PREDICTED MALIGNANCY OF PULMONARY LESIONS USING THE TUMOR INSPECTOR PROGRAM, VERSION 1, PHRAMONGKUTKLAO HOSPITAL

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Abstract

Background: Pulmonary nodules can originate from any cause, ranging from benign to malignant. Surgical lung resectioning at the early stage of lung cancer provides the best chance for cure. As a result, establishing the etiology of pulmonary nodules accurately is critically important. Rapid identification can also avoid unnecessary surgery among patients with benign diseases. Currently, endobronchial ultrasound (EBUS) is a standard procedure used to investigate pulmonary nodules. The characteristics of pulmonary nodules from EBUS can differentiate benign from malignant. However, the interpretation of EBUS findings depends on the pulmonologists' experience. Thus, we developed and analyzed the performance of software, called "Tumor Inspector Program, Ver. 1" to help interpreting characteristics of pulmonary nodules from EBUS.

Objective: To evaluate accuracy in interpreting EBUS findings using the Tumor Inspector Program, Ver.1 compared with three pulmonology interventionists' agreements.

Methods: We conducted a cross-sectional study of patients undergoing radial-probe EBUS-guided bronchoscopy to investigate pulmonary nodules between May 2015 and December 2016, Phramongkutklao Hospital. For diagnosis, we obtained pathological tissue from bronchial brushing and transbronchial biopsy. The characteristic findings from EBUS were analyzed and diagnosed using the Tumor Inspector Program, Ver.1 and three pulmonary interventionists.

Results: Two hundred and eight patients with a mean age of 61 ± 1 years were included in the study. The pathological reports comprised 80 (38.46%) benign and 128 (61.54%) malignant cases The sensitivity, specificity, negative predictive value and diagnostic accuracy by pulmonary interventionists were 90.%, 22.5%, 60%, and 64.4%, respectively. On the other hand, the diagnosis using the Tumor Inspector Program, Ver.1 showed a sensitivity of 90.0% and specificity of 81.2%, negative predictive value of 84.4% and an accuracy of 87%.

Conclusion: Among patients with pulmonary nodules, the Tumor Inspector Program, Ver.1 had significantly higher specificity and accuracy to predict malignancy possibility than three pulmonology interventionist agreements.

Keywords : Endobronchial ultrasound, Malignancy, Pulmonary nodule

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Introduction

Bronchoscopy has been applied for decades in evaluating pulmonary nodules. Among patients with peripheral lung nodules, bronchoscopy has been reported to give variable diagnostic yields in the range of 16.7 to 65.6% through BAL, bronchial brushing cytology, or transbronchial biopsy.[1–4]

Various procedures have been developed to diagnose peripheral pulmonary lesions (PPLs). The transbronchial biopsy (TBB) procedure, using a bronchoscope under fluoroscopic guidance, has been performed since the 1970s, with 36 to 86% diagnostic accuracy.[5-9] Diagnostic accuracy is influenced by lesion size; Schreiber and Mc Crory [5] reported a systematic review revealing that the diagnostic accuracy of lesions <20 mm in mean diameter was 33%. Other studies[6-9] have reported that the diagnostic accuracy of benign lesions was 35 to 50%, lower than that of malignant lesions. So far, small-caliber, radial-type ultrasound probes can be used for clinical applications of ultrasonography to tracheal-bronchial lesions and PPLs. Endobronchial ultrasonography (EBUS) has been used for imaging guidance in the TBB of PPLs.[10-11]

In 2002, Kurimoto et al.[12] found that endobronchial ultrasonography (EBUS) images of peripheral pulmonary lesions could be visually classified in three types and six subtypes and concluded that the images helped differentiate benign and malignant lesions.

