Comparison Of Accuracy Levels Beetween Cell Block And Conventional Cytology Smear Methods On Pleural Effusion Fluid Evaluation In Lung Cancer Patients

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Abstract: Background: Lung cancer is the second most common type of cancer in men and women. Lung cancer at a certain stage can spread to the lining of the lung cover or pleura with clinical manifestation of pleural effusion. Identification of malignant cells is known through pleural fluid cytology examination. This histology type of malignant cells is very important for clinicians in determining prognosis, and the most effective type of management for lung cancer patients.The common pleural fluid cytology examination is the conventional cytology smear (CSS. Another pleural fluid examination method namely cell block (CB) was tried to evaluate the preparation of pleural effusion, and it was found that according several studies it was considered superior to conventional method.

Methods: This study will compare the accuracy level between histopathology-based cell block (CB) method and cytology-based conventional cytology smear (CSS) method. The sensitivity, specificity, predictive value and accuracy will be calculated in both methods by reffering to the gold standard histopathological examination of lung cancer.

Results: The sensitivity value of CB method (97%) higher than CSS method (59%); the specificity value of CB is the same as CSS method (87%); positive predictive value of CB method (82%) is higher than CSS method (73%); negative predictive value of CB method (98%) is higher than CSS method (78%); and accuracy value of CB method (90%) is higher than CSS method (76%).

Conclusions: The accuracy rate of CB method is higher than CSS method in examining pleural effusion in lung cancer patients.

Keywords: lung cancer, pleural fluid, cell block, conventional cytology smear, accuracy

I. INTRODUCTION

Lung cancer is the second most common type of cancer in men and women. About 13% of all cancer cases in the world are lung cancer. It is estimated that there will be approximately 228,150 new cases of lung cancer in the United States and approximately 142,670 deaths from lung cancer in 2019.[1] In Indonesia alone, of all cancer patients, more than 20% are lung cancer sufferers, and this cancer is the number one cause of death for men in Indonesia. This is because 2 out of 3 Indonesian men are active smokers.[2]

Lung cancer at certain stages can spread to the lining of the lung called the pleura with clinical manifestations of pleural effusion. This can also occur when malignant cells block or change the flow of lymph fluid in the pleural cavity. Cancers in other organs, such as breast cancer and lymphoma, can also metastasize to the pleura, but the most common cancer involving the pleura and causing a malignant effusion is lung cancer. Malignant effusion is found in about 23.1% of lung cancer patients.[3] To identify the presence of malignant cells in the pleural fluid, it is necessary to perform a cytologic examination of the pleural fluid. This examination is a relatively fast method and is very minimally invasive.[4] Identification of malignant cells and further identification of the histological types of these malignant cells is very important for clinicians in determining the prognosis, and the most effective type of lung cancer management for lung cancer patients.[3,4,5,6] For this reason, accurate, fast and easy diagnostic techniques are needed.[3,6] Pleural fluid cytology examination that is commonly done so far is the conventional cytology smear (CSS). With this method, it is sometimes difficult to distinguish between reactive mesothelial cells (benign lesions) and malignant cells (malignant lesions).[3,4] The difference in techniques used by different laboratories, overlapping cells, and the absence of malignant cells are the reasons that are very often a diagnostic problem among pathologists.[3,6] Another method of examining pleural fluid, namely the cell block (CB) method, was tried to evaluate the preparation of pleural effusion, and it was found that according to several studies it was considered superior to CSF examination. With the CB method, cellularity is increased, cell morphology details are clearer to observe, histochemical and immunohistochemical staining can be performed. In addition, this method is relatively easy to do because it does not require special staining and special instruments.[3,4] Based on this background, the problem in this study is how to compare the

level of accuracy between pleural fluid examination with histopathology-based cell block method and cytology-based conventional cytology smear method in lung cancer patients? For this reason, researchers will calculate the sensitivity, specificity, predictive value, and accuracy values of the two methods by referring to the gold standard histopathological examination of lung cancer.

