



Comparison of the Effectiveness of the Cell Block Method with Core Tissue Biopsy for Adequate Diagnosis of Lung Malignant

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Abstract

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BACKGROUND: An adequate diagnosis of lung malignancy can be detected through examination of pleural fluid and transthoracic needle aspiration (TTNA) based on the cell block method and tissue core biopsy. The cell block method is an immunocytochemical examination method that is useful for the adequate diagnosis of lung malignancy.

AIM: This study was to compare the effectiveness of the cell block method with tissue core biopsy on pleural fluid cytology and TTNA cytology to establish the diagnosis of lung malignancy.

METHODS: This study is a diagnostic test with an analytical cross-sectional approach on 15 respondents suspected of lung cancer at Dr. Moewardi Hospital, Surakarta, in September 2021. Subjects underwent pleural fluid cytology, TTNA cytology based on the cell block method, and tissue core biopsy examination. Data analysis used the kappa test and bivariate analysis to calculate the p-value.

RESULTS: The results of the combined examination of pleural fluid cytology and TTNA cytology based on the cell block method gave a very good level of conformity to the tissue core biopsy with a kappa value of 0.857 and $p = 0.001$. The results of the combined examination of pleural fluid cytology and TTNA cytology with cell block method showed the highest percentage for sensitivity (100%), NPV (100%), and accuracy (93%); while the results of the TTNA cytology examination using the cell block method showed the highest percentage of specificity (100%) and PPV (100%) of the tissue core biopsy method.

CONCLUSION: The cell block method is very effective and significant in assessing the results of combined pleural fluid cytology and TTNA cytology against the tissue core biopsy method so that it is useful for the adequate diagnosis of lung malignancy.

Introduction

The incidence of cancer cases is growing rapidly worldwide. The Global Burden of Cancer Study (GLOBOCAN) in 2018 reported that the incidence of lung cancer was in the first rank of malignancy in the entire world population, which was 11.6% or 2,093,876 patients. Epidemiological data of lung cancer show a trend of increasing cases through research at the Friendship Hospital in 2005 with 140 cases, in 2006 with 218 cases, and in 2007 with 282 cases. Friendship Hospital data reported the finding of malignant cells in the pleural effusion fluid in 52.4% of cases of malignancy with the type of adenocarcinoma being 40%. Cell block extract of pleural effusion fluid can be used for cytological analysis based on immunohistochemistry and molecular. Immunostaining (IMS) examination on cell block preparations can be used to check the status of human epidermal growth factor receptor 2 (HER2). Cell block examination can be used as an immunohistochemical examination material that contributes to immunotherapy in lung cancer [1], [2], [3], [4], [5], [6], [7].

Primary lung cancer is malignant cancer originating from the bronchial epithelium or bronchial

carcinoma (bronchogenic carcinoma). Lung cancer is divided into subtypes: Lung cancer non-small cell carcinoma (KPKBSK) and lung cancer small cell carcinoma (KPKSK). The clinical manifestations of primary lung cancer depend on the location. Signs and symptoms of lung cancer are caused by local tumor growth, invasion, obstruction of adjacent structures, regional lymph node enlargement through the lymphatic spread, distant metastatic growth through the hematogenous spread, and paraneoplastic syndromes. Lung tumors are small and located peripherally can give a normal appearance on physical examination. Large tumors with atelectasis, pleural effusion, venous compression, and nerve tissue compression can provide more informative value in the diagnosis of lung cancer. Laboratory tests are needed to evaluate the presence of paraneoplastic syndromes, the requirements for diagnostic invasive procedures, and the examination of serum tumor markers. Diagnostic modalities used in diagnosing pulmonary nodules in the middle of the lung tissue are bronchial lavage, bronchial brushing, forceps biopsy, and transbronchial lung biopsy (TBLB). Nodules measuring more than 3 cm and located in the periphery can be performed percutaneous biopsy procedures with TTNA, transthoracic biopsy (TTB),

fine-needle aspiration (AJH), core biopsy, and pleural biopsy. Invasive biopsy procedures can be performed with pleuroscopy, video-assisted thoracoscopic surgery (VATS), and thoracotomy [5], [8].

