is a challenging task for pulmonologists. It is well recognised that flexible bronchoscopy (FB) is a minimally invasive and useful method for investigating patients with these conditions. In order to sample the specimen, the accurate location of the pulmonary nodule or mass must be known. Various techniques have been developed to pinpoint the precise location of pulmonary nodules or masses during the bronchoscopic procedure. With fluoroscopic guidance, an internationally acceptable technique, pulmonary nodules or masses > 2 cm in diameter can be correctly diagnosed with a sensitivity of 0.63.[1] Recently, using endobronchial ultrasonography with a guide sheath, Kurimoto et al achieved a diagnostic yield of 69%–76% in pulmonary nodules < 2 cm.[2] Electromagnetic navigation bronchoscopy is another technique that has been developed, and a yield of 74% has been reported in pulmonary nodules < 2 cm in size.[3]

Although many studies have clearly identified the factors that affect the diagnostic yield of FB with fluoroscopic guidance,[4-6] and various other techniques have also proved their efficacy, routine FB with fluoroscopic guidance is not generally available in most hospitals due to the limited availability of resources, especially in developing countries. Therefore, it is necessary to determine the factors that influence the diagnostic yield of FB in the evaluation of pulmonary nodules or masses without guidance in order to select the appropriate cases in daily bronchoscopic practice.

METHODS

A total of 1,496 bronchoscopies, performed between June 2004 and May 2008 at Ramathibodi Hospital, a tertiary university referral hospital in Bangkok, Thailand, were retrospectively reviewed. All procedures in which bronchoscopy involved obtaining samples from

Table I. Final diagnostic procedures performed on the pulmonary nodules or masses in 330 patients.

Final diagnostic procedure	No. (%)
First bronchoscopy	184 (55.8)
Repeated bronchoscopy with fluoroscopic guidance	5 (1.5)
Repeated bronchoscopy with TBNA/TBNB	4 (1.2)
Postbronchoscopic sputum cytology	1 (0.3)
Transthoracic needle aspiration/biopsy	19 (5.8)
Pleural biopsy	1 (0.3)
Open lung biopsy/lobectomy	16 (4.8)
Lymph node aspiration/biopsy	2 (0.6)
Sampling from organs other than lung, lymph node	4 (1.2)
Clinical diagnosis of metastasis cancer	4 (1.2)
Clinical response with antituberculous medication	8 (2.4)
Lost to follow-up with no definite diagnosis	82 (24.8)

TBNA: transbronchial needle aspiration; TBNB: transbronchial needle biopsy

Table II. Final diagnoses of the pulmonary nodules or masses in 330 patients.

Final diagnosis	No. (%)
Total	248 (100)
Malignant	206 (83.1)
Primary lung cancer	186 (75.0)
Non small cell carcinoma	168 (67.7)
- Squamous cell carcinoma	44 (17.7)
- Adenocarcinoma	69 (27.8)
- Bronchioloalveolar cell carcinoma	10 (4.0)
- Adenosquamous cell carcinoma	1 (0.4)
- Large cell carcinoma	2 (0.8)
- Undifferentiated NSCLC	42 (16.9)
Small cell carcinoma	17 (6.9)
Others – mucoepidermoid carcinoma	1 (0.4)
Metastases	18 (7.3)
Adenocarcinoma	9 (3.6)
Squamous cell carcinoma	4 (1.6)
Breast cancer	1 (0.4)
Sarcoma	2 (0.8)
Melanoma	1 (0.4)
Hepatocellular carcinoma	1 (0.4)
Haematologic malignancy – lymphoma	2 (0.8)
Benign	42 (16.9)
Tuberculosis	31 (12.5)
Nontuberculous mycobacterium	1 (0.4)
Nocardiosis	1 (0.4)
Cryptococcosis	3 (1.2)
Aspergillosis	2 (0.8)
Healed lung abscess	1 (0.4)
Pneumonia	1 (0.4)
Silicotic nodule	1 (0.4)
Castleman's disease	1 (0.4)

NSCLC: non small cell lung cancer

a lesion of a pulmonary nodule or mass for diagnosis were eligible for inclusion in the study. Only patients with pulmonary nodules or masses who did not have any signs of atelectasis on chest radiography were enrolled for analysis.

