

# Utility of Cell Block Preparation From CT-Guided FNAC with Immunohistochemistry in Diagnosing Primary Lung Carcinoma: A Prospective Study in A Tertiary Care Hospital

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## ABSTRACT

**Introduction:** Lung cancer remains a leading cause of cancer mortality globally, making early diagnosis critical. While core needle biopsy provides tissue samples, it carries risks including pneumothorax and hemothorax. Fine needle aspiration cytology offers a safer alternative with negligible complications. Cell block preparation can improve diagnostic accuracy of cytological specimens. Limited research exists on cell block utility with immunohistochemistry for primary lung cancer diagnosis.

**Materials and Methods:** This prospective observational study evaluated cell block efficiency versus conventional cytological smears. One hundred twenty patients with CT-guided fine needle aspiration specimens underwent both conventional smear and cell block preparation. Immunohistochemical staining using TTF-1, p63, and synaptophysin was performed on cell block sections. Results were correlated with histopathological findings.

**Results:** Cell block with immunohistochemistry demonstrated sensitivity of 95.4% (95% CI: 89.2-98.5%) and specificity of 91.2% (95% CI: 82.1-96.3%). Positive and negative predictive values were 96.5% (95% CI: 91.0-99.0%) and 88.6% (95% CI: 78.5-94.8%), respectively.

**Conclusions:** Cell block preparation showed superior diagnostic performance compared to conventional smears alone. The combination of cell block immunohistochemistry with conventional cytology provides enhanced diagnostic accuracy for lung cancer evaluation. This approach can be routinely implemented for improved characterization of aspirated specimens.

**Key Words:** Lung cancer, CT- guided FNAC, cell block, immunohistochemistry, diagnostic accuracy

## INTRODUCTION

Lung cancer is the fourth most common cancer diagnosed in India, contributing to 81748 cases annually (5.8% of all new cancers) and accounting for 75031

deaths in 2022 alone. It accounted for 8.5% of all new cancer cases in males in 2022, making it India's second most common cancer.[1] This high death rate is mainly because most patients are diagnosed with advanced-stage cancer, for which the conventional treatment does

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not work.[2] Current targeted therapy protocols necessitate the appropriate morphological diagnosis, along with molecular characterization of the tumours, making it diagnostically challenging. The erstwhile preliminary separation of Small Cell Lung Carcinoma (SCLC) and Non-Small Cell Lung Carcinoma (NSCLC) is increasingly being discouraged as different molecular therapeutic aspects are the current go-to strategies for NSCLC. [3,4] The American College of Chest Physicians guidelines state that minimally invasive techniques should be used as first-line diagnostic tests, and cytological specimens are preferred over histological ones.[5] Compared to biopsy specimens, cytological specimens are usually less contaminated by non-neoplastic cells and are favourable for sensitive molecular genetic analysis.[6] In this context, the utility of the cell block study is being widely touted because of its role in ancillary testing, including molecular diagnosis. Moreover, formalin-fixed paraffin-embedded (FFPE) tissue, being common for both cell blocks and molecular diagnosis platforms, additional validation is not needed.[7] The cell blocks have been traditionally stored for future diagnostic and research purposes and are useful in relapse cases, particularly when re-biopsy cannot be performed.[6] However, sometimes low cellularity can cause dissatisfaction. Additionally, there is a loss of DNA material with each extra section from cell blocks.[8] Developing a protocol for specimen collection and usage is crucial for optimizing cell blocks.[9]

After cell block preparation, immunohistochemistry (IHC) should be executed for FNA cytological samples. Presently, immunohistochemistry is recommended for all cases of NSCLC that cannot be classified on morphology alone. It plays an important role in the subtyping of lung cancer. Although cell block is frequently used as a technique, its utility for diagnosing primary lung carcinoma has not been studied in the Indian context. This study aims to evaluate the diagnostic utility of cell blocks with IHC compared to conventional smears in CT-guided FNAC for primary lung carcinoma.

## MATERIALS AND METHODS

The study was carried out at the Pathology department of a tertiary teaching hospital over 18 months from February 2020- July 2021. This was an institution-based, prospective, observational, and analytical cross-sectional study. Consecutive 120 cases who were diagnosed as primary lung carcinoma on initial radiological examination using CT scan, undergoing CT-guided Fine needle aspiration, and had further lung biopsies by either CT-guided or bronchoscopy-guided method were sampled.