In 2007, Kuo CH et al.[13] showed that characteristics of EBUS pictures could distinguish benign and malignant tumors. The characteristic of EBUS pictures which favor malignancy include: 1) heterogeneity 2) continuous margin and 3) linear-discrete air bronchogram. When the results are positive in two of the three characteristics, that pulmonary lesion has a chance of 89.2% to be malignant. In contrast, when the results are negative for all of the three characteristics, the chance to be benign is about 93.7%. Thus, interpreted outcome depends on the pulmonologists' experience as well as pathological diagnosis. In this study, we developed a Tumor Inspector Program, Ver.1 to aid in interpreting characteristics of EBUS pictures to increase consistency, reduce time to interpret and use for treatment planning. However, the accuracy of this new program has not yet been validated. Using the pathological diagnosis as a gold standard, we aimed to evaluate the accuracy in interpreting characteristics of EBUS pictures of the Ver.1 Tumor Inspector Program compared with agreements of three pulmonary interventionists.

Methods

Study design and inclusion criteria

A cross-sectional study was conducted among patients undergoing EBUS for tissue diagnosis at Phramongkutklao Hospital. Consecutive adult patients with a clinical indication for EBUS-GS, i.e., age ≥18 years, presenting pulmonary lesions, having computed tomography (CT) scan of chest 1-1.5 mm in thickness, undergoing EBUS for the first time and having a pathological diagnosis. Exclusion criteria comprised incomplete radiological examination, undergoing previous EBUS, poor quality of video files, and other standard exclusions for EBUS (coagulopathy, uncontrolled underlying diseases, e.g., unstable cardiovascular system and hypertension). A total of 272 patients were recruited in the study from May 2015 to December 2016. Of these, 208 patients met the criteria and were enrolled in the study. All patients or their relatives provided written informed consent to participate. This study was approved by the Institutional Review Board of the Royal Thai Army Medical Department.

Study design

This trial analyzed the accuracy of predicted malignancy of pulmonary lesions between interpretation using the Tumor Inspector Program, Ver.1 and agreements of three pulmonology interventionists. For enrolled patients who met the criteria and underwent EBUS, we recorded video files while performing EBUS at a range of 4 cm. Then we assigned these video files to three pulmonology interventionists to interpret the outcomes. All three pulmonology interventionists were blinded for each interpretation as well as patients' medical records. Simultaneously, these video files were assigned to interpreted outcomes using the Tumor Inspector Program, Ver.1.

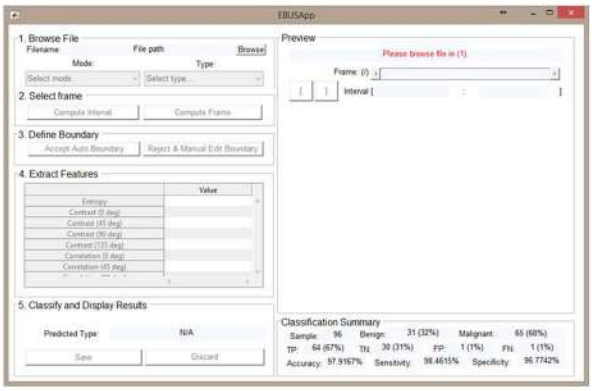
Data interpretation using three pulmonology interventionists

Before interpreting all video files, we provided standardized EBUS pictures of 20 cases for the three pulmonology interventionists to practice to achieve consensus for each characteristic. In addition, we assigned video files to three pulmonology interventionists. Each video file was interpreted

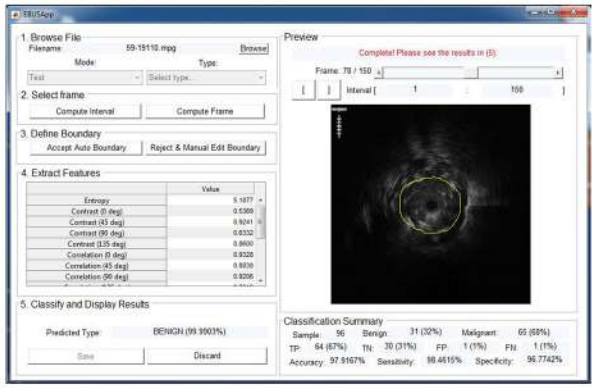
simultaneously and based on characteristics of EBUS pictures, i.e., heterogeneity, continuous margin, linear discrete air bronchogram, arcs, dots, anechoic and provisional diagnosis (benign or malignant). Their independently interpreted outcomes without knowing patients' medical record were compared. The agreement diagnoses of two of three pulmonary interventionists were compared with the pathological diagnosis to evaluate the sensitivity, specificity and accuracy.