The bronchoscopic procedures were performed by staff members or fellows under supervision from the pulmonary department. All patients underwent posteroanterior and lateral chest radiographs, and the targeted segmental bronchi were identified to obtain the samples. The procedure was carried out via the transnasal route under local anaesthesia using flexible bronchoscopes (EB-1570K, Pentax, Tokyo, Japan). The entire endobronchial tree, including the subsegmental bronchi, was examined. The presence or absence of endobronchial abnormalities was recorded. Endobronchial abnormalities were categorised as an endobronchial mass, endobronchial infiltration, abnormal bronchial swelling or external bronchial compression. When a bronchoscopically visible lesion was identified, the choice of sampling technique of FB was left to the examiner's discretion. The routine sequence of the sampling technique was washing, brushing and forceps biopsy. Bronchial washings (BW) were obtained by instillation with 20 ml of normal saline over the lesion and by aspiration into a trap. At least two specimens from bronchial brushings (BB) were then obtained from the surface of the lesions. Lastly, at least three tissue samples were taken by endobronchial biopsies (EBB). In the absence of bronchoscopically visible lesion, the bronchoscope was advanced toward the selected segmental branch in order to obtain the specimens. At this point, the examiners were free to use any technique deemed most appropriate to obtain the specimens. The routine sequence of bronchoscopic procedure utilised was bronchoalveolar lavage (BAL), brushing and forceps biopsy. BAL was performed by instilling with 50 ml of normal saline and by aspiration into a trap. Repeated instillations of 50 ml normal saline adding to a total of 100–150 ml, or a collection of 50 ml of retrieved fluid, can be considered adequate lavage. Subsequently, brushing and transbronchial biopsy (TBB) specimens were obtained blindly without fluoroscopic guidance. Generally, two samples from brushing and at least three to four samples from biopsy were obtained. If an infection was suspected, the BAL fluid was processed for Gram, acid-fast and Giemsa stains and cultures.

A definite diagnosis was defined as malignant disease or specific non-neoplastic disease. Cytological or histological diagnosis of nonspecific inflammation was considered to be non-diagnostic, although the final diagnosis proved to be a benign process. When a definite diagnosis was not obtained, the patient underwent

Table III. Baseline characteristics and effects on the diagnostic yield of flexible bronchoscopy

Variables	Total (n = 330)	Definite diagnosis by FB		p-value
		Yes (n = 185)	No (n = 145)	
Mean age ± SD (yrs)	60.2 ± 13.0	61.1 ± 12.7	59.1 ± 13.3	0.17
Male gender (%)	63.0	62.2	64.1	0.71
Smoking (%)				
Non-smoker	44.0	42.0	46.5	
Current smoker	21.0	23.7	17.5	
Quit smoking	35.0	34.3	36.0	0.47
Cough (%)	72.4	78.9	63.6	0.005
Haemoptysis (%)	18.4	22.3	13.3	0.06
Mean size by CXR ± SD (cm)	3.7 ± 1.8	4.1 ± 2.0	3.3 ± 1.6	< 0.001
Localisation by CXR (%)				
Right upper lobe	37.3	40.0	33.8	
Right middle lobe	6.4	6.5	6.3	
Right lower lobe	19.3	20.0	18.3	
Left upper lobe	23.2	20.5	26.8	
Left lower lobe	13.8	13.0	14.8	0.64
Endobronchial visibility (%)	42.1	60.5	18.6	< 0.001
Endobronchial mass	48.9	54.5	25.9	
Endobronchial infiltrative	23.7	22.3	29.6	
Bronchial swelling	10.1	8.0	18.5	
External compression	17.3	15.2	25.9	0.047

SD: standard deviation; FB: flexible bronchoscopy; CXR: chest radiograph

repeated bronchoscopy by conventional bronchoscopy with either fluoroscopy or other diagnostic procedures such as transbronchial needle aspiration or biopsy, computed tomography (CT)-guided biopsy, video-assisted thoracoscopy or clinical and radiologic follow-up, to confirm the diagnosis of the pulmonary nodule or mass.