**Inclusion criteria:** Patients with unilateral lung lesions diagnosed as primary lung carcinoma radiologically using a CT scan, undergoing CT-guided Fine needle aspiration, and having subsequent lung biopsies were included in the study after obtaining written consent.

**Exclusion Criteria:** Patients with known multifocal or

metastatic disease was excluded. Cystic fluid and paucicellular aspiration material (less than 50 cells) were not included in the study.

Relevant information regarding age, sex, presenting clinical features, radiological, and laboratory findings was recorded. Samples were collected from lung masses by aspiration to produce both cytological slides and cell block preparations for subsequent analysis. Under CT scan guidance, a 22-gauge (22 G) Spinocan® spinal needle (B. Braun, Melsungen, Germany) was advanced into the lesion, after which its inner stylet was withdrawn to confirm accurate targeting. An FNAC gun attached to a 10-cc syringe was then connected to the needle hub. Slight suction was applied and sustained while the needle was vigorously moved to and from along the needle tract in the mass, thereby dislodging and drawing cells into the syringe. The needle was then separated from the syringe for further processing. The procedure showed no complications, and patients could be discharged after a brief observation of 15 minutes.

Several smears were made on glass slides one was immediately fixed in alcohol, while the others were left to air dry. Any remaining specimen was expressed onto a slide and allowed to coagulate. The solid fragments were transferred into a centrifuge tube containing 10% neutral buffered formalin. This tube was spun at 3000 rpm for ten minutes. After fixation, the specimen was enclosed in filter paper, placed in a cassette, and subjected to routine tissue processing, resulting in FFPE cell blocks stained with hematoxylin and eosin. The air-dried and alcohol-fixed smears proceeded to staining with both Leishman Giemsa and hematoxylin & eosin, respectively, for microscopic evaluation.

Smears with malignant cells were regarded as Positive for Malignancy (PFM). Smears with no tumor cells or small cells with nuclear atypia were regarded as Negative for Malignancy (NFM). Highly suspicious tumor cells were used to identify samples as Suspicious for Malignancy (SFM).

The cell blocks were subjected to immunohistochemistry using the standard Horseradish Peroxidase (HRP)-anti-peroxidase technique on Poly-L-Lysine coated slides. An abbreviated panel of immunomarkers (as recommended by IASLC) comprising TTF-1 (Biogenex, San Ramon, CA, USA, 1:100), p63 (Biogenex, San Ramon, CA, USA, 1:60), and Synaptophysin (Biogenex, San Ramon, CA, USA, 1:100) was used to distinguish types of lung carcinoma with appropriate positive and negative controls.

Three blinded separate pathologists conducted the conventional smear examination, Cell block H & E and IHC examination, and Histopathological examination of lung biopsies. A comparative evaluation was conducted on the results of conventional smears and cell block immunohistochemistry (CB IHC). The results obtained were compared with the histopathological findings of the matched samples. Statistical analysis was done using SPSS software (IBM Corp., Armonk, NY, USA).



**Ethical consideration:** This study was approved by the Institutional Ethics Committee, NRS Medical College and Hospital (no. NMC/690, Dated: 10/02/2020).