Data interpretation using the Tumor Inspector Program, Ver.1

After patients underwent EBUS, videos were recorded at 4 cm in range. We selected file videos simultaneously and assigned three pulmonologists to interpret the outcomes. **Picture 1** shows the screen of the Tumor Inspector Program, Ver.1. The boundary was the next step that was chosen for an auto or manual boundary. In this study, we used a manual boundary and a region of interest, which was 2 cm in radius (or 4 cm in diameter) from the center. Using an auto boundary, a lesion that was larger than 4 cm in range could not be used. After completing the manual boundary, the Tumor Inspector Program, Ver.1 was used to analyze the outcome as shown in **Picture 2**. A circle was drawn five times for data analysis and the outcomes were chosen, which were predominant as a provisional diagnosis. Finally, we compared these outcomes with the pathological report to evaluate the sensitivity, specificity, negative predictive value and diagnostic accuracy.



Picture 1. Window of tumor inspector program, Version 1



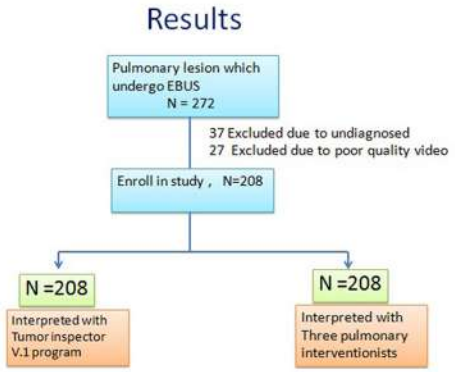
Picture 2. Window of tumor inspector program, Version 1

Data analysis

Categorical data were compared using Chi-square or Fisher's exact test. To determine the accuracy, sensitivity and specificity and differences between both groups, Pearson's Chi-squared test analysis was performed. Fisher's exact test was used for baseline characteristics, presented as mean, median (IQR; interquartile range) and proportion (%). For inter-observer correlation, 208 patients were analyzed using three different pulmonology interventionists. Inter-observer correlation was assessed by measuring outcomes which were interpreted by three pulmonology interventionists simultaneously. Inter-observer correlation coefficients were used at the following cut-off points; <0.5 = fair agreement, 0.51-0.75 = moderate agreement and >0.75 = substantial agreement. Statistical significance was set at p-value <0.05. Data analyses were performed using the SPSS, Version 23 and Stata, Version 14.

Results

Two hundred and seventy-two patients were screened for the inclusion criteria. Of these, 208 patients were enrolled in the study. Sixty-four patients were excluded because 37 had no pathological diagnosis and 27 had poor quality video files. Subject enrollment, exclusion and analyses are summarized in a flowchart **(Fig 1)**.



Baseline characteristics of patients are shown in **Table 1**. Most patients had age more than 60 years (58.65%), and mean age was 61.9 years. More than one half were male (60.58%), nonsmokers (40.87%), had no history of airway or structural lung diseases (87.02%) and no history of any cancers (83.65%).

