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Original Research Article

Analysis of positive predictors in diagnosing lung cancer on transthoracic and transbronchial procedure

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ABSTRACT

Background: Lung cancer remains the most cause of death due to cancer. Due to high mortality rate of lung cancer, early diagnosis of lung cancer plays a very important role in therapeutic management. Clinical symptoms and tumor characteristics such as size and location are found to vary in lung cancer patients. Various modalities can be used to obtain materials or samples include transthoracic and transbronchial methods. Research was conducted to analyze positive predictors of cancer between transthoracic and transbronchial procedures in lung cancer patients.
Methods: This research is an analytical observational study with a cross-sectional design in using secondary data through medical records from January 2022 to December 2023. Univariate analysis presents data in the form of frequency, mean and standard deviation. Bivariate analysis was carried out using chi-square and multivariate analysis using multiple logistic regression. The measure used as a predictor is the adjusted odds ratio. Inference or conclusion is based on the 95% confident interval and p value at the alpha value limit of 0.05. The entire data process above uses SPSS 26.0 statistical software
Results: The total research subjects who met the research requirements were 111 patients. The characteristics of the research subjects were symptoms of cough (n=97; 87.4%), hemoptyisis (n=51; 45.9%), breathlessness (n=104; 93.7%) and chest pain (n=87; 78.4%), mostly peripheral tumor (n=70; 63.1%) and size >3 cm (n=103; 92.8%). Logistic regression analysis showed cough symptoms and peripheral tumor location each had an adjOR value of 5.247 (95% CI 1.432-19.552; p=0.013) and adjOR 0.088 (95% CI 0.034-0.229; p=0.000) for lung cancer positivity on transbronchial procedure. On transthoracic procedure, cough symptoms and peripheral tumor location respectively had an adjOR value of 0.190 (95% CI 0.051-0.703; p=0.013) and adjOR 11.407 (95% CI 4.374-29.747; p=0.000) for lung cancer positivity.
Conclusions: Cough is a positive predictor of lung cancer in transbronchial procedures. Meanwhile, peripheral tumor location is a positive predictor of lung cancer in transthoracic procedures.

Keywords: Clinical symptoms, Breathlessness, Cough, Hemoptyisis, Chest pain, Transbronchial, Transthoracic, Positivity, Lung cancer

INTRODUCTION

Lung cancer remains the main cause of cancer deaths, with an estimated 1.8 million deaths (18%), followed by colorectal (9.4%), liver (8.3%), colon (7.7%) and breast cancer in women (6.9%). The overall incidence is 2-fold to 3-fold higher in developing countries compared to developing countries, mortality rates vary <2-fold for men and less for women.[1] Considering the high mortality rate of lung cancer, early diagnosis plays a very important role in lung cancer management.

Symptoms of malignant lung lesions depend on the initial location, tumor size, and involvement of surrounding structures. Typically, tumor location is classified as central (endobronchial or mediastinal) or peripheral (distal to the greater bronchus, pleura, or chest wall). Local growth of centrally or peripherally located malignant lung lesions can both cause symptoms such as coughing, hemoptysis and breathlessness. Peripheral malignant lung lesions may be associated with the pleura or chest wall (or both).[2,3] Apart from clinical symptoms, characteristics of tumor can also support malignancy, including unclear borders or irregular edges and sometimes accompanied by pleural indentation which can be found on additional procedures, both chest X-rays and chest CT scans. A thoracic CT scan with contrast can detect tumors less than 1 cm in size and can also determine the size, location and characteristics of the primary tumor better. In terms of size, a lesion less than 3 cm is called a nodule and a mass if the size of the lesion is more than 3 cm.

Various modalities that can be used to obtain samples include transthoracic and transbronchial methods. Transthoracic modalities consist of transthoracic needle aspiration (TTNA) biopsy, core biopsy, thoracentesis, closed pleural biopsy, and video-assisted tomography surgery (VATS). The sensitivity and specificity of TTNA are higher in diagnosing lung cancer with peripheral lesions compared to bronchoscopy.[4] VATS has now become an invaluable modality in diagnosing lung cancer. Many studies show that lung biopsy using the VATS method has sensitivity and specificity approaching 100%. Failure occurs mainly in small nodules located deep in the lung parenchyma.[5] The next modality is transbronchial which can be done at RSUP Prof. DR. I.G.N.G Ngoerah namely bronchoscopy (bronchial lavage, bronchial brushing, bronchial forceps) and non-invasive modalities such as sputum cytology.