Research on the effectiveness of the cell block method on immunocytochemical examination of pleural fluid and core biopsy transthoracic needle aspiration (TTNA) can be used to diagnose lung cancer, is a new thing, and has never been done in Indonesia. The cell block method has many advantages, namely, being representative with high accuracy so that it can be used as early detection of lung cancer, avoiding repeated tissue sampling, thereby reducing the risk of pneumothorax complications and the occurrence of pulmonary parenchymal bleeding complications in the transthoracic biopsy (TTB) procedure with a core biopsy needle [7], [8], [9].

This study aims to determine the effectiveness of the cell block method on cytological examination of pleural fluid and TTNA against the tissue core biopsy method for adequate diagnosis of lung malignancy. The results of the study can contribute scientific information, basic data for further research, early detection of lung malignancy, and alternative procedures for taking small tissue specimens in clinical conditions that radiologically cannot be applied using the TTB procedure with core biopsy.

Methods

This study is a diagnostic test with an analytical cross-sectional approach on cytological examination of pleural fluid and TTNA based on the cell block method to the tissue core biopsy method to diagnose lung malignancy. Respondents were patients diagnosed with lung cancer who had undergone thoracentesis, TTNA, and tissue core biopsy procedures at Dr. Moewardi Hospital, Surakarta, as a patient who came for treatment and/or underwent lung cancer treatment during September 2021. The sample used in this study was from the respondents based on the inclusion criteria.

Patients diagnosed with suspected pulmonary malignancy from the history, physical examination, and supporting chest X-ray and chest CT scan showed pleural effusion accompanied by a tumor mass picture of peripheral lesions and underwent thoracentesis or water-sealed drainage (WSD) procedures, TTNA, and core biopsy. Thoracentesis is a diagnostic and therapeutic procedure of taking fluid in the pleural cavity percutaneously from the chest wall using a 14G size needle equipped with a negative pressure syringe with or without imaging modalities for therapeutic purposes, pleural fluid analysis, cytologic examination, and microbiological examination. WSD is the act of draining air or fluid quickly and continuously from the pleural cavity followed by the installation of a pipe or hose

with the aim of introducing drugs into the pleural cavity, removing air from the pleural cavity, and removing fluid from the pleural cavity. Transthoracic needle aspiration is a diagnostic procedure for percutaneous thoracic wall sampling of peripheral lung tumors using a 25G needle for cytologic examination using local infiltration anesthesia. The TTNA procedure in this study utilized a thoracic CT scan imaging guide. The specimens from the TTNA examination with the guidance of a chest CT scan were rinsed using a 50% alcohol solution to be used as material for the cell block method. The main principles of the cell block method include centrifugation, removal of the supernatant, fixation of cellular grains, manufacture of cassettes, immersion in paraffin, and tissue processing. The cell block method has the advantages of high concentrations of cellular components tissue description of cytological components, can explain small fragments, and documentation for future examinations. The results of other studies show that TTNA cytologic examination based on the cell block method has a lung cancer cell finding rate of 57.7% [13], [14]. Core needle biopsy is a diagnostic measure of percutaneous sampling through the thoracic wall of peripheral lung tumors using a core biopsy needle size of 18G using local infiltration anesthesia for histopathological examination of tissue with hematoxylin-eosin staining. Cell block is a sample examination using cytological specimens of pleural fluid and small tissue resulting from transthoracic needle aspiration/TTNA processed in paraffin blocks [15].