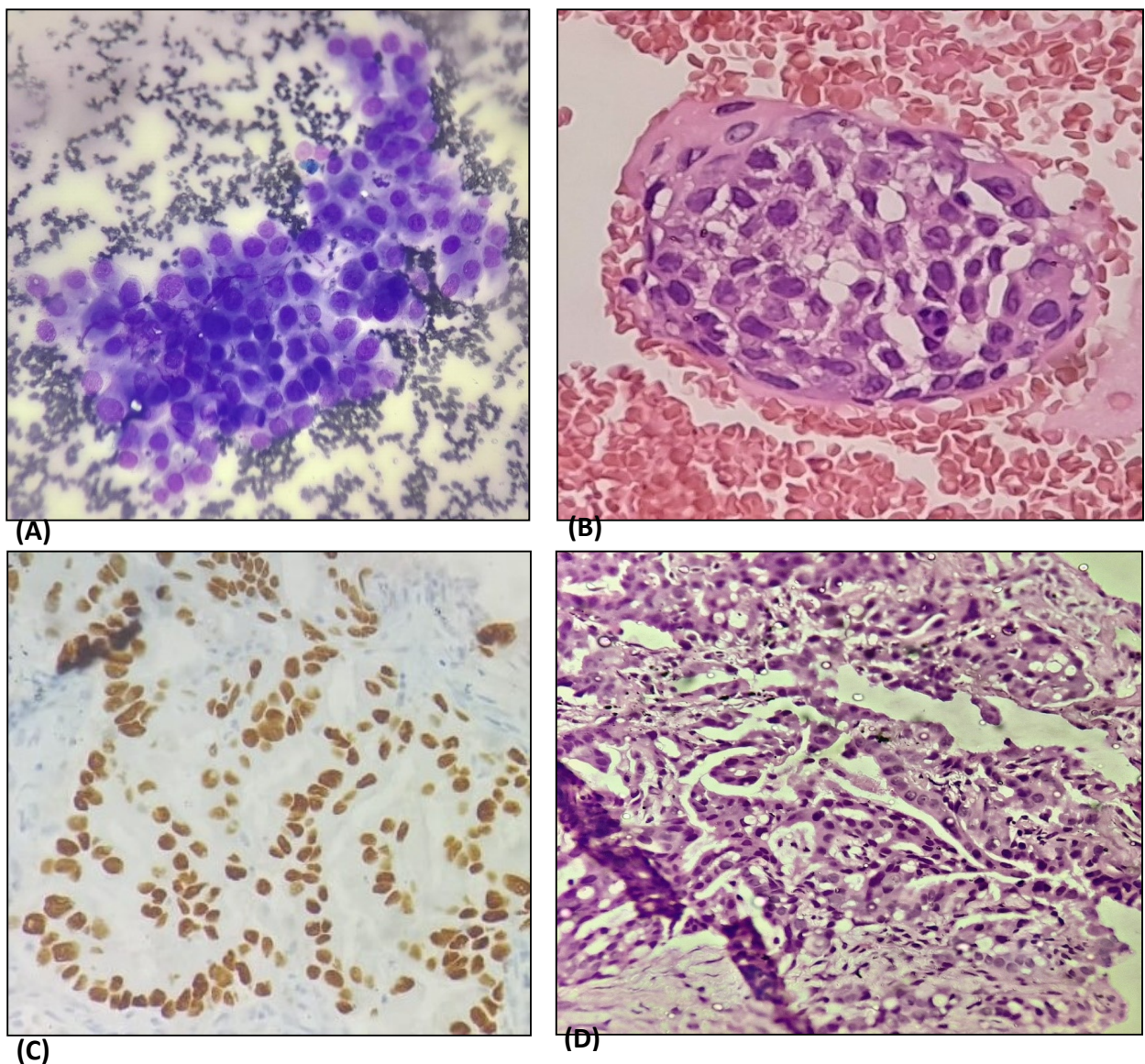
## RESULTS

The present study processed 120 aspirated material samples for conventional smears and cell block preparations. The age of the patients ranged from 32 years to 80 years, with a mean of 57.2 years. The maximum number of samples was from 61 years to 70 years age group (39 cases), while the least number of patients was from 71 years to 80 years age group (15 cases) (table 1) Male patients (n=79) outnumbered female patients (n=41), (male: female ratio being 1.92:1). Out of 120 subjects sampled, 64(53.3%) were smokers and 56(46.7%) never smoked. Only 25 out of 79 males were

non-smokers, whereas only 10 of 41 females were smokers. On categorizing histopathologically, 86 out of the 120 were malignant and 34 were benign. Out of 86 such cases, the highest concordance was seen with small cell carcinoma at 91.7% (n=11/12), followed by SCC, 79.2% (n=19/24). Adenocarcinoma showed the least concordance, 47.5% (n= 19/21).