The continuous variables were expressed as mean ± standard deviation (SD), and the categorical variables were presented as percentages. To illustrate the association between the independent variables and the diagnostic yield, the continuous variables were analysed using the student's two-tailed *t*-test and the categorical variables were tested using the chi-square (χ^2) test. The variables that were identified as having statistical significance in the analysis were subsequently tested using logistic regression analysis to identify the factors that affect the diagnostic yield. Using the regression coefficient technique, the predicted diagnostic yield equation was finally developed from the statistically significant factors and identified by multivariate analysis ($p \leq 0.05$). The yield predicted by the equation was then compared with the actual diagnostic yield in this retrospective cohort. All statistical tests were two-sided, and a p-value < 0.05 was considered to be statistically significant. All the data was analysed using the Statistical Package for the Social Sciences version 11.5 for Windows (SPSS Inc, Chicago, IL, USA). This retrospective study protocol was approved by the Ethics Committee on Human Experimentation of the Ramathibodi Hospital, Faculty of Medicine, Mahidol University.

RESULTS

A total of 330 patients fulfilled the inclusion criteria and were enrolled in the study. The diagnoses of 184 (55.8%) patients were established during the first attempt at bronchoscopy. For the remaining 146 patients whose initial bronchoscopy yielded negative results, the diagnostic procedure that they subsequently underwent and their final diagnoses are presented in Tables I and II.

The baseline characteristics of the patients are shown in Table III. In univariate analyses, the presence of cough, tumour size, endobronchial visibility and characteristics of endobronchial abnormalities were predictors of a higher diagnostic yield. As our aim was to identify the factors affecting the diagnostic yield before bronchoscopy, the bronchoscopic findings were not included in the multivariate model. In the multivariate approach, it was found that only the tumour size was independently associated with the diagnostic yield ($p = 0.001$). Based on the regression coefficient, the prediction model was formulated with the following equations: Odds = Exp [(0.247 × size in cm) – 0.659] and Predicted diagnostic yield = odds/(odds + 1).

The predicted diagnostic yield for each patient was calculated and compared with the actual diagnostic yield. The predicted and actual diagnostic yields were found

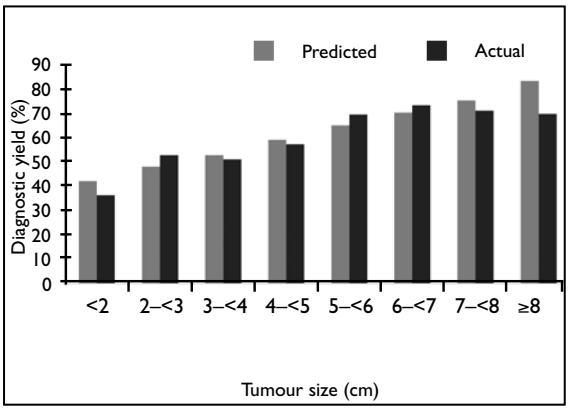

Fig. 1 Bar chart shows the predicted diagnostic yield calculated using the equation as compared to the actual diagnostic yield.