The accuracy of cytological and histopathological procedure of bronchial brushes in lung cancer patients in several hospitals in Jakarta was found to have a sensitivity value of 45.5-50%.[6,7] Sputum cytology is very useful in patients with centrally located tumors (e. g., SCLC or squamous carcinoma). Of the 17 studies that provided data on sputum cytology characteristics for the diagnosis of suspected lung cancer, sensitivity ranged from 0.42 to 0.97; the specificity ranges from 0.68 to 1.0.[2]

Choosing the right procedure can determine lung cancer diagnosis early so that patients have a better quality of life. This became the author's basis for analyzing positive predictors of cancer between transthoracic and transbronchial procedures in lung cancer patients at RSUP Prof. DR. I.G.N.G Ngoerah Denpasar for the period January 2022- December 2023.

METHODS

This research is an analytical observational study with a cross-sectional design in Prof. Dr. I.G.N.G. Ngoerah hospital, Bali using secondary data through medical records from January 2022 to December 2023.

Inclusion criteria

Subjects aged ≥ 18 years had lung cancer; have the results of a thoracic CT scan with contrast in the period January 2022 to December 2023; undergo transthoracic and transbronchial procedures in the period January 2022 to December 2023 were included.

Exclusion criteria

Subjects with incomplete medical record data were excluded.

Data analysis

Univariate analysis presents data in the form of frequency, mean and standard deviation. Bivariate analysis was carried out using chi-square and multivariate analysis using multiple logistic regression. The measure used as a predictor is the adjusted odds ratio. Inference or conclusion is based on the 95% confident interval and p value at the alpha value limit of 0.05. The entire data process above uses SPSS 26.0 statistical software

RESULTS

The total research subjects who met the research requirements were 111 patients. The characteristics of the research subjects (Table 1) were symptoms of cough (n=97; 87.4%), hemoptysis (n=51; 45.9%), breathlessness (n=104; 93.7%) and chest pain (n=87 people; 78.4%). Subjects were predominantly with peripheral tumor (63.1%) and tumor size >3 cm (92.8%). Majority of subjects had adenocarcinoma as lung cancer histology.

In this study, subjects underwent both transthoracic and transbronchial procedure to obtain samples. Based on Table 2, most of the subjects were diagnosed by transthoracic procedure (62,2%) with the most common method being TTNA (41.4%). Meanwhile, the remaining subjects were diagnosed with lung cancer by bronchoscopy with combination of washing+brushing method being the most common (n=21).

Bivariate analysis in table 4 and 6 demonstrated significant relationship between peripheral tumor and lung cancer positivity on both transbronchial and transthoracic procedure. Our study did not find significant relationship between clinical symptoms (Tabel 3 and 5) and lung cancer positivity on both procedures.

Based on the results of multivariate analysis in this study in table 7 and 8, it was found that cough and peripheral tumor have a significant relationship with lung cancer positivity on both procedures.

Table 1: Characteristics of research subjects.

Characteristics	N (%)
Age (in years)	
Mean±SD	58.04±10.437
Sex	
Male	57 (51.4)
Female	54 (48.6)
Clinical symptoms	
Cough	97 (87.4)
Hemoptysis	51 (45.9)
Breathlessness	104 (93.7)
Chest pain	87 (78.4)
Tumor location	
Central	41 (36.9)
Peripheral	70 (63.1)
Tumor size	
>3 cm	103 (92.8)
<3 cm	8 (7.2)
Histological type	
Adenocarcinoma	91 (59.9)
Squamous cell carcinoma	12 (7.9)
Adenosquamous carcinoma	8 (5.3)

Table 2: Lung cancer positivity based on transthoracic and transbronchial procedure.

Procedure	N (%)
Transthoracic procedure	69 (62.2)
TTNA	46
Core biopsy	4
Pleural punction	9
Pleural biopsy	1
VATS biopsy	9
Transbronchial procedure	42 (37.8)
Bronchoscopy	42
Washing	13
Washing+ brushing	21
Washing+ brushing+forceps	8
Sputum cytology	0 (0)

Table 3: Bivariate analysis of clinical symptoms with lung cancer positivity on transbronchial procedure.

Clinical symptom	Lung positivity on transbronchial procedure, N (%)		OR (CI 95%)	P value
	Positive	Negative		
Cough				
Yes	34 (35.1)	63 (64.9)	0.405 (0.130-1.263)	0.111
No	8 (57.1)	6 (42.9)		
Hemoptysis				
Yes	18 (35.3)	33 (64.7)	0.818 (0.378-1.771)	0.610
No	24 (40.0)	36 (60.0)		
Breathlessness				
Yes	38 (36.5)	66 (63.5)	0.432 (0.092-2.033)	0.243
No	4 (57.1)	3 (42.9)		
Chest pain				
Yes	34 (39.1)	53 (60.9)	1.283 (0.495-3.323)	0.607
No	8 (33.3)	16 (66.7)		

Table 4: Bivariate analysis of tumor characteristics with lung cancer positivity on transbronchial procedure.