II. MATERIAL AND METHODS

This study is a descriptive-analytic study with a cross-sectional design, conducted at a private hospital in the city of Medan. The research sample was 84 people with suspected lung cancer with clinical manifestations of pleural effusion, which were taken by non-probability consecutive sampling, with inclusion and exclusion criteria. Variables will first be analyzed descriptively, then continued with diagnostic test analysis to see sensitivity, specificity, predictive value, and accuracy of conventional cytology smear and cell block method for histopathological examination which is the gold standard for lung cancer diagnosis.

III. RESULTS

This study was conducted on 84 samples of pleural fluid from patients suspected of having lung cancer. To identify the cells contained in the pleural fluid, the fluid is processed using the conventional cytology smear (CSS) and cell block (CB) methods, then the accuracy of these two methods will be compared. Cytological examination that shows a picture of lung cancer will be confirmed histopathologically as lung cancer.

The 32 of 84 pleural fluid samples were histopathologically confirmed as lung cancer, and 52 samples were not lung cancer. The following are the results of the research obtained.

Table 1. Characteristics of Patients

Variable	N	(%)
Mean age	54,32 ±16,26 (min-max : 14-92)	
Sex:		
Male	50	59,52 %
Female	34	40,48 %
Diagnosis:		
Lung cancer	32	38,10 %
Not lung cancer	52	61,90 %
Lung cancer histology		
Adenocarcinoma	30	93,75 %
Squamous cell carcinoma	2	6,25 %

Table 2. The results of pleural fluid examination using the conventional cytology smear (CSS) method.

Description	Histopathology examination			
	Lung Cancer		Not Lung Cancer	
	n	%	n	%
CSS Positive	19	59,38	7	13,46
CSS Negative	13	40,62	45	86,54
Total	**32**	**100**	**52**	**100**

Based on the table above, the sensitivity value for pleural fluid examination using the conventional cytology smear (CSS) method is 59%, specificity value is 87%, positive predictive value is 73%, negative predictive value is 78%, and accuracy value is 76%.

Table 3. The results of the pleural fluid examination using the cell block (CB) method.

Description	Histopathology examination			
	Lung Cancer		Not Lung Cancer	
	n	%	n	%
CB Positive	31	96,88	7	13,46
CB Negative	1	3,12	45	86,54
Total	**32**	**100**	**52**	**100**

Based on the table above, the sensitivity value for pleural fluid examination using the cell block (CB) method is 97%, specificity value is 87%, positive predictive value is 82%, negative predictive value is 98%, and accuracy value is 90%.

Table 4. The results of the pleural fluid examination using the conventional cytology smear (CSS) and cell block (CB) method.

Description	Histopathology examination			
	Lung Cancer		Not Lung Cancer	
	n	%	n	%
CSS (+) *CB* (+)	18	56,25	7	13,46
CSS (-) *CB* (-)	0	0	45	86,54
CSS (+) *CB* (-)	1	3,12	0	0
CSS (-) *CB* (+)	13	40,63	0	0
Total	**32**	**100**	**52**	**100**

Table 5. Comparison of the accuracy of pleural fluid examination with conventional cytology smear (CSS) and cell block (CB) methods.

	CSS Method	CB Method
Sensitivity value	59%	97%
Specificity value	87%	87%
Positive Predictive Value	73%	82%
Negative Predictive Value	78%	98%
Accuracy value	76%	90%

IV. DISCUSSION

In this study, 2 methods of pleural fluid examination were used with the same objective, namely to detect lung cancer and non-lung cancer lesions in patients suspected of having lung cancer (suspected lung cancer) with clinical manifestations of pleural effusion. Assessment of the level of accuracy in each

method is very important to determine the best method that can be chosen in determining benign and malignant lesions in pleural fluid. The conventional cytology smear (CSS) and cell block (CB) methods will be compared for their accuracy in this study.