The sampling technique was consecutive sampling that met the inclusion criteria of 15 patients. Inclusion criteria were patients aged at least 18 years, chest X-ray and chest computer tomography (CT) scan showed pleural effusion accompanied by a peripheral lesion tumor mass and underwent thoracentesis or water-sealed drainage (WSD) procedures, TTNA, and core biopsy who were willing to participate in this study. Exclusion criteria were lung tumor patients with signs of sepsis, history of chemotherapy and/or radiotherapy, thrombocytopenia less than 50,000, international normalized ratio (INR) <1.5, use of mechanical ventilation, history of contralateral pneumonectomy, symptomatic heart failure, uncontrolled cough, and/or no cooperative, suspected hydatid cyst, arteriovenous malformation, bullae around tumor lesions, and mediastinal tumors [10], [11], [12].

The specimens from the TTNA examination with the guidance of a CT scan of the thorax were rinsed using a 50% alcohol solution to be used as material for the cell block method. The main principles of the cell block method include centrifugation, removal of supernatant, fixation of cellular grains, manufacture of cassettes, immersion in paraffin, and tissue processing [6].

Histological examination of tissue by core biopsy is used as the standard for the examination of lung malignancies which is an action guided by the CT scan modality which is usually done at RSDM,

Surakarta. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of the cell block method on pleural fluid cytology or TTNA cytology or a combination of both are based on the cell block method for tissue core biopsy based on the percentage of cross-tabulation results.

Descriptive or univariate analysis for numerical data is presented in terms of mean \pm standard deviation, while for categorical data, it is presented with frequency distribution and percentage. Statistical analysis of the suitability of the results of pleural fluid cytology and TTNA based on the cell block method to the tissue core biopsy using the kappa test; with the criteria, if the kappa value is 0.00–0.200: The suitability is very weak, the kappa value is 0.200–0.400: The suitability is weak; kappa value 0.400–0.600: Moderate suitability; kappa value 0.600–0.800: High suitability; and kappa value 0.800–1000: Very high or excellent fit. Bivariate analysis determines the p-value; if $p < 0.05$ was considered, it means statistically significant. Data analysis using SPSS version 21 for Windows.

The research was carried out after obtaining an Ethical Clearance Letter from the Health Research Ethics Commission, Dr. Moewardi General Hospital, Surakarta, number: 870/IX/HREC/2021.

Results

The study involved 18 patients with a working diagnosis of lung cancer who underwent thoracentesis or WSD, TTNA, and core biopsy procedures at RSDM, Surakarta. In this study, there were three subjects with low-grade thymoma results so it included the study exclusion criteria. The description of the characteristics of the 15 research subjects who met the research inclusion criteria is shown in Table 1 as follows.

Based on Table 1, it is known that patients with an average age of 51.00 ± 14.273 years, male gender, namely, 9 (60%) and female 6 patients (40%), average weight 53.87 ± 6.567 kg, average height-average 161 ± 6.256 cm, body mass index (BMI) was mostly normal, there were 12 patients (80%), the education level of most high school students was 6 people (40%), most of the workers were 4 people (26, 7%), comorbidities that often appear are hypertension, namely, 4 people (26.7%), the diagnosis that is often found in lung malignancies is adenocarcinoma, namely, 9 people (60%).

Description of lung malignancy based on cytological examination of pleural fluid, TTNA, and their combination using the cell block method on tissue histology by core biopsy is listed in Table 2.

Table 2 shows that there is a significant difference in $p < 0.05$ in the results of pulmonary malignancy based on pleural fluid cytology, TTNA, and

