ORIGINAL ARTICLE

Diagnostic utility of pleuroscopic guided pleural biopsy versus pleural fluid cell block in the diagnosis of malignant pleural effusion

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ABSTRACT

Introduction: Pleural biopsy using flex-rigid pleuroscopy or pleural effusion cell block analysis is useful for diagnosing malignant pleural effusion. However, the current literature lacks documented comparisons between pleural biopsies and cytological cell blocks. This study aims to compare the diagnostic accuracy of pleural biopsy and cytological cell block in identifying malignant pleural effusion.

Materials and Methods: A retrospective review was conducted on patient data from those who underwent pleuroscopy at Hospital Canselor Tuanku Muhriz from January 2021 to December 2023. We included patients with pleural effusion who underwent both cell block and pleural biopsy with a confirmed diagnosis of malignancy through histopathological examination. At least 200 ml of pleural fluid was collected, followed by the biopsy of six or more pleural tissue samples.

Results: Out of the 196 pleuroscopy procedures analysed, 91 patients were diagnosed with malignant pleural effusion. Malignancy was diagnosed in 50 (54.9%) cases using cell block analysis, whereas pleural biopsy identified malignancy in 81 (89%) cases. The diagnostic yield was significantly higher for pleural biopsy compared to pleural fluid cell block [89% (81/91) vs. 54.9% (50/91); p < 0.001]. Among patients with negative results on pleural fluid cell block, 33 (36.3%) had positive results on pleural biopsy. The definitive diagnoses of malignancy included 64 (70.3%) cases of lung adenocarcinoma, 4 (4.4%) cases of lung squamous carcinoma, 2 (2.2%) cases of small cell lung cancer, 2 (2.2%) cases of mesothelioma, and 19 (20.9%) cases of metastatic carcinoma. Eight (8.8%) patients exhibited negative findings on both pleural fluid cell block and pleural biopsy. Further diagnoses were achieved through computed tomography-guided needle tru-cut biopsy of the lung in 6 patients (6.6%), transbronchial lung biopsy in 1 patient (1.1%), and cervical lymph node biopsy in 1 patient (1.1%).

Conclusion: Pleural biopsy exhibits superior diagnostic accuracy compared to pleural fluid cell block analysis for malignant pleural effusion. In cases where cell block results are negative but suspicion remains high, pleural biopsy remains a crucial diagnostic tool.

KEYWORDS:
Malignant pleural effusion; pleuroscopy; cell block; pleural biopsy

INTRODUCTION

Determining the underlying aetiology of pleural effusion is crucial for guiding appropriate management and predicting the clinical course of malignant diseases.[1-2] Accurate diagnosis is essential for making informed decisions regarding treatment options. Thoracentesis, followed by cytosmear or cell block analysis, is commonly employed as the initial diagnostic step due to its safety and minimally invasive nature.[3] Pleural fluid (PF) cell block analysis has also emerged as a valuable alternative to pleural tissue biopsy, particularly for patients who are unsuitable candidates for flex-rigid pleuroscopic biopsy due to anatomical challenges, comorbidities, or other factors.

However, the current diagnostic pathways for pleural effusion, including cytosmear and cell block analysis, face several limitations. The reduced sensitivity of these methods can be attributed to factors such as limited morphological features, overcrowding of cells, cell loss, and variations in laboratory processing techniques.[4] These issues may contribute to false-negative results, potentially leading to delayed or incorrect diagnoses. The implications of false negatives are particularly concerning, as they can impact staging and delay timely therapeutic interventions, which may ultimately affect patient prognosis.

Although both pleuroscopic pleural biopsy and PF cell block analysis are widely used in the diagnosis of malignant pleural effusion, limited studies have directly compared their

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diagnostic efficacy. This gap in the literature highlights the need for a more comprehensive evaluation of these diagnostic modalities. This study aims to fill this gap by assessing the effectiveness of these two modalities in diagnosing malignant pleural diseases and improving clinical outcomes.