Sensitivity value is a value that measures how well a screening test classifies sick people as really sick. This sensitivity value is described as the percentage of people with the disease who also test positive. While the specificity value is a value that measures how well a screening test classifies people who are not sick really don't have the disease in fact. This specificity value is described as the percentage of people without the disease with negative test results (Najmah, 2016, and Ismah, 2018). Based on the results of the study above (Table 5), it is known that the sensitivity value of pleural fluid examination with the CSS method is 59% and the specificity value is 87%, meaning that the CSS method can clarify pleural fluid in patients who actually have lung cancer in 59%, and confirmed that the pleural fluid was free of lung cancer by 87%. As for the CB method, the sensitivity value is 97% and the specificity value is 87%, meaning that the CB method can clarify pleural fluid in patients who actually suffer from lung cancer in reality by 97%, and confirm that the pleural fluid is free from lung cancer by as much as 87%.

Positive predictive value is the percentage of all people with positive results in people who are really sick, while negative predictive value is the percentage of all people with negative results in people who are really healthy (Najmah, 2016, and Ismah, 2018). Based on the results of the study above (Table 5), it is known that the positive predictive value of pleural fluid examination with the CSS method is 73%, and the negative predictive value is 78%, meaning that the CSS method can predict the likelihood of developing lung cancer in patients with pleural fluid. positive by 73%, and can also predict the possibility of not suffering from lung cancer in negative pleural fluid by 78%. As for the CB method, the positive predictive value was obtained by 82%, and the negative predictive value was obtained at 98%, meaning that the CB method can predict the possibility of suffering from lung cancer in patients with positive pleural fluid by 82%, and can also predict the possibility of not suffering from lung cancer. lung cancer in negative pleural fluid by 98%.

Accuracy value is a value that shows the closeness of the measurement results to the actual value (Najmah, 2016, and Ismah, 2018). In this study (Table 2), it is known that the accuracy of the pleural fluid examination using the CSS method is 76%, while the accuracy value for the CB method is 90%. This indicates that the pleural fluid examination with the CB method is more accurate than the CSS method.

In this study (Table 4), from 84 pleural fluid samples processed by the CSS method, 19 cases of lung cancer and 45 cases of non-lung cancer were obtained. Of the 19 cases of lung cancer, 1 case did not find tumor cells on CB examination (Table 4.3 and Table 4.4). Several possibilities that can cause this situation, for example, are the relatively small number of tumor cells in the pleural fluid or may be missing at the pre-analytic stage, especially in terms of carrying out histopathological procedures, for example in the process of cutting paraffin blocks using a microtome that has not yet reached the group. tumor cells so that tumor cells were not found on the CB histopathology slide. In addition, from 32 cases of lung cancer, 13 cases were found which were initially negative on CSF examination, but positive on CB examination. This may be due to the fact that in the CB method the cellularity of the preparation is increased, and the details of cell morphology are clearer to observe.[1,4] In table 4.4, it is also known that of the 52 non-lung cancer cases, there were 7 cases whose pleural fluid examination results, both CSS and CB showed positive results. This could be due to the presence of atypical mesothelial cells suspected of being an adenocarcinoma-type lung cancer in the two preparations.