Table 1: Characteristics of respondents

Characteristics	Results (n = 15)
Age	51.00 \pm 14.273 years
Height	161.00 \pm 6.256 cm
Weight	53.87 \pm 6.567 kg
Gender	
Male	9 (60%)
Female	6 (40%)
BMI	
Low	1 (6.7%)
Normal	12 (80%)
High	2 (13.3%)
Education	
Elementary school	4 (26.7%)
Junior high school	2 (13.3%)
High school	6 (40.0%)
College	3 (20%)
Profession	
Labor	4 (26.7%)
Teacher	1 (6.7%)
Trader	2 (13.3%)
Farmer	2 (13.3%)
Civil servant	1 (6.7%)
Artist	1 (6.7%)
Non-civil	3 (20%)
Self-employed	1 (6.7%)
Comorbidities	
Adeno sinus nasal	1 (6.7%)
Diabetes mellitus	1 (6.7%)
Hypertension	4 (26.7%)
Brain metastases	1 (6.7%)
None	11 (61.1%)
Lung malignancy	
Adenocarcinoma	9 (60%)
Non-lung malignancy	
Non-malignant cells	6 (40%)

a combination of the two based on the cell block method against the tissue core biopsy method. The analysis was used to determine the level of conformity of the results of pleural fluid cytology, TTNA cytology, and a combination of the two based on the cell block method of tissue core biopsy for the diagnosis of lung malignancy using the kappa suitability test. Based on Table 2, the results of the combined pleural fluid cytology and TTNA cytology based on the cell block method gave a very good level of conformity to the histology of the core biopsy tissue with a kappa value = 0.857 (very high concordance) and $p = 0.001$ ($p < 0.05$). The suitability of the results of pleural fluid cytology with the cell block method showed kappa value = 0.595 (moderate agreement) and $p = 0.02$ ($p < 0.05$). While the suitability of the results of the TTNA cytology examination with the cell block method showed a kappa value = 0.737 (good fit) with $p = 0.003$ ($p < 0.05$).

Table 2: Description of lung malignancy based on cytological examination of pleural fluid, TTNA, and a combination of the two based on the cell block method for tissue core biopsy

No.	Examination method	Lung malignancy	Non-lung malignancy	Kappa	p value
1	Pleural fluid cytology cell block method	8	7	0.595	0.02
2	Core biopsy tissue	9	6	0.737	0.003
	Cytology of TTNA cell block method	7	8		
3	Core biopsy tissue	9	6	0.857	0.001*
	Pleural fluid cytology and TTNA cytology cell block method	10	5		
	Core biopsy tissue	9	6		

The results of cytological examination of pleural fluid and TTNA or a combination of both using the cell block method can be used to determine the percentage of sensitivity, specificity, PPV, NPV and accuracy based on Crostab analysis as listed in Table 3.

Table 3: Results of sensitivity, specificity, PPV, NPV, and accuracy of pleural fluid cytology examination results, TTNA, and their combination based on the cell block method for tissue core biopsy

Examination method	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Pleural fluid cytology cell block method	77.8	83.5	87.5	71.4	80
TTNA cytology cell block method	77.8	100	100	75	86.7
Pleural fluid cytology and TTNA cytology cell block method	100	83.3	90	100	93

Based on Table 3, it is known that the results of the combined pleural fluid cytology and TTNA cytology using the cell block method showed the highest percentage of sensitivity (100%), NPV (100%), and accuracy (93%) while the results of TTNA cytology using the cell block method showed the highest percentage of specificity (100%) and PPV (100%) on tissue histology examination with core biopsy method.

Discussion

The results show the characteristics of the respondents in Table 2, namely based on gender there are 9 persons male (60%), with an average weight of 53.87 Kg; the average height is 161.00 cm, the highest BMI is in the normal category - 12 people (80%), the highest education is high school - 6 people (40%); most professions are laborers - 4 people (26.7%) and the most comorbid is hypertension, namely 4 people (26.7%) and the most lung malignancy is adenocarcinoma as many as 9 people (60%). The results of another study showed that the incidence of lung malignancy was most common in men over the age of 40 years [13]. The results of this study indicate that the most common lung malignancies were lung adenocarcinoma cases, namely, nine out of 15 respondents who were examined. This study agrees with the theory that pleural effusion reaches 66% as a manifestation of adenocarcinoma lung malignancy [14], [15].