MATERIALS AND METHODS

Patients

This single-centre retrospective cohort study was conducted at Hospital Canselor Tuanku Muhriz, University Kebangsaan Malaysia, from January 2021 to December 2023. The UKM Research Ethics Committee approved the study with the ethics code JEP-2024-411. The hospital database was utilised to identify patients who underwent both cell block analysis and pleural biopsy for pleural effusion via pleuroscopy. We included only those with a confirmed malignancy diagnosis through histopathological examination. Patients with inadequate samples for either cell block or pleural biopsy, as well as those with non-malignant pleural effusion, were excluded from the study. Patient demographics, clinical profiles, chest radiography results, pleuroscopic observations, pleural fluid results and histopathological findings were recorded for analysis.

Procedure

Vital signs were recorded before the procedure. A pulmonologist, assisted by two endoscopy staff, performed flex-rigid pleuroscopy in a fully equipped endoscopy room. Conscious sedation was achieved with intravenous fentanyl and midazolam, with doses adjusted as needed.

The patient was placed in the lateral decubitus position, and the entry site was identified using the liner-type ultrasonographic probe. Topical anaesthesia with 2% lidocaine was infiltrated to the skin, subcutaneous tissue, intercostal muscle, periosteum of ribs, parietal pleura and intrapleura. The needle was carefully manoeuvred along the superior aspect of the rib, drawing a small amount of fluid first and then gradually injecting lidocaine as it advanced towards the pleura. This procedure continued until the pleural fluid was successfully drained.

The single port entry method was employed for pleuroscopy. Initially, a scalpel was utilised to create a skin incision, followed by careful blunt dissection of the intercostal muscles until reaching the parietal pleura. Subsequently, an 8 mm inner diameter rigid trocar was inserted. The inner part of the trocar was then retracted, allowing the flex-rigid pleuroscope (LTF-260; Olympus, Tokyo, Japan) to be introduced through the trocar.

The procedure comprised the following sequential steps: (1) Aspirating the pleural fluid (at least 200 ml); (2) Conducting adhesiolysis to enable thorough examination of the pleural space; (3) Examining the pleural space; and (4) Collecting multiple biopsy samples (typically 4-6) directly from any abnormal regions in the parietal pleura or diaphragm using biopsy forceps under direct visualisation.

Once satisfactory biopsy specimens were acquired, the pleuroscope was withdrawn, and a 24 Fr chest drain was inserted through the trocar and then connected to an underwater seal device.

Following the procedure, a post-procedure chest X-ray was performed. The chest tube was promptly removed upon lung re-expansion, with a minimal amount or resolution of pleural effusion confirmed by chest ultrasonography.

Biopsy specimen and cell block

Histological specimens obtained through pleuroscopy were evaluated using the standard protocol employed in the Department of Histopathology and Cytopathology. Biopsy samples were promptly fixed in formalin, processed into paraffin blocks, and sectioned. Paraffin-embedded sections underwent staining with Haematoxylin and Eosin (HE) and were subjected to immunohistochemical staining.

The pleural fluid was used to prepare conventional smears and cell blocks. For cell blocks, the fluid specimen was centrifuged at 2500 rpm for 15 minutes. The supernatant was discarded, leaving a cell pellet. Plasma, thromboplastin, and calcium chloride were added to promote clot formation. The cell pellet and clot were then fixed in 10% buffered formalin for 24 hours. After fixation, the sample was wrapped in filter paper and processed in a tissue processor. Following embedding in paraffin, the cell block was prepared, sectioned, and stained with HE. Special stains, such as PAS, were applied as needed.

Statistical analysis

Descriptive statistics were used to summarise the data, with results presented as means with standard deviations, frequencies, and percentages. To evaluate the significance of the findings, a p-value of less than 0.05 was considered indicative of statistical significance. The analysis was performed to compare and interpret the diagnostic accuracy and yield between the pleuroscopic guided pleural biopsy versus the pleural fluid cell block, ensuring that the results were appropriately summarised and evaluated based on these descriptive measures.