Another study which also compared the accuracy of CSS and CB methods was conducted by Santoshpawar et al. in 2016. From 75 samples of pleural fluid processed by the CSS method, 42 samples of lung cancer and 8 samples of suspected lung cancer were obtained. All samples were followed by the CB method, and the results obtained were 48 samples of lung cancer and 2 samples of non-lung cancer. The results of the calculation of the sensitivity value and specificity value of the CB method in this study were quite high, namely 96% and 92.59%. While research conducted by Ugurluoglu in 2015, from 194 samples of pleural fluid processed by the CSS method, the results obtained were 154 samples of non-lung cancer, 33 samples of lung cancer, and 7 samples of suspected lung cancer. After being processed by the CB method, 12 samples that were initially diagnosed as non-lung cancer by the CSS method showed positive results for lung cancer. In addition, 2 samples that were initially diagnosed as lung cancer and 3 samples of suspected lung cancer using the CSS method were confirmed not to be lung cancer on the CB method. The sensitivity value and specificity value for the CSS method in this study were 50% and 96%; while for the CB method, the sensitivity value and specificity value reach 100%. Positive and negative predictive values in the CSS method are 96% and 33%; while for the CB method the predictive value also reaches 100%. Accuracy value for CSS method is 90% and 100% for CB method. This study also shows the advantages of the CB method, where the accuracy value of the CB method is higher than the CSS method. Although CSS is a routine method and is easy to use so far, the most difficult thing to evaluate in the CSS method is to distinguish malignant lesions from reactive mesothelial cells. This is because reactive mesothelial cells can form cell balls similar to adenocarcinoma. In addition, the accumulation of cells, prominent inflammatory cells, the lack of cell numbers obtained or lost during processing, coupled with poor fixation and artifacts make it difficult to make a diagnosis of malignancy in the CSF method.[4,7,8]

The superiority of the CB method was also demonstrated in the research conducted by Basnet et al. in 2012. The diagnosis of neoplastic lesions using the CB method is superior to the CSS method, especially in terms of better tumor staging and rapid identification. According to the research of Koksal et al. in 2013, apart from being able to identify malignant cells that were not found in the CSS method, the histologic type of lung cancer could also be determined using the CB method. The most common histological type is adenocarcinoma. Similar to this study, the most common histological type found was adenocarcinoma as much as 93.54%, and the rest was squamous cell carcinoma.[4]

When compared with more invasive thoracoscopy, the CB method is also more comfortable for the patient, moreover, this method is accompanied by a high predictive value. In addition,

since the histological subtype of lung cancer is very important to know in order to select the most suitable type of therapy for lung cancer patients, the CB method is more recommended than the CSS method.[5,9] With the CB method, it is possible to perform multiple sections with routine staining, special staining, and immunohistochemistry. The CB method allows for better interpretation of cell morphology with minimal background staining. Starting from increased cellularity, clearer cell morphology details, such as cell balls, papillary structures, three-dimensional cell groups, clear nuclear and cytoplasmic morphology, intact cell membranes, and clear chromatin details. CB allows for longer storage of preparations and molecular examination as is the case for histopathological preparations. Immunohistochemical tests, such as MOC-31, D2-40, and calretinin, used preparations from CB to differentiate adenocarcinoma from reactive mesothelial cells.[4] Research conducted by Khoor et al., 2011, used TTF-1 immunohistochemistry through CB to differentiate between adenocarcinoma and non-adenocarcinoma and malignant mesothelioma types.[9]

Despite the various advantages of the CB method, there are still many clinicians who have not recommended CB as a combination of the CSS method which has been routinely done so far. The high cost for this CB method causes clinicians not to recommend it for any pleural fluid sent to the Anatomical Pathology laboratory. CB is only applied to patients who are suspected of having lung cancer.

V. CONCLUSION

After conducting a study that aims to compare the accuracy of the Cell Block (CB) method and the Conventional Cytology Smear (CSS) method in the examination of pleural effusion fluid in lung cancer patients, the following results were obtained:

a. The sensitivity value of the CB method is higher than the CSS method.
b. The specificity value of the CSS method is the same as that of the CB method.
c. The positive predictive value of the CB method is higher than the CSS method.
d. The negative predictive value of the CB method is higher than the CSS method.
e. Accuracy value of CB method is higher than CSS method.

Based on the results of the research above, it can be concluded that: the accuracy rate of the cell block (CB) method is higher than the conventional cytology smear (CSS) method so that the cell block method can be suggested to be the first choice of method used in distinguishing benign and malignant lesions on examination. pleural effusion in lung cancer patients.

VI. COMPETING INTERESTS

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VII. ETHICAL APPROVAL

This research has been approved by the Research Ethics Commission of the University of North Sumatra based on the approval letter of the Ethics Committee for Health Research Implementation No: 234/KEP/USU/2020.

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