**Table 1: Age distribution of patients with lung lesion sampled**

Age in years	Cases (%)
31-40	17 (14.1)
41-50	19 (15.8)
51-60	29 (24.1)
61-70	39 (32.5)
71-80	15 (12.5)
Total	120 (100)



**Figure 1: Adenocarcinoma of the Lung**

- (A) Conventional smear (Leishman Giemsa, 400X) showing acinar cluster
- (B) Cell block (Hematoxylin & eosin, 400X) showing well demarcated acini with prominent nucleoli.
- (C) Strong nuclear TTF-1 positivity in cell block adenocarcinoma (TTF-1, 400X)
- (D) Histopathology, adenocarcinoma (Hematoxylin & eosin, 400X)

**Table 2: Comparative analysis for an additional yield of malignancy between conventional smear, Cell Block H&E, and Cell Block IHC**

Diagnosis	Conventional smear Positive (%)	Cell Block H&E Positive (%)	Cell Block IHC Positive (%)
Positive For Malignancy	54 (45)	66 (55)	85 (70.8)
Suspicious For Malignancy	38 (31.6)	23 (19.2)	0 (0)
Negative For Malignancy	28 (23.4)	31 (25.8)	35 (29.2)
Total	120 (100)	120 (100)	120 (100)

H &amp; E: Hematoxylin and eosin, IHC: immunohistochemistry

**Table 3: Relative positivity of TTF-1, p63, Synaptophysin in Adenocarcinoma, Squamous cell carcinoma, and small cell carcinoma, respectively. N denotes the number of cases detected by the immunostains out of the total subtype cases**

Marker	Subtype	Positive Rate (No. of Positively detected cases/total subtype cases)
TTF-1	Adenocarcinoma	87.5% (N=35/40)
p63	Squamous cell carcinoma	79.2% (N=19/24)
Synaptophysin	Small cell carcinoma	91.6% (N=11/12)

**Table 4: Comparative analysis between Cell Block Immunohistochemistry (IHC) and Histopathological diagnosis. (Gold Standard). P<0.0001**

Cellblock with immunohistochemistry (CB IHC)	Histopathological Diagnosis			Total (n=120)
	Malignant (n=84)	Suspicious for Malignancy (n=0)	Benign (n=34)	
Positive for malignancy (PFM)	82 (95.34%)	0	3 (8.83%)	85
Suspicious for Malignancy (SFM)	0	0	0	0
Negative for Malignancy (NFM)	4 (4.66%)	0	31 (91.17%)	35

Sensitivity 95.4%, Specificity 91.2%, PPV: Positive predictive value 95.5%, NPV: Negative predictive value 88.6%

A comparative yield of diagnosis (conventional vs cell block H&E vs Cell Block IHC) is depicted in table 2. TTF-1, p63, and Synaptophysin constitute a useful panel in resource-limited settings for subtyping lung cancer in Cell block preparations. TTF-1 was positive in 87.5% of cases of lung adenocarcinoma (35/40), p63 was positive in 79.2% of squamous cell carcinoma (19/24), and synaptophysin was positive in 91.6% of small cell carcinoma cases (11/12). (table 3) (Fig 1 and 2)

On histopathological diagnosis, the most common malignancy was adenocarcinoma of the lung (46%), followed by Squamous cell carcinoma (28%) and small cell carcinoma (14%). When compared with histopathology (gold standard), cell block showed sensitivity of 95.4% (95% CI: 89.2-98.5%) and specificity of 91.2% (95% CI: 82.1-96.3%). Positive and negative predictive values were 96.5% (95% CI: 91.0-99.0%) and 88.6% (95% CI: 78.5-94.8%), respectively. (table 4) Chi-square test was applied with Yates' correction (two-tailed P value <0.0001).

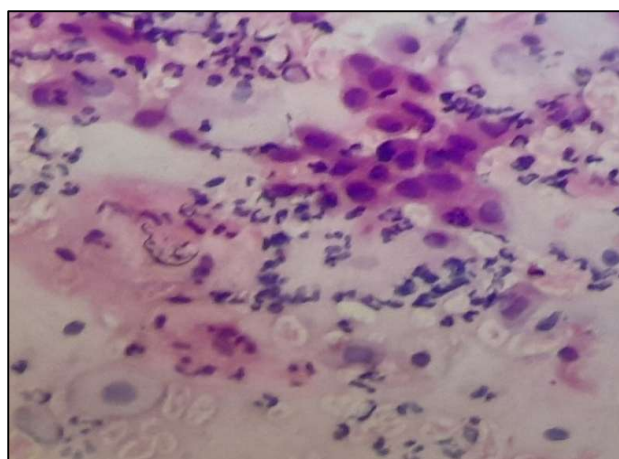
## DISCUSSION

This study was conducted to assess the effectiveness of the cell block method with a minimal panel of immunohistochemical antibodies comprising TTF-1, p63, and Synaptophysin. The use of cell blocks has been widely advocated in the diagnostic workup of patients with masses amenable to FNA since they provide diagnostic architectural information that complements FNA smears.