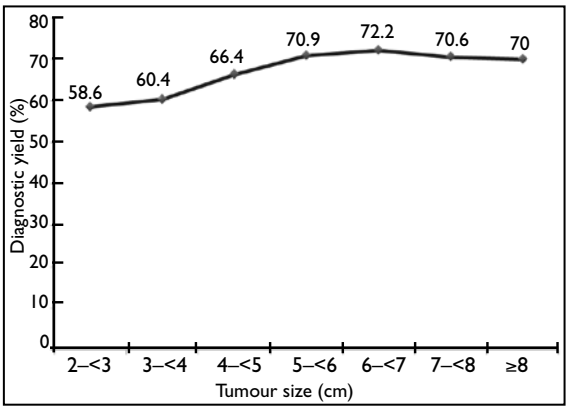

Fig. 2 Line graph shows the diagnostic yield according to the tumour size.

to be similar for all tumour sizes (Fig. 1). Additionally, bronchoscopy was able to provide a diagnosis in 66.4% of the patients whose tumour size was ≥ 4 cm in diameter (Fig. 2). Endobronchial abnormalities were detected in 42.1% of the patients. Of these, the diagnostic yield of the bronchoscopic procedures was 80.6%, whereas the diagnostic yield in patients with non-visible lesions was only 38.2% ($p < 0.001$). Furthermore, visible lesions were associated with a larger tumour size (4.4 cm in visible lesions compared with 3.2 cm in non-visible lesions, $p < 0.001$).

Table IV shows the diagnostic yield of different bronchoscopic sampling techniques. In bronchoscopically visible lesions, no additional advantages of BB were observed after BW and EBB were performed. In contrast, BW and EBB provided additional benefits for each other. For non-visible lesions, BAL and TBB provided additional diagnostic yield for each other. Although brushing seemed to enhance diagnostic advantages, TBB was not performed in these two instances.

DISCUSSION

Although new bronchoscopic procedural techniques have been developed to facilitate accuracy in locating a lesion, they are not used in routine practice, especially in developing countries, where even the fluoroscope is not available for routine bronchoscopy in the diagnosis of a localised lesion.[7] Consequently, there have been a number of unsuccessful bronchoscopic localisations of pulmonary nodules and masses. Therefore, it is important for pulmonologists to be able to predict the diagnostic yield of pulmonary nodules or masses by FB without guidance so that low diagnostic tests can be avoided and a decision for referral of patients can be made based on these predictors. Currently, few studies have identified the factors affecting the diagnostic yield of bronchoscopy without guidance.[7,8] However, the vast majority of these studies have not focused solely on pulmonary nodules or masses in general, but have included those with lobar collapse and hilar abnormalities, which could be predicted to have high diagnostic yield. Studies should be conducted on all pulmonary nodules or masses rather than focusing only on malignant proven nodules because physicians are urged to provide a diagnosis of abnormal radiographic findings. Importantly, the nature of the aetiology (benign or malignant disease) also affects the diagnostic yield;[5] hence, high diagnostic yields will be obtained if only malignant proven nodules or masses are enrolled when evaluating the diagnostic procedure.

This study has demonstrated that the diagnostic yield of FB without guidance in pulmonary nodules or masses depends on the size of the lesion. Su et al have recommended FB for the evaluation of a mass ≥ 4 cm on chest radiograph. Without any guidance, they found that the incidence of positive bronchoscopy yield was 65.7% in patients with a localised mass ≥ 4 cm in diameter, whereas the yield fell to 24.5% in lesions < 4 cm.[8] In this study, we developed an equation for forecasting the diagnostic yield before the procedure so that bronchoscopists can consider the use of other guidance techniques to enhance the efficacy of the bronchoscopic procedure in case of a low predicted yield.

In keeping with reports in the literature,[1,4,7,8] the diagnostic yield in this study was higher in patients with bronchoscopically visible lesions than in patients with non-visible lesions. Likewise, we found that visible lesions on bronchoscopy were associated with larger tumour sizes, and this is similar to the findings of a previous study.[8] We did not include in our analysis the position of the lesion, which is defined by its location relative to some reference point such as the distance from the hilum because we had observed inter-observer variations in the measurement of this distance by chest radiograph. During this retrospective period, we did not

Table IV. The diagnostic yield of different bronchoscopic sampling techniques.