Tumor characteristic	Lung positivity on transbronchial procedure, N (%)		OR (CI 95%)	P value
	Positive	Negative		
Size				
>3 cm	38 (36.9)	65 (63.1)	0.585 (0.138-2.474)	0.462
<3 cm	4 (50.0)	4 (50.0)		
Location				
Peripheral	14 (20.0)	56 (80.0)	0.116 (0.048-0.280)	0.000
Central	28 (68.3)	13 (31.7)		

Table 5: Bivariate analysis of clinical symptoms with lung cancer positivity on transthoracic procedure.

Clinical symptom	Lung positivity on transthoracic procedure, N (%)		OR (CI 95%)	P value
	Positive	Negative		
Cough				
Yes	63 (64.9)	34 (35.1)	2.471 (0.792-7.707)	0.111
No	6 (42.9)	8 (57.1)		
Hemoptysis				
Yes	33 (64.7)	18 (35.3)	1.222 (0.565-2.646)	0.610
No	36 (60.0)	24 (40.0)		
Breathlessness				
Yes	66 (63.5)	38 (36.5)	2.316 (0.492-10.902)	0.243
No	3 (42.9)	4 (57.1)		
Chest pain				
Yes	53 (60.9)	34 (39.1)	0.779 (0.301-2.019)	0.607
No	16 (66.7)	8 (33.3)		

Table 6: Bivariate analysis of clinical symptoms with lung cancer positivity on transthoracic procedure.

Tumor characteristic	Lung positivity on transthoracic procedure, N (%)		OR (CI 95%)	P value
	Positive	Negative		
Size				
>3 cm	65 (63.1)	38 (36.9)	1.711 (0.404-7.238)	0.462
<3 cm	4 (50.0)	4 (50.0)		
Location				
Peripheral	56 (80.0)	14 (20.0)	8.615 (3.571-20.786)	0.00
Central	13 (31.7)	28 (68.3)		

Tabel 7: Multivariate logistic regression analysis of clinical symptoms and tumor characteristics with lung cancer positivity on transbronchial procedure.

Variables	adjOR	CI 95%	P value
Cough	5.247	1.432-19.552	0.013*
Hemoptysis	2.043	0.776-5.381	0.148
Breathlessness	4.405	0.029-0.207	0.099
Chest pain	1.380	0.430-4.427	0.588
Peripheral tumor	0.088	0.034-0.229	0.000*
Tumor size >3 cm	0.800	0.206-7.738	0.800

*Has a significant influence ($p<0.05$).

Tabel 8: Multivariate logistic regression analysis of clinical symptoms and tumor characteristics with lung cancer positivity on transthoracic procedure.

Variables	adjOR	CI 95%	P value
Cough	0.190	0.051-0.703	0.013*
Hemoptysis	0.489	0.186-1.289	0.148
Breathlessness	0.227	0.039-1.325	0.099
Chest pain	0.725	0.226-2.325	0.588

Continued.

Variables	adjOR	CI 95%	P value
Peripheral tumor	11.407	4.374-29.747	0.000*
Tumor size >3cm	0.791	0.129-4.846	0.800

*Has a significant influence (p<0.05).

DISCUSSION

Lung cancer remains the leading cause of cancer deaths, with an estimated 1.8 million (18%) deaths. The prevalence of cancer in Indonesia increased from 1.4 per 1000 population in 2013 to 1.79 per 1000 population in 2018. The diagnosis of lung cancer needs to be carried out as soon as possible in order to increase patient survival rates. Therefore, choosing the correct modality to make a correct diagnosis faster is necessary. This study analyzes subjects with lung cancer who were diagnosed using transthoracic and transbronchial modalities.

Based on age characteristics, the subjects had a mean age of 58.04±10.437 (Table 1). These results are not much different from three previous studies on lung cancer patients at Prof Ngoerah hospital, Bali.[8-11] As many as 90% of lung cancer patients are over 40 years old when diagnosed with lung cancer.[12]

In this study, number of male subjects were higher than females one (Table 1). Previous research at Prof. Ngoerah general hospital also obtained similar results.[13] The incidence of lung cancer was found to be more frequent in men namely 19.4 per 100,000 population with an average death rate of 10.9 per 100,000 population.[14]