RESULTS

Demographic

Table I shows the demographic characteristics of the study subjects. Among the 91 patients, 46 (50.5%) were men, and 45 (49.5%) were women, with a mean age of 66.5 years (range 23-88 years).

Pleuroscopy morphology and chest drainage procedures

The mean (SD) time from referral to the pleuroscopy procedure was 3.5 (2.7) days. The median procedure duration was 30 minutes, with a range of 20 to 50 minutes. Pleuroscopic examination revealed adhesions and loculations in 8 patients (8.8%). Within our study population, pleuroscopy predominantly identified nodules on the parietal pleura. Specifically, 58 patients (63.7%) had nodules, 13 patients (14.3%) had nodules with hyperaemia, 13 patients (14.3%) had hyperemia alone, and 7 patients (7.7%) had a yellowish-white membrane.

Table I: Demographics and clinical characteristics of patients with malignant pleural disease

Variable	n = 91
Gender, no. (%)	
Male	46 (50.5)
Female	45 (49.5)
Age	
Mean (years), mean (SD)	66.5 (12.4)
Range (years)	23-88
> 60 years old, no. (%)	67 (73.6)
< 60 years old, no. (%)	24 (26.4)
Smoking history, no. (%)	
Current or former	20 (22)
Never	71 (78)
Length of stay, mean (SD)	14.6 (6.5)
Pleurodesis, no. (%)	21 (23.1)
Number of pleuroscopic biopsies, mean (SD)	8.9 (3.1)
Median chest tube drainage period (days), mean (SD)	9.9 (5.5)
Time lag from admission till pleuroscopy date	3.5 (2.7)
Tumour types, no. (%)	
Lung adenocarcinoma	64 (70.3)
Lung squamous carcinoma	4 (4.4)
Small cell lung cancer	2 (2.2)
Breast carcinoma	8 (8.8)
Ovarian cancer	3 (3.3)
Malignant pleural mesothelioma	2 (2.2)
Renal cell cancer	2 (2.2)
Lymphoma	2 (2.2)
Melanoma	1 (1.1)
Urothelial cancer	1 (1.1)
Esophageal cancer	1 (1.1)
Nasopharyngeal carcinoma	1 (1.1)
Procedure-related complications, no. (%)	
Persistent air leak	1 (1.1)
Subcutaneous emphysema	2 (2.2)
Empyema thoracic	1 (1.1)
Non-expandable lung	2 (2.2)
Re-expansion pulmonary edema	1 (1.1)
Chest tube dislodge	1 (1.1)

Table II: Radiographic and pleuroscopic characteristics of malignant pleural diseases

Variables	n = 91
The severity of pleural effusion is based on a chest radiograph; no. (%)	
Mild pleural effusion	13 (14.3)
Moderate	37 (40.7)
Massive	41 (45)
Pleural effusion laterality, no. (%)	
Right	49 (53.8)
Left	42 (46.2)
Colour of pleural fluid, no. (%)	
Straw-coloured	50 (54.9)
Haemorrhagic	41 (45.1)
Pleuroscopic findings, no. (%)	
Nodules	58 (63.7)
Nodules and hyperaemic	13 (14.3)
Hyperaemia	13 (14.3)
Yellowish white membrane	7 (7.7)
Loculation on pleuroscopic examination, no. (%)	8 (8.8)

Table III: Diagnosis of the pleural fluid by cell block and pleural biopsy

Diagnosis	Cell smear		Cell block		Pleural biopsy	
	n	%	n	%	n	%
Suspicious of malignancy	18	19.7	0	0	0	0
Malignancy	44	48.4	50	54.9	81	89
Non-specific inflammation	29	31.9	41	45.1	10	11

Chest tube drainage lasted for a mean (SD) of 9.9 (5.5) days. In patients undergoing pleurodesis, the median duration of drainage was 8 days (range, 2-23 days), whereas in those not undergoing pleurodesis, it was 9 days (range, 1–28 days). Pleurodesis was performed in 21 patients (23.1%) prior to chest tube removal.