Technique	No. of patients (%)		
	Application	Diagnostic yield	Only diagnostic modality with a positive result
Bronchoscopically visible lesions (n = 139)			
Bronchial washing	137 (98.6)	84 (61.3)	17 (12.4)
Bronchial brushing	29 (20.9)	19 (65.5)	0 (0.0)
Endobronchial biopsy	130 (93.5)	89 (68.5)	24(18.5)
Bronchoscopically non-visible lesions (n = 191)			
Bronchoalveolar lavage	189 (99.0)	56 (29.6)	29 (15.3)
Brushing	6 (3.1)	3 (50.0)	2 (33.3)
Transbronchial biopsy	176 (92.1)	42 (23.9)	15 (8.5)

perform CT, although it provides a better measurement of the distance from the reference point in every case before bronchoscopy. Nevertheless, other studies have found that the effect of the distance on diagnostic yield is inconclusive.[4,5,9,10]

Endobronchial visibility was found to be another predictor of diagnostic yield. The diagnostic yield of the patients with a visible lesion in our study was high compared to those in previous studies.[4,7,8,10,11] However, in patients with pulmonary nodules or masses without any sign of atelectasis on chest radiographs, endobronchial visibility could not be predicted before bronchoscopy. Currently, using the regular diagnostic flexible bronchoscope with an outer diameter of 4.9 mm, bronchoscopists are able to examine down to the level of the subsegmental bronchi. Although CT is poor at differentiating the pattern of endobronchial abnormalities, it has been found to be more accurate in the detection of airway abnormalities compared with FB.[10,12] Thus, CT is considered to be a necessary investigation before the evaluation of pulmonary nodules or masses by FB without guidance. If the lesion is < 4 cm in diameter and CT does not demonstrate any involvement of subsegmental or larger-sized airways, FB should not be performed in view of the low diagnostic yield, and other guidance techniques should be considered.

In terms of the bronchoscopic sampling techniques, our bronchoscopists were not familiar with the use of a brush to obtain the specimens. This resulted in the under-utilisation of this technique. In bronchoscopically visible lesions, it has been shown that BB augments the diagnostic yield of bronchoscopy.[4,7,11] However, we did not find any additional advantages to performing BB when BW and EBB were performed simultaneously. Moreover, we experienced some bleeding after this technique due to the prolonged contact with the rough surface of the equipment. For non-visible lesions, some studies have reported the usefulness of the brushing technique, but fluoroscopy was performed in these cases.[2,5,13,14] Without fluoroscopic control of the placement of the bronchial brush, it is difficult to place the instrument correctly, and it may result in pneumothorax. Furthermore, it is impossible to perform transbronchial needle aspiration in a non-visible lesion without fluoroscopic guidance.

There are some limitations to our study. Because of the nature of the retrospective study, the final diagnosis of 24.8% of the patients was not available as they were lost to follow-up. Our purpose, however, was to assess the diagnostic yield of the problems at presentation, and not the specific diseases, so the final results of non-diagnosis cases did not reduce the reliability of our study. Another limitation is associated with the bronchoscopic sampling methods, which were left to the judgement of the examiners. As a result, only familiar techniques were mostly performed. Further research into bronchoscopic procedures without guidance for non-visible lesion is required to order to demonstrate the benefits of various sampling techniques.

In conclusion, this study has demonstrated that the size of pulmonary nodules or masses and endobronchial visibility are significant predictors of high diagnostic yield. We have also generated the equations for predicting diagnostic yield before performing the bronchoscopic procedure in order to help bronchoscopists decide whether it is efficient to undertake FB without guidance. It is recommended that CT be performed before bronchoscopy. If the lesion is < 4 cm in diameter and CT does not demonstrate any involvement in subsegmental or larger-sized airways, FB with a guidance technique or an alternative method to obtain a tissue diagnosis should be considered. With these findings, our policy regarding the investigation of pulmonary nodules or masses may undergo some changes.

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