Based on the characteristics of clinical symptoms, subjects in this study mostly complained coughing, breathlessness and chest pain. Chronic cough was the first symptom reported most frequently (39.6%) by lung cancer patients at Prof. Ngoerah hospital based on previous study.[11] This is in line with previous cross-sectional research (n=400) where 80% of lung cancer patients complained of cough symptoms and 64.8% of them had a persistent cough.[15] Another study with a sample size of 400 found that more than 95% of lung cancer patients experienced symptoms of breathlessness.[16] Latest cohort study with a sample of 13,159 NSCLC patients reported that 71.7% (n=9,434) of patients experienced symptoms of moderate to severe breathlessness.[17] A study found that 6.3% of their research sample with lung cancer complained chest pain as their first symptoms. Chest pain can be caused by several factors such as local invasion of the tumor or regional spread to the pleura or chest wall and nerve compression due to the size and location of the tumor.[11]

In this study, fewer subjects suffered from hemoptysis. According to previous research, hemoptysis in lung cancer patients accounted for around 20% of cases and massive coughing up of blood tended to be found in lung cancer patients whose tumors were centrally located; there is spread to the main airway or a cavitary lesion.

Based on tumor characteristics, majority of subjects in this study had peripheral tumors (n=70; 63.1%) and were >3 cm in size (n=103; 92.8%). A study with lung cancer patients predominantly had adenocarcinoma as histological type, showed that the most common tumor sizes were 20 to <30 mm and >40 mm.[18]

Predictor of lung cancer positivity on transbronchial procedure

In this study, there was a relationship between coughing and positive lung cancer in transbronchial procedures. The cough group had a 5.247 times higher risk of being positive for lung cancer in the transbronchial approach (95% CI 1.432-19.552; p=0.013). Cough is the main symptom found in central location primary lung cancer patients (37.1%) who underwent diagnosis via bronchoscopy procedure.[19]

In this study, there was no association between the symptom of hemoptysis and lung cancer positivity on transbronchial procedure. This result may be cause by the operational definition of hemoptysis in this study is only the presence or absence of coughing up blood without explaining the duration and volume of hemoptysis. Meanwhile, in the study about the relationship between symptoms of coughing up blood in lung cancer patients diagnosed by bronchoscopy, the majority of patients (64%) had persistent symptoms of hemoptysis for more than two weeks (p=0.0001).[20]

The insignificance of other clinical symptoms may be caused by uncontrolled factors such as hoarseness, decreased appetite, fatigue and others. Respiratory symptoms have a low diagnostic rate for lung cancer.[21] Symptoms such as hemoptysis, breathlessness and chest pain are also often found in other lung diseases such as tuberculosis infection, bronchiectasis and diseases caused by other processes. Therefore, it needs to be combined with systemic symptoms and also based on laboratory results. In addition, the stage of cancer when the patient is diagnosed and the histology type of cancer can also influence the appearance of symptoms in lung cancer patients.[22-23]

Peripheral tumor locations had a lower risk of lung cancer positivity on transbronchial procedure (adjOR 0.088; 95% CI 0.034-0.229; p=0.000). These results are supported by several studies. The diagnostic sensitivity of conventional flexible bronchoscopy was found to be low for the diagnosis of lung cancer in patients with peripheral lung tumors (57%=TBLB; 43%=BAL/washing).[24] Research by Silvestri et al also found a lower diagnostic value for patients with peripheral tumor lesions (50%) compared to

the group with central one (75%) (p<0.001).[25] Meanwhile, research at Persahabatan hospital, Jakarta, found that the accuracy of bronchoscopy was quite good in determining centrally located lung cancer, where 86.6% were diagnosed using the forceps biopsy method, 81.8% brushing method and 69.0% conventional TBNA method.[19]

Several factors can explain why peripheral tumor locations have a lower risk of lung cancer positivity on bronchoscopy procedure. First, peripheral tumor lesions require more modern bronchoscopy methods such as electromagnetic navigation (EMN) to increase the cancer detection rate while in this study only used conventional methods, making it more difficult. The use of EBUS and EMN in bronchoscopy increases the diagnostic yield of lung cancer by 73% and 71%. Second, the small size of peripheral tumors can reduce the detection rate of lung cancer during bronchoscopy procedure. The size of peripheral tumor lesions with a diameter of <2 cm is reported to reduce the sensitivity of bronchoscopy procedure.[24] The diagnostic value of bronchoscopy is lower in the group of patients with peripheral tumor size ≤2 cm (43%) compared to the group with peripheral tumor size > 2 cm (63.1%) (p<0.0001).[26]