Baseline characteristics of EBUS pictures are shown in **Table2**. Tumor sizes more than 3 cm totaled 55.7%. Most characteristics of EBUS pictures were heterogeneity (89.9%), incomplete margin (75.50%), present dots (54.3%), absent arcs (55.8%), absent air bronchogram (94.2%) and absent anechoic (63.8%). Statistically significant differences of the specificity, accuracy, positive predictive value and negative predictive value were observed between both methods. The specificity was higher using the interpretation by the program showing 22.5% by pulmonology interventionists' consensus and 81.25% using the Tumor Inspector Program, Ver.1 (p <0.001). The accuracy was higher using the program, i.e., 64.42% by pulmonology interventionists' consensus and 87.02% using the Tumor Inspector Program, Ver.1 (p <0.001). The positive predictive value (PPV) and negative predictive value (NPV) were higher using the program. In pulmonology interventionists' consensus, PPV and NPV were 65.2% and 60%, respectively while using the Tumor Inspector Program, Ver.1, PPV and NPV were 88.54% and 84.41%, respectively (p = <0.001 and 0.007, respectively). However, no significant difference in sensitivity was observed between the two methods. The sensitivity was 90.6%, performed by pulmonology interventionists and 90.62% using the Tumor Inspector Program, Ver.1 (p = 1.00) **(Table 3)**.

Table 1. Baseline characteristics of the enrolled patients

Characteristics		N	%	Mean
Age group	<30	7	3.37	
	31-60	79	37.98	
	>60	122	58.65	
Age				61.90
Sex	Male	126	60.58	
	Female	82	39.42	
Previous pulmonary disease	Old lung disease	11	5.29	
	Airway disease	16	7.69	
	No both	181	87.02	
Pulmonary disease	Asthma	2	0.96	
	Bronchiectasis	3	1.44	
	COPD	16	7.69	
	NTM or Pulmonary tuberculosis	2	0.96	
	Old pulmonary tuberculosis	4	1.92	
Smoking	Yes	34	16.35	
	No	85	40.87	
	Not record	29	13.94	
	Ex-smoker	60	28.85	
Previous Cancer	Present	34	16.35	
	Absent	174	83.65	

Table 2. Baseline characteristics of EBUS pictures

		N	%
Tumor size	<3 cm	92	44.23
	>=3	116	55.77
Echogenicity	Homogenous	21	10.10
	Heteogenous	187	89.90
Margin	Complete	51	24.50
	Incomplete	157	75.50
Dots	Yes	113	54.30
	No	95	45.70
Arcs	Yes	92	44.20
	No	116	55.80
Air bronchogram	Yes	12	5.80
	No	196	94.20
Anechoic	Yes	75	36.20
	No	132	63.80

Table 3. Sensitivity, specificity, accuracy, PPV and NPV between tumor inspector program and agreement of three pulmonology interventionists

	Pulmonology interventionists	Tumor inspector program	*p*-value
Sensitivity	90.60%	90.62%	1.00
Specificity	22.50%	81.25%	<0.001
Accuracy	64.42%	87.02%	<0.001
PPV	65.20%	88.54%	<0.001
NPV	60%	84.41%	0.007

In addition, we also analyzed the correlation among three pulmonology interventionists and predominant characteristics of EBUS pictures. For the inter-observer correlation, we found that each characteristic of EBUS pictures included echogenicity, dots and anechoic exhibiting fair agreement (ICC = 0.30, 0.43, and 0.46; $p = 0.001$, <0.001 and <0.001, respectively) and continuous margin, arcs and air bronchogram showed moderate agreement (ICC = 0.73, 0.60 and 0.52; all had p <0.001, respectively). Whereas, outcomes from each of three pulmonology interventionists revealed fair agreement (ICC= 0.14; $p = 0.098$), as shown in **Table 4**.

We also observed the predominant characteristic of EBUS pictures favoring malignancy from the interpretation using three pulmonology interventionists. No significant difference favoring malignancy was found among all characteristics of EBUS pictures . Heterogeneity was 90.63% in malignant cases and 88.75% in benign cases (p = 0.66; 95% CI = 0.49-3.05). Complete margin was 74.22% in malignant cases and 77.50% in benign cases which did not differ significantly (p = 0.88; 95% CI = 0.62-2.31). Linear discrete air bronchogram was 7.03% in malignant cases and 3.75% in benign cases (p = 0.28; 95% CI= 0.51-7.40), as shown in **Table 5**.