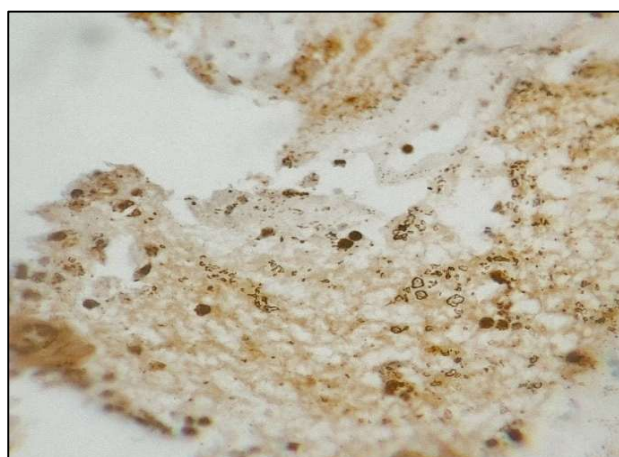
[10] Although there are disadvantages like reduced morphological quality, compared to conventional cytology, some studies have reported cell blocks to be helpful for a better demonstration of the architectural pattern. [11] Small tissue fragments appear as "mini biopsies," which are useful for diagnosis, pattern recognition, subclassification, and identification of certain features. [12,13] When adequately cellular, cell blocks are a source of additional sections valuable for ancillary studies such as special staining, immunostaining, ultrastructural analysis, and molecular testing. [14] Like Boller AK et al., clot formation of aspirated material in our study was achieved by the natural mechanism of the clotting cascade following tissue injury. [15] The addition of other substances, as done in other methods to coagulate the cell pellets, was not done here.

In the present study, the most common age group was 61 to 70 years, accounting for 27.9% (n=24/86) of cases of lung cancer, attributed to the increased incidence of malignancies with age. In our study, the mean study population age was 57.2 years, like most of the previous relevant studies. In a recent study by Burt JR et al., non-smokers showed predominantly adenocarcinoma (77.9%), while smokers exhibited similar frequencies of both adenocarcinoma (49.4%) and squamous cell carcinoma (43.7%). [16] In our study, among adenocarcinoma patients, only 47.5% were smokers. The incidence of adenocarcinoma was the highest among the 86 lung cancer cases in the present study. This agrees with the study done by Dela Cruz CS et al.[17] but contrasts with other Indian studies like that of Saha R et al.[18].

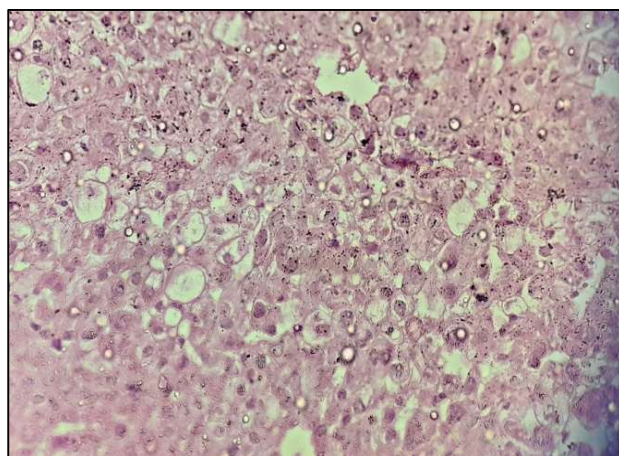




A



B



C

**Figure 2: Squamous cell carcinoma of the lung**

(A) Conventional smear (Leishman Giemsa, 400X) showing monolayered sheets of neoplastic cells  
 (B) p63 nuclear positivity on cell block in a case of Squamous cell carcinoma (p63, 400X)  
 (C) Histopathology, squamous cell carcinoma (Hematoxylin & eosin, 400X), showing sheets of neoplastic squamous cells.

CB IHC provided an additional yield of malignancy compared to CB H&E and Conventional Smear. Suspicious For Malignancy (SFM) cases were reduced from 38 (31.6%) in conventional smear to zero in CB IHC. Cell

Block H&E also proved significantly better than conventional smear, reducing SFM cases to 23 (19.2%). This was consistent with the findings of Saha R et al.[18] In their study, out of 104 samples, 19 (18.27%) cases were positive for malignancy on conventional smear, whereas, on the cell block, 39 (37.5%) cases were diagnosed as malignancy.

Due to resource constraints, a minimal panel of immunomarkers consisting of TTF-1, p63, and Synaptophysin on all cell blocks was used. The positivity of one or more immunomarkers was taken as PFM. This method found 85 out of 120 cases as malignant. Independent histopathological diagnosis of corresponding biopsy sections revealed 86 cases to be malignant. Four cases detected as malignant by histopathological diagnosis were diagnosed NFM by CB IHC. Three cases diagnosed as Benign by histopathological diagnosis were detected as PFM by CB IHC. TTF-1, p63, and Synaptophysin constitute a useful panel in resource-limited settings for subtyping lung cancer in Cell block preparations. TTF-1 was positive in 87.5% of cases of lung adenocarcinoma, p63 was positive in 79.2% of squamous cell carcinoma, and synaptophysin was positive in 91.6% of small cell carcinoma cases. This result corresponds with Dong et al., who found the positivity rate of TTF-1 in adenocarcinoma to be 92.59%. [19] Our study revealed CB IHC method had a sensitivity of 95.4%, specificity of 91.2%, positive predictive value of 96.5%, and negative predictive value of 88.6% in comparison with histopathological diagnosis. This result was comparable to a study by Nathan et al., who found cell block sensitivity to be 89.4%. [20] Out of 86 cases of lung carcinoma detected by histopathological diagnosis, the most common malignancy was adenocarcinoma of the lung (46%), followed by Squamous cell carcinoma (28%) and small cell carcinoma (14%). Singh N et al. [21] and Rawat J et al. [22] found SCC as the most common subtype in their studies, whereas Burt JR et al found adenocarcinoma to be the most common type among smokers as well as non-smokers [16]. Kaur H et al., in their study on 1301 lung cancer patients, found that adenocarcinoma (36.4%) was as common as squamous cell carcinoma (36.4%). [23]

Our study had certain limitations. Firstly, ours was an institution-based single-center study, which is prone to tertiary hospital-based selection bias. Due to resource constraints, a limited number of immunohistochemical markers were used. Also, the histopathology diagnoses were based on small biopsy specimens, because larger resections were unavailable. A larger study period with a larger sample size would also be more impactful as research. However, keeping in mind the prevalence of these limitations in developing countries, this study can have its place as a stepping stone for further larger studies.

Future studies should focus on developing and standardizing cell block preparation protocols across laboratories and tap into opportunities of automated systems for efficiency and consistency. Clinical validation through multicentric trials, including larger panels, is also needed to

test the diagnostic accuracy across diverse populations. Integration of molecular diagnostics, telepathology, and artificial intelligence-assisted protocols can further enhance the accessibility and diagnostic capability of cell block techniques.

## CONCLUSION

Cell block technique provides a better preservation of architectural pattern and morphological features of the cell clusters, which is particularly important in cases with a diagnostic dilemma between benign or non-neoplastic lesions and malignancy. This method offers high sensitivity and specificity, enabling faster and more accurate diagnoses. Cellblock specimens are sufficient for primary diagnosis, and IHC analysis aids in cell typing. In a resource-limited setting like India, using a focused antibody panel with the cell block method can be a game-changer and can be incorporated into routine practice.

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**Author's contribution:** **SM** was involved in all aspects of the study, including the conception, design, data collection, analysis and interpretation, and manuscript preparation. **PB** contributed to the study conception and design, as well as data analysis and interpretation. **AC** and **RB** were responsible for data analysis and interpretation, and also participated in the preparation of the manuscript.

**Availability of Data:** The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Declaration of Non-use of generative AI Tools:** No generative AI tool was used in the preparation of the manuscript. The authors take full responsibility for the content of the publication.

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