The results of the examination of malignant cell findings from pleural fluid cytological examination materials in this study were influenced by several factors, namely, the collection of pleural fluid specimens at minimal production, tumor expansion, type of malignancy, and specimen processing techniques with cell block. The findings of malignant cells in the pleural cavity showed stages of the development of cancer cells attached to the pleura, avoidance of the immune response of pleural tissue, invasion of pleural tissue, and growth of malignant cells that can be described in all research subjects with a picture of tumors growing to the periphery of the lung and increased permeability of the pleural capillaries causing pleural effusion in all research subjects so that all subjects can be done TTB

and thoracentesis or WSD.

Examination for malignant cell findings or an adequate diagnosis of lung malignancy can be performed on pleural fluid cytological examination materials. The results of the examination can be influenced by several factors, namely, the technique of preparation of examination specimens, pathophysiology, type of malignancy, and tumor area on the pleural surface. The finding of malignant cells in the pleural fluid cytology examination material with the cell block method corresponds to the reference that the pleural fluid cytology examination material is more often found in adenocarcinoma cases and has a diagnostic accuracy of 40–87%. The increase in malignant cell findings in pleural fluid cytology with the cell block method in this study is in accordance with the results of a study that reported that examination of pleural fluid specimens with the cell block method could increase the sensitivity and specificity of malignant cell findings by 35% [16], [17], [18], [19].

The cell block method has the advantages of high concentration of cellular components, tissue description of cytological components, can explain small fragments, and documentation material for future investigations. The results of another study showed that the TTNA cytology examination based on the cell block method had a lung cancer cell finding rate of 57.7% [6].

The results of the combined study of pleural fluid cytology and cell block cytology had the highest kappa value = 0.857 (very good match) with a significance of $p = 0.001$ ($p < 0.05$) compared to the results of pleural fluid cytology using the cell block method (kappa = 0.595; $p = 0.02$) and the results of TTNA cytology examination using cell block method (kappa = 0.737; $p = 0.001$). This is in accordance with the results of other studies that reported the results of examination of pleural effusion and TTNA specimens with guided imaging based on the cell block method that can increase the number of malignant cell findings, good sensitivity and specificity and are in accordance with the core biopsy method. Factors that play a role in influencing the high findings of lung malignancy include the use of imaging in cell block TTNA examination [3], [11], [20], [21].

The sensitivity and specificity values in the combined examination of pleural fluid cytology and TTNA cytology with cell block methods in this study were influenced by factors, namely, the histological type of adenocarcinoma, the management of the specimen using the cell block technique, and the use of chest CT scan as a guide for TTNA and tissue core biopsy [3], [6], [11], [16]. The results of TTNA cytology examination with an imaging guide based on the cell block method have a sensitivity value of 95.4% and a specificity of 100% which are close to the accuracy of core biopsy [9], [11], [18].

The accuracy of the findings of malignant cells through the combined examination of pleural fluid cytology and TTNA cytology based on the cell block method is in accordance with the results of the

study that the results of the combined examination of TTNA cytology with imaging guidance, pleural effusion specimens, and bronchial washings based on the cell block method have good sensitivity [9],[11]. The results of the TTNA examination with the guidance of a thoracic CT scan and the cell block method in the processing of pleural fluid specimens and TTNA carried out in this study can contribute to increasing the number of findings of lung malignancy so that it can be used for an adequate diagnosis of lung malignancy.

Conclusion

The results of the combined examination of pleural fluid cytology and TTNA cytology based on the cell block method gave a very high level of conformity to the tissue core biopsy with a kappa value = 0.857 (very high concordance) and $p = 0.001$ ($p < 0.05$). The cell block method is very effective and has a significant $p < 0.05$ in assessing the results of combined pleural fluid cytology and TTNA cytology against the tissue core biopsy method so that it is useful for adequate diagnosis of lung malignancy.

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