In this study, no association was found between tumor size and lung cancer positivity in transbronchial procedures. The reason may be because in this study the majority of patients had peripheral lung tumors, although most were more than 3 cm in size. Meanwhile, sampling for bronchoscopy procedure only uses conventional methods where the bronchoscope is only able to reach subsegmental bronchi. Conventional bronchoscopy has good diagnostic value for lung lesions located in the proximal bronchial tree, but this diagnostic value decreases to 14% in lesions located in the 5th generation bronchi and their branches. Using this method, it is difficult to get cancer cells in patients whose lesions are more than 3 cm but are located on the periphery.[27] The sensitivity of conventional bronchoscopy for peripheral bronchogenic carcinoma with a size of >20 mm is only 63%.[28] The diameter of the bronchoscope used also influences lung cancer positivity. Research by Lee et al found that the diagnostic value of lung cancer was higher in the group of patients with peripheral lung tumor measuring 3-4 cm and 4-6 cm using a bronchoscope with a diameter of 4.9 mm (57.1%; 52.0%) compared to with a diameter of 5.1 mm (37.9%; 33.3%). Bronchoscopes with smaller diameters make it easier for operators to reach peripheral tumor lesions.[29]

Predictor of lung cancer positivity on transthoracic procedure

In this study, cough had a significant relationship with lung cancer positivity on transthoracic procedure (OR 0.190; 95% CI 0.051-0.703; p=0.013). The group with cough had a lower risk of getting positive lung cancer status on transthoracic procedure compared to the group without cough. This is supported by previous research where in peripheral lung cancer patient by transthoracic procedure, only 18.5% had cough while 48.1% had no symptoms and were diagnosed incidentally.[30] These results may be due to the pathophysiology of the cough itself. Cough are more often associated with problems in the respiratory tract. The respiratory tract has more cough receptors than the lung parenchyma.[31] In this study, most of the research subjects had tumor locations in the lung parenchyma, so this may be the reason why cough symptoms are not a positive predictor for cancer. However, this study did not divide cough symptoms based on etiology so it is necessary to carry out further studies with a larger number of samples to examine whether there is a relationship between cough symptoms and lung cancer caused by other etiologies such as extrapulmonary pressure such as pleural effusion or chest wall tumors and as a result of radiation or chemotherapy.[32]

In this study, the group with peripheral tumor was 11.407 times more likely to get a positive result for lung cancer than the group with central one on transthoracic procedure (95% CI 4.374-29.747; p=0.000). These results are supported by previous research by Zhu et al which examined the detection rate of lung cancer with CT TTNA where the distance between the pleura and the tumor lesion was <100 mm increasing the chance of obtaining sufficient biopsy samples.[18] USG TTNA has a good diagnostic value for lung cancer in patients with peripheral lung tumors, namely 80.7% and increases in patients with tumor lesions > 2 cm in diameter (p=0.03).[33] Another study found that Electromagnetic guiding TTNA had good diagnostic value (83%) in patients with peripheral pulmonary nodules.[34] In patients with malignant pleural effusion, pleural fluid cytology is reported to have a mean sensitivity of 72%. The diagnostic rate of closed pleural biopsy ranges from 38% to 47% and from 75% to 88% for imaging-guided closed biopsy.[24]

In this study, no relationship was found between tumor size and lung cancer positivity in transthoracic procedures. This result may be because this study did not control for confounding factors such as the extent of ground glass opacity (GGO) and the presence or absence of obstructive pneumonitis from chest CT scan images. The appearance of a lung tumor accompanied by a GGO area of more than 50% indicates a less invasive nature of the tumor. Meanwhile, the presence of obstructive pneumonitis makes it difficult to identify tumor location. This causes an increase in the failure rate for TTLB procedure in tumor patients. In previous research, GGO area >50% and the presence of obstructive pneumonitis significantly reduced the diagnostic value of lung cancer in patients with lung tumors measuring >3 cm with an OR of 7.534 (95% CI 2.806-20.225) respectively, p<0.001 and OR=2.310 (1.533-3.481), p<0.001.[35]

This research has several strengths. First, this study to analyze positive predictors of lung cancer using transbronchial and transthoracic procedure in Bali. Second, the results of this research can provide

information and input in selecting the procedure that needs to be carried out first in order to shorten diagnostic time of lung cancer. In this way, lung cancer patients can be treated immediately.

Limitations

This study used secondary data taken from medical records. Second, not all bronchial sampling methods (brushing, forceps, bronchial lavage) were carried out on each subject so the number of specimens was limited. Third, systemic symptoms that are often found in patients with lung cancer such as decreased appetite and fatigue are not controlled as confounding variables.

CONCLUSION

Cough is a positive predictor of lung cancer in transbronchial procedures. Meanwhile, peripheral tumor location is a positive predictor of lung cancer in transthoracic procedures.

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