Cytology examination and histopathological diagnosis

The definitive diagnoses of malignancy comprised 64 cases (70.3%) of lung adenocarcinoma, 4 cases (4.4%) of lung squamous carcinoma, 2 cases (2.2%) of small cell lung cancer, 2 cases (2.2%) of mesothelioma, and 19 cases (20.9%) of metastatic carcinoma. Cell block analysis identified malignancy in 50 cases (54.9%), while pleural biopsy detected malignancy in 81 cases (89%). This represents a significantly higher diagnostic yield for pleural biopsy compared to pleural fluid cell block [89% (81/91) vs. 54.9% (50/91); $p < 0.001$].

Among patients with negative results on the pleural fluid cell block, 33 (36.3%) had positive findings on pleural biopsy. Eight (8.8%) patients had negative results on both pleural fluid cell block and pleural biopsy. Diagnoses were also made in 6 patients (6.6%) through computed tomography-guided needle tru-cut biopsy of the lung and in 1 patient each (1.1%) via transbronchial lung biopsy and cervical lymph node biopsy. The radiographic and pleuroscopic characteristics of malignant pleural diseases and diagnosis of the pleural fluid by cell block and pleural biopsy are shown in Tables II and III.

DISCUSSION

Most cases of malignant pleural effusion result from metastatic spread to the pleura. Accurate differentiation between malignant pleural effusion and paramalignant effusion is essential, as it affects disease staging and treatment strategy. Flex-rigid pleuroscopy under local anaesthesia is utilised to obtain pleural tissue in cases of suspected malignant pleural disease.[5-9] Studies have reported a sensitivity of 91% and a specificity of 100% for flex-rigid pleuroscopic biopsy in diagnosing exudative pleural effusion.[5] While tissue biopsy followed by histological examination remains the gold standard, it may not always be feasible, especially for patients who are unfit for flex-rigid pleuroscopy. An alternative approach is the collection of pleural effusion cell blocks, which provides a more accessible method for diagnosis.

In this study, pleural effusions were evaluated by comparing the cell block technique with pleural biopsy methods. The primary objective was to assess the effectiveness of cell block analysis relative to pleural biopsy, which is widely recognised as the gold standard for pathological diagnosis. The British Thoracic Societypleural disease guidelines emphasise that the diagnostic accuracy for malignant pleural effusion improves when both cell blocks and smears are prepared from pleural fluid samples.[10] The American College of Chest Physicians and the National Comprehensive Cancer Network recommend pleural biopsy as the next step after at least two negative thoracenteses.[11-12]

The 2000 American Thoracic Society statement on managing malignant pleural effusions recommends pleuroscopy for exudative effusions of unknown aetiology.[13] Pleuroscopy is regarded as a safe and minimally invasive procedure, with procedure-related mortality being rare when performed by skilled practitioners.[14] However, there is a risk of life-threatening severe bleeding if intercostal vessels are injured. In our study, no mortalities or major complications were reported. A few patients experienced minor complications, including prolonged air leaks, subcutaneous emphysema, wound infections, and empyema. These findings align with previously reported complications, which commonly include persistent air leaks, subcutaneous emphysema, and infections.[15-16]

Pleuroscopy facilitates the collection of sufficient tissue specimens for histological examination and allows for the evaluation of chest wall invasion or mediastinal involvement. However, studies suggest that approximately 10% of effusions may remain undiagnosed despite pleuroscopy.[17,18] Our study's pleuroscopic diagnostic yield was lower than that reported in previous studies, which may be due to factors such as inadequate or non-representative biopsies or adhesions obstructing access to neoplastic tissues.[19] Nonetheless, our findings are consistent with Miyoshi et al., who reported that pleural biopsy using flex-rigid pleuroscopy achieved significantly higher diagnostic rates (94.2%) compared to pleural fluid cell block (71.4%) for malignant pleural disease.[20]