Table 4. Inter-observer correlation coefficient model among three pulmonology interventionists.

	ICC	**95%CI**		***p*-value**
Echogenicity	0.30	0.12	0.45	0.001
Margin	0.73	0.66	0.79	<0.001
Dots	0.43	0.28	0.55	<0.001
Arcs	0.60	0.50	0.69	<0.001
Air bronchogram	0.52	0.39	0.62	<0.001
Anechoic	0.49	0.35	0.60	<0.001
Outcome	0.14	-0.08	0.33	0.098

Table 5. Predominant characteristic patterns which favor benign or malignancy

		Pathology							
		Malignancy		Benign					
Human agreement		N	%	N	%	OR	95%CI		*p*-value
Echo	Heterogenous	116	90.63	71	88.75	1.26	0.49	3.05	0.660
	Homogenous	12	9.38	9	11.25				
Margin	Complete	33	74.22	62	77.50	1.20	0.62	2.31	0.880
	Incomplete	95	25.78	18	22.50				
Dot	Yes	70	54.69	43	53.75	1.04	0.59	1.82	0.900
	No	58	45.31	37	46.25				
Arcs	Yes	53	41.41	39	48.75	0.74	0.42	1.30	0.300
	No	75	58.59	41	51.25				
Air bronchogram	Yes	9	7.03	3	3.75	1.94	0.51	7.40	0.280
	No	119	92.97	77	96.25				
Anechoic	Yes	50	39.37	25	31.25	1.43	0.79	2.58	0.240
	No	77	60.63	55	68.75				

Discussion

This cross-sectional study investigated the accuracy of the first developed program (Tumor Inspector Program, Ver.1) which interpreted characteristics of EBUS pictures compared with agreements among three pulmonology interventionists. All enrolled patients underwent EBUS for the first time at Phramongkutklao Hospital from May 2015 to December 2016. In this study, we found that the interpretation between the Tumor Inspector Program, Ver.1 and the three pulmonology interventionists showed no significant difference for the sensitivity, but significantly differed in specificity, accuracy, positive predictive value and negative predictive value. These could be explained by the difference of experiences among the three pulmonology interventionists. Before reading all video files, case practices were preliminary provided for the three pulmonology interventionists. Using the Tumor Inspector Program, Ver.1 by one operator was more feasible and easy to perform because it did not depend on human experience. This program could be used as diagnostic test for pulmonary lesions among patients undergoing EBUS. In this study, fewer benign cases were enrolled; thus, we suggest using clinical characteristics, history of risk factors and tumor doubling time to follow up those cases presenting benign results. In addition, we also observed characteristics of EBUS pictures of malignant cases, reported by Kurimoto et al.[12] and Kuo et al.[13] In this study, the characteristics of EBUS pictures didn't reveal the predominant pattern favoring malignant or benign cases. These can be explained by the different experiences of the three pulmonology interventionists to read the video files because mild to moderate agreement was recorded.

In this study, an under diagnosis of benign pulmonary lesions could have occurred due to the fewer cases of benign lesions. In addition, cases presenting pulmonary lesions larger than 4 cm using the ultrasound range or cases having the ultrasound probe adjacent to the lesion could cause a problem when analyzing video files. Notably, the region of interest chosen was about 2 cm in diameter from the center. The Tumor Inspector Program Ver.2 was used to correct these weak points and gain more accuracy to detect benign pulmonary lesions. Thus, a further study is needed, which should be based on clinical manifestations, other risk factors, e.g., smoking behavior, history of contact tuberculosis, history of cancer, characteristics of CT lesion etc. However, limitations were observed in this study, that is, variable quality of video records as well as unequal experiences of the three pulmonology interventionists.

Conclusion

Among patients with pulmonary lesions, the Tumor Inspector Program, Ver.1 showed significantly higher accuracy to predict malignancy possibility than that of the three pulmonology interventionists.

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