ORIGINAL RESEARCH PAPER
Volume - 9 | Issue - 10 | October - 2020 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

MINIMALLY INVASIVE EVALUATION OF PLEURO-PULMONARY NODULES AND MASS LESIONS –EXPERIENCE FROM TERTIARY CARE HOSPITAL

Pathology

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ABSTRACT

Background: Pleuropulmonary neoplastic diseases and some nonneoplastic lung lesions appear in the form of pulmonary nodules and mass lesions on imaging. Clinical symptoms and radiological findings in some of these pulmonary diseases are overlapping. For therapeutic management of these cases it becomes most imