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The yield of rigid thoracoscopy in patients of undiagnosed exudative pleural effusion and comparison of pleural fluid and thoracoscopic findings between tuberculosis and malignancy

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Abstract

Background Medical thoracoscopy is an essential tool in the evaluation of patients with pleural effusion who remain undiagnosed despite a thorough pleural fluid workup. Malignancy and tuberculosis are the two most common etiologies in such patients having completely different prognoses. Therefore, correct diagnosis is very important before starting treatment.

This study was planned to study the yield of rigid thoracoscopy in such patients and to observe its associated complications. Furthermore, the difference in the profile of patients with malignancy and tuberculosis was also evaluated.

Methods This was a single-center, exploratory, observational study done between 1st May 2021 to 31st December 2022. Patients with undiagnosed exudative pleural effusion defined as exudative pleural effusions as per Light's criteria with negative Gene X pert and twice negative pleural fluid cytology for malignancy, underwent rigid thoracoscopy for confirmation of their diagnosis.

Results A total of 160 patients, who fulfilled our inclusion criteria, were included in our study. Male to female ratio was 1.25:1, with a mean age of 57.3 years. The most common etiology observed was malignancy, seen in 120 out of 160 patients (75%), followed by tuberculosis, which was seen in 27 (17%) patients. A final diagnosis could be made in 158 patients, giving a diagnostic yield of 98.8%. 11.8% showed procedure-related complications without any mortality.

Conclusion Rigid medical thoracoscopy has a very high diagnostic yield with few complications. A significant proportion of patients with straw-colored effusion can present with malignancy and vice versa. A few with ADA above 40 were diagnosed as having malignancy. Therefore, tissue-based biopsy with thoracoscopy can be easily performed to make a correct diagnosis with huge future implications in such patients.

Keywords Medical thoracoscopy, Rigid thoracoscopy, Undiagnosed pleural effusion, Low pleural fluid ADA

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Introduction

The very first experience of thoracoscopy was observed in the nineteenth century by a urologist named Francis Richard Cruise in Ireland [1].

Later on, in the twentieth century, the Swedish internist Hans Christian Jacobaeus again used thoracoscopy and published his first article describing its clinical applications [2].

Pleural effusions are one of the most common entities encountered by pulmonologists worldwide. The most common etiologies of exudative pleural effusion in India are malignancy, tuberculosis, and pneumonia.

Tubercular pleural effusion is basically a hypersensitivity reaction to tuberculous protein in the pleural space with paucibacillary tuberculosis, therefore, the yield of positive culture or CBNAAT is quite low. In a study done by Jain J et al. [3], they reported that the yield of pleural fluid CBNAAT was 16.6% among 158 study participants.

Cytological analysis of pleural fluid can establish the diagnosis of malignant pleural effusions, but the test has an overall sensitivity of approximately 60% [4], which may increase by 15% with a second thoracentesis pleural fluid sample [5].

Pleural biopsy is the gold standard for the diagnosis of various pleural diseases, which can be done by closed pleural biopsy techniques or under direct vision by using thoracoscopy.

Closed pleural biopsy by Cope or Abrams needle has a poor overall sensitivity of just 38% [6] which was higher in tubercular pleurisy up to 80% due to diffuse involvement of pleura while it was lesser in malignancy due to patchy involvement [7].

CT- or ultrasound-guided cutting needle pleural biopsy is useful in diagnosing malignancy when pleural-based soft tissue masses are identified. In a randomized trial, CT-guided biopsy had a sensitivity of 87% in patients with suspected malignant effusions [8].

The diagnostic yield of USG-guided pleural biopsy was comparable to CT-guided Tru-Cut biopsies [9].

Despite thorough clinical assessment and initial investigations including closed pleural biopsy, the cause of around 20% of PE may remain undetermined [10].

Medical thoracoscopy is one of the most commonly performed diagnostic tools especially when multiple attempts at thoracentesis with pleural fluid analysis in the form of malignant cytology and CBNAAT have failed to achieve a definitive diagnosis in patients with a recurrent exudative pleural effusion and this procedure was recommended by British Thoracic Society Pleural Disease Guideline 2010 [5]

This study was planned to evaluate the yield of rigid thoracoscopy in the diagnosis of exudative pleural effusion of undiagnosed etiology and to look for its associated complications.

Aims and objective

1. To find out the diagnostic yield of rigid thoracoscopy in diagnosing patients of undiagnosed exudative pleural fluid.
2. To compare pleural fluid and thoracoscopic findings between tuberculosis and malignancy.
3. To study the complications associated with Rigid Thoracoscopy.

Materials and methods

This is a single-center, exploratory, observational study done in a university teaching hospital in north India.

Duration of study

1st may 2021 to 31st December 2022.

Ethical approval

Ethical approval of this study was taken from the Institutional Ethics Committee (IEC) (IEC Ref. code: V-PGTSC-11A/P2I).

Inclusion criteria

- Age > 18 years for both males and females
- Undiagnosed pleural effusion (defined as exudative pleural effusions as per Light's criteria with negative Gene X pert and twice negative pleural fluid cytology for malignancy).

Exclusion criteria

- Patients who are not fit for performing thoracoscopy as in the following cases:
- Those with severe uncorrected hypoxemia despite continuous oxygen administration.
- Patients who could not withstand the lateral decubitus position for a period long enough to perform the procedure.
- Patients with unstable hemodynamics.
- Patients with coagulation defects.
- Pregnant female patients.
- Patients who did not give consent for thoracoscopy.

Sample size

A total of 160 patients were enrolled in the study after qualifying inclusion and exclusion criteria.

Method

All enrolled patients were subjected to thorough history, clinical examination, and routine blood investigations like complete hematogram, kidney function test, liver function test, viral markers, coagulation profile, radiology like chest X-ray, and computed tomogram of thorax.

All eligible patients were screened under ultrasound for pleural anatomy like the maximum collection of fluid, septations, pleural nodules, and mass, and the site of thoracoscopy was marked.

Patients were then asked to lie down in a recumbent position with the affected side upward.

Then patients were subjected to thoracoscopy under conscious sedation (IV Midazolam 2–5 mg) and analgesia (IV Fentanyl 100–200 mcg). The thoracoscope used was the rigid thoracoscope of Carl Storz.

The whole pleural cavity was examined thoroughly, and septations were broken, if present. Multiple pleural biopsies ('lift and peel' technique) were taken from abnormal areas on the parietal pleura or from different multiple sites of the parietal pleura when the parietal pleura was found to be grossly normal.

Biopsy samples were sent for histopathological examination, CBNAAT, and MGIT culture for mycobacterium tuberculosis.

All procedures went uneventful except few minor complications which were managed successfully.

Statistical analysis

All the data were collected, tabulated, and analyzed using the statistical package for the social sciences (SPSS version 25). The results were presented as mean ± SD or percentage. Differences in categorical data were compared using the chi-square test of the Fisher exact test. A p value of < 0.05 was considered statistically significant.

Results

A total of 160 patients were enrolled in the study. Out of 160, 89 (55.6%) were male and 71 (44.4%) were female. So, the proportion of male and female patients was comparable. The mean age of the study population was 57.3 years (ranging from 20 to 88 years). In this study, male patients were comparatively older with a mean age of 59.26 (SD ± 0.12.8) years than 54.8 (SD ± 13.3) years of the female patients. This difference in mean age between the two groups was significant statistically (P value 0.033).

The baseline parameters of all enrolled patients were recorded and are shown in Table 1. The most common symptom observed in the study group was a cough, which was seen in 87.5% of patients, followed by loss of appetite and breathlessness, which were reported by 78% and 68% of the patients respectively.

Diabetes was the most common co-morbidity observed (22%) in our study. Thirty-five percent of patients were tobacco chewers while smoking history was observed in 28.7% of the patients.

Thirty-nine patients presented to us with a history of anti-tubercular drug treatment. Out of these, 12 patients were taking ATT on an empirical basis for their current episode of effusion when they presented to us.

Table 1 Baseline characteristics of patients

Variable	Number/mean
Mean age (years)	57.3
Gender (*n*)	
• Male	89 (55.6%)
• Female	71 (44.4%)
Clinical parameters, *n* (%)	
Breathlessness	109 (68%)
Cough	140 (87.5%)
Chest pain	96 (60%)
Fever	24 (15%)
Loss of appetite	126 (78.7%)
Loss of weight	95 (59.4%)
Co-morbidity, *n* (%)	
Diabetes	35 (21.9%)
Hypertension	25 (15.6%)
Coronary artery disease	9 (5.6%)
Chronic kidney disease	5 (3.1%)
Chronic liver disease	02 (1.25%)
Addiction, *n* (%)	
Smoker	46 (28.7%)
Tobacco chewer	56 (35%)
Smoker + tobacco chewer	16 (10%)
Biomass fuel exposure	45 (28.1%)
History of anti-tubercular treatment (ATT)	39 (24.4%)
Clinical examination, *n* (%)	
Pallor	48(30%)
Clubbing	30 (18.8%)
Peripheral lymph nodes	18 (11.25%)
Baseline investigation (mean ± SD)	
Haemoglobin (gm%)	11.39 ± 1.70917
Bilirubin (mg%)	0.56 ± .30648
Total protein (gm%)	6.23 ± .95990
Albumin (gm%)	3.43 ± .54692
Alkaline phosphatase (ALP)	313.9 ± 237.0798
Urea (mg%)	32.23 ± 18.46824
Creatinine (mg%)	0.91 ± .40898
Sodium (mEq/L)	133.2 ± 5.2114

All routine blood investigation were within normal limits in our study population except for Alkaline phosphatase levels, which was higher in the study group (mean 313.9).

Based on the results of thoracoscopy-guided biopsy, the most common diagnosis seen was malignancy, observed in 120 out of 160 patients (75%), followed by tuberculosis, which was seen in 27 (17%) patients. Non-specific inflammation and pyogenic effusion were observed in 10 and 1 patients respectively. No diagnosis can be made even after thoracoscopy in 2 patients (Table 2). Therefore, an etiological diagnosis could be made in 158 out of 160 patients based on the results of thoracoscopy, giving a diagnostic yield of 98.8% (Table 2).

The most common malignancy observed in our study was metastatic adenocarcinoma (110/120), followed by squamous cell carcinoma (4/120) and mesothelioma (3/120). We had 1 patient each with small cell carcinoma, high-grade NHL, and undifferentiated carcinoma.

In patients of metastatic adenocarcinoma, the primary tumor was seen in the lungs in 80 patients, followed by breast in 9 patients, FGT in 5 patients, oropharynx, and GIT in 02 patients each. No primary could be found in 12 patients.

Twenty-seven patients were diagnosed with tuberculosis, all had granuloma formation on histopathology and 5 patients were also concomitantly positive on CB-NAAT of pleural biopsy tissue.

Table 2 Histopathological examinations

Histopathological examination	*N* (%)
Malignancy	120 (75%)
• Metastatic adenocarcinoma	110 (68.75%)
○ Lungs	80
○ Breast	09
○ Female genital tract	05
○ Oropharynx	02
○ Gastro-intestinal tract	02
○ Unknown primary	12
• Squamous cell carcinoma	4 (2.5%)
• Mesothelioma	3 (1.87%)
• Small cell carcinoma	1 (0.62%)
• High-grade NHL	1 (0.62%)
• Undifferentiated carcinoma	1 (0.62%)
Tuberculosis	27 (16.9%)
• Granuloma formation	27 (16.9%)
• CBNAAT positive	5 (3.2%)
Non-specific inflammation	10 (6.3%)
Pyogenic	1 (0.6%)
Inconclusive	2 (1.2%)
Total patients	160

When we compare the characteristics of effusion in patients of malignancy and tuberculosis as depicted in Table 3, there was no significant difference between the age and site of effusion. However, if we look at the gender, in those having malignancy, 55% were females while in those with tuberculosis, only 15% were females.

When we look at the color of effusion, it is a well-known fact that malignancy and tuberculosis are characteristically present with hemorrhagic and straw-colored effusion respectively, which was also seen in our study.

In routine pleural fluid biochemical evaluation, all parameters were comparable between the two groups, except for ADA levels, which were significantly higher in the tuberculosis group (mean = 37.28) than in the malignancy group (mean 19.2).

The most common gross thoracoscopic findings in patients of tuberculosis were pleural thickening with septations, while in those with malignancy, pleural nodules were most commonly observed, followed by pleural thickening with puckering. This difference in gross findings was statistically significant.

The complications associated with rigid thoracoscopy as observed in our study are shown in Table 4. Seven (4.3%) patients had major complications. Five patients had persistent Bronchopleural fistula beyond 72 h, 2 of them developed post-procedure infections in the form of empyema and required systemic antibiotics. In the remaining 3 patients, the BPF resolved with conservative management in around a week. Massive re-expansion pulmonary edema requiring intensive care unit (ICU) admission and major post-procedure bleeding requiring PRBC transfusion were seen in 1 patient each. No mortality was seen in our study.

Minor complications were seen in 12 (7.5%) patients.

Discussion

In our study, a total of 160 patients were enrolled, who presented with undiagnosed exudative pleural effusion after initial pleural fluid workup as per our inclusion and exclusion criteria.

There was no difference based on gender in our study population. But if we look at the subgroup analysis, females were more common in the malignancy group than in the tuberculosis group. As the most common malignancy seen in our study was adenocarcinoma, and females are well known to have a higher frequency of adenocarcinoma, our findings are in line with that [11].

The mean age of patients was 57.3 years. In this study, the mean age of male patients was higher (59.26 years) than that of female patients (54.8 years) (*P* value 0.033). The majority of the patients were ultimately diagnosed with malignancy having adenocarcinoma, and it is well known that adenocarcinoma is common in Asian

Table 3 Comparison of pleural fluid and thoracoscopic findings between malignancy and tuberculosis

Variables	Malignancy ($n=120$)	Tuberculosis ($n=27$)	*P* value
Demographic variable			
Age in years (mean ± SD)	57.72 ± 12.55	56.70 ± 14.1	$P=0.71$
Sex			
• Male (*n* %)	54 (45%)	23 (85.2%)	$P=0.001$
• Female (*n* %)	66 (55%)	04 (14.8%)	
History of ATT			
• Yes (*n*%)	28 (23.3%)	09 (33.3%)	$P=0.279$
• No (*n*%)	92 (76.7%)	18 (66.7%)	
Co-morbidities			
Diabetes			
• Yes (*n*%)	19 (15.8%)	10 (37%)	$P=0.012$
• No (*n*%)	101 (84.2%)	17 (63%)	
Hypertension			
• Yes (*n*%)	18 (15%)	05 (18.5%)	$P=0.65$
• No (*n*%)	102 (85%)	22 (81.5%)	
Chronic kidney disease			
• Yes (*n*%)	01 (0.8%)	03 (11.1%)	$P=0.003$
• No (*n*%)	119 (99.2%)	24 (88.9%)	
Pleural effusion and pleural fluid characteristics			
Side of pleural effusion			
• Left side	57 (47.5%)	12 (44.4%)	$P=0.11$
• Right side	58 (48.3%)	14 (51.8%)	
• Bilateral	5 (4.2%)	01 (3.7%)	
Colour of pleural fluid			$P=0.001$
• Hemorrhagic	76 (63.3%)	08 (29.6%)	
• Straw color	44 (36.7%)	19 (70.4%)	
Pleural fluid protein (Gm%) (Mean ± SD)	4.44 ± 1.06	4.53 ± 0.97	$P=0.70$
Pleural fluid ADA (IU/L)	19.2 ± 11.15	37.28 ± 26.77	$P=0.001$
Pleural fluid lymphocyte (%)	77.43 ± 23.12	82.17 ± 17.48	$P=0.263$
Thoracoscopic findings (*n*)			
Loculations/adhesions (image 1)	40 (33.3%)	17 (63%)	$P=0.004$
Nodules (images 3 and 5)	89 (74.2%)	10 (37%)	$P=0.001$
Mass	25 (20.8%)	03 (11.1%)	$P=0.245$
Puckering pleura (image 4)	61 (50.8%)	01 (3.7%)	$P=0.001$
Pleural thickening (image 2)	70 (58.3%)	24 (88.9%)	$P=0.003$
Sago grains nodules	0 (0%)	04 (14.8%)	$P=0.001$

females, non-smoker, and younger age groups [11]. There was no difference between the mean age of those diagnosed with malignancy and those having tuberculosis.

The most common symptoms observed were dry cough followed by lack of appetite and chest pain. These are nonspecific symptoms in pleural effusion due to local irritation by pleural fluid and systemic inflammation by cytokines [12].

In this study, we could diagnose 158 patients out of 160 patients. Therefore, the diagnostic yield of rigid thoracoscopy was 98.8%. Our result shows malignancy in 120 (75%) patients while 27 (16.9%) patients showed tuberculosis. These findings are similar to other published studies. The comparison of the findings of our study with other similar studies is depicted in Table 5.

In various studies, the diagnostic yield of thoracoscopy varied from 74.3 to 99.2% [13–16].

In contrast to the studies mentioned above, there was a low prevalence of tuberculosis in our study. A probable explanation for this could be the rising incidence of lung malignancy, especially adenocarcinoma. Another reason could be that as Tuberculosis is endemic in our country

Table 4 Complications of rigid thoracoscopy

Complications	*N* (%)
Major complications	**07 (4.3%)**
• Persistent bronchopleural fistula beyond 72 h	3
• Post-operative infections (empyema)	2
• Post-operative major bleeding requiring blood transfusion	1
• Re-expansion pulmonary edema requiring ICU	1
• Death	0
Minor complications	**12 (7.5%)**
• Post-procedure pain	04
• Hypoxia during procedure	03
• Post-operative minor bleeding	03
• Sub-cutaneous emphysema	02
Total	**19 (11.8%)**

with empirical prescription of ATT from primary health care centers in patients of pleural effusion, only those who did not show response to ATT were referred for further evaluation to tertiary care centers.

In tuberculosis-endemic areas like India, diagnosis of malignant pleural effusion is often delayed due to multiple factors including socioeconomic, inappropriate trials of ATT by local practitioners, etc. We have compared the pleural fluid and thoracoscopic findings between those with tuberculosis and malignancy (Table 3).

Around 63% of malignant pleural effusions had hemorrhagic color fluid in contrast to tubercular pleural effusions where 70% of effusions were straw-colored and this difference was significant statistically ($p < 0.05$). Kuwal A et al. [17] compared malignant pleural effusion with non-malignant pleural effusion and they found similar findings as 77.4% of malignant effusions had hemorrhagic pleural fluid while non-malignant 4pleural effusion patients had 33% hemorrhagic fluid.

But still, a large percentage of patients with malignant pleural effusion had straw-colored effusion (37%) and vice versa (30%). Therefore, the empirical assumption of malignancy based on the effusion being hemorrhagic or tubercular because it is straw-colored could be drastic as both these diseases have an extremely different prognosis. Therefore, every attempt should be made to confirm the diagnosis as it has a huge impact on the final outcome for the disease and patient.

Adenosine deaminase (ADA) is the enzyme that catalyzes the conversion of adenosine to inosine. ADA is a predominant T-lymphocyte enzyme. In our study, there is a significant difference in pleural fluid ADA levels with mean ADA levels in malignant and tubercular pleural effusion were 19.2 and 37.28 IU/L respectively ($p < 0.05$). Maturu VN et al. [18] compared 104 malignant and 76 patients with tubercular pleural effusions and found out mean ADA level in malignant and tubercular pleural effusion is 47 and 26 IU/L respectively. Mehta AA et al. [19] studied 171 exudative pleural effusions and found the median ADA value as 45.3, and 18 in tubercular and malignant pleural effusion respectively. In above mentioned studies, there were higher values of ADA in tubercular pleural effusion. The probable reason is that higher ADA values have more chance of tuberculosis and are put on ATT from other primary centers, therefore, they usually do not reach our center.

There is no definitive cut-off value of ADA for the diagnosis of tuberculosis. The most widely accepted cut-off level of ADA for the diagnosis of tubercular pleural effusion is 40 IU/l [20].

In this study, 11.58% of patients had tuberculosis in the low ADA group (ADA < 40 IU/L) while 50% of patients had tuberculosis in the high ADA group (ADA > 40 IU/L). This difference was significant statistically (Fig. 1). Also, the probability of having TB increases with increasing values of ADA and vice versa. In our study, as 50% of

Table 5 Comparison of the results of our study with other similar studies

Variables	Our study	Mootha VK et al. [13]	Eman Sobh et al. [14]	Patil CB et al. [15]	Tousheed SZ et al. [16]
Sample size (*n*)	160	35	542	129	373
Male (*n*%)	89 (55.6%)	25 (71.4%)	316 (58.3%)	92 (71.3%)	246 (65.9%)
Female (*n*%)	71 (44.4%)	10 (28.6%)	226 (41.7%)	37 (28.7%)	127 (34.1%)
Mean age (years)	57.3	48.68	57	54	51.9
Diagnosis achieved	158	26	476	110	370
Diagnostic yield (*n*%)	98.75%	74.3%	87.8%	85.3%	99.2%
• Malignancy	120 (75%)	17 (48.6%)	329 (60.7%)	73 (56.6%)	120 (32.2%)
• Tuberculosis	27 (16.9%)	8 (22.9%)	112 (20.7%)	31 (24%)	125 (33.5%)
• Non-specific inflammation	10 (6.3%)	–	35 (6.5%)	18 (14%)	42 (11.2%)
• Other	1 (0.6%)	1 (2.9%)	–	6 (4.6%)	83 (22.3%)

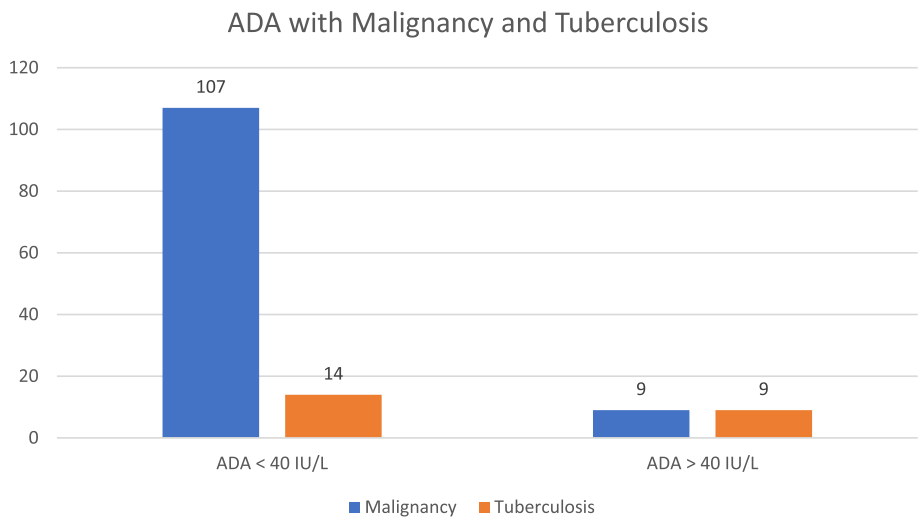

Fig. 1 Relation of malignancy and tuberculosis with ADA

patients having ADA > 40 were ultimately diagnosed as having malignancy on biopsy, taking a fixed cut-off of 40 would lead to a wrong diagnosis in a significant number of patients.

Other pleural fluid markers like protein and lymphocytes were comparable in malignant and tubercular pleural effusions and this was similar to other studies.

In this study, we found pleural loculations/adhesions, pleural thickening, and sago grains nodules were more common in tubercular pleural effusion, and nodules and puckering pleura were more common in malignant pleural effusions and these differences were significant statistically (Table 3). These findings were similar to other studies. Kuwal A et al. [17] also found nodules were common in malignant pleural effusion while adhesions and pleural thickening were most common in non-malignant pleural effusion. In malignancy, nodules are usually larger and variable in size while in tuberculosis nodules are smaller and uniformly distributed [18, 21].

Medical thoracoscopy is a relatively safe procedure without significant procedure-related morbidity or mortality. Complications of thoracoscopy are usually procedure-related like pain and minor bleeding or anesthesia-related like hypotension and drowsiness. Complications in our study were comparable with other studies [16, 22, 23].

Conclusion

Medical rigid thoracoscopy is a safe procedure for diagnosing pleural effusion of undiagnosed etiology. It had a diagnostic yield of 98.8% in this study with few complications without mortality. In tuberculosis-endemic countries like India, many pleural effusion patients are wrongly prescribed ATT based on pleural effusion findings which leads to significant delay in correct diagnosis and management. Also, a significant number of patients having ADA < 40 IU/L had tuberculosis and vice versa. There are many significant differences in pleural fluid characteristics and findings of thoracoscopy between malignancy and tuberculosis which can help in predicting etiology even prior to the histopathological examination report.

Authors' contributions
Dr. Hemant Kumar, Dr Mohammad Arif, Dr Sachin Kumar and Dr Ved Prakash- Planning of study, Designing, performance of procedures, data collections, data analysis and manuscript writing. Dr. Ajay kumar verma and Dr. RAS Kushwaha- Designing of study, supervising study, sample collection and proof reading of manuscript. Dr. Saumya shukla and Dr Chanchal Rana- Designing study, Supervising study, Histopathological Examination and proof reading of manuscript.

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Declarations

Ethics approval and consent to participate
The project is approved by the Institutional Ethical Committee. (Ref.Code: V-PGTSC-2A/P21).

Competing interests
The authors declare that they have no conflict of interest.

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