The cell block technique is increasingly recognised for its efficacy in effusion cytology and fine-needle aspiration cytology.[4,21] Utilizing cell blocks from pleural fluid samples offers advantages over conventional cytology by preserving morphological architecture more effectively. This method provides enhanced detail of cellular morphology, including better preservation of nuclear and cytoplasmic features, intact cell membranes, and well-defined chromatin.[22-24] Additionally, cell blocks reduce cellular dispersal, which aids in the recognition of histological disease patterns and enhances the effectiveness of immunohistochemical staining and molecular testing.[22-24] Studies have reported a wide range of diagnostic yields for cell block in detecting malignant pleural effusion, from 15% to 89.4%, with variations likely influenced by factors such as specimen size, specimen type, and aspiration techniques.[21-30] In our study, pleural fluid cell block was able to diagnose approximately 54.9% of cases. The lower yield of malignant cells in cell blocks in our study may be attributed to factors such as low cellularity and bleeding during the preparation process.

For inconclusive pleural biopsy results, advanced imaging modalities such as contrast-enhanced computed tomography (CT), positron emission tomography (PET), or PET-CT can help identify suspicious areas that may have been missed during initial sampling. These imaging techniques enhance lesion localisation and guide repeat biopsies, improving diagnostic accuracy. In addition, alternative biopsy approaches, including image-guided percutaneous needle biopsy or CT-guided biopsy of pleural or extrapleural lesions, can be employed. These methods are particularly useful for targeting areas that are inaccessible during pleuroscopy, thereby increasing the overall diagnostic yield.

Patients with suspected malignant pleural effusion should undergo stratification based on clinical suspicion, imaging findings, and individual risk factors to guide the diagnostic approach. For patients with low to moderate suspicion, pleural fluid cytology and cell block analysis should considered as the initial diagnostic modalities due to their minimally invasive nature and reasonable diagnostic yield. In cases where cell block analysis produces negative or inconclusive results, particularly in patients with moderate to high pre-test probability, pleuroscopic-guided biopsy is advised to confirm the diagnosis and ensure accuracy.

While pleuroscopy is a valuable diagnostic tool, it carries inherent risks, including bleeding and other procedural complications. To mitigate these risks, a thorough pre-procedural evaluation is essential. This includes assessment for coagulopathies, review of antiplatelet or anticoagulant therapies, and evaluation of vascular abnormalities identified through imaging. Optimising patient conditions, such as correcting coagulopathy or adjusting medications, can further reduce the likelihood of complications. Close monitoring following pleuroscopy allows for the early detection and prompt management of potential complications, such as bleeding, infection, or pneumothorax. By integrating risk stratification, appropriate pre-procedural optimisation, and vigilant post-procedural care, the safety and efficacy of pleuroscopy in diagnosing malignant pleural effusion can be maximised.

CONCLUSION

Pleural biopsy demonstrates superior diagnostic accuracy compared to pleural fluid cell block analysis in the evaluation of malignant pleural effusion. If cell block results are negative but there is still a high clinical suspicion of malignancy, pleuroscopy-guided pleural biopsy is an essential diagnostic tool. To improve clinical outcomes, we propose a diagnostic pathway where pleural fluid cytology is used as an initial screening tool to determine the need for subsequent pleural biopsy.

Future research should focus on conducting multicenter prospective studies to validate these findings across diverse populations and healthcare settings. Additionally, comparative analyses exploring the cost-effectiveness of pleuroscopy versus cell block techniques are essential to inform resource allocation and optimise diagnostic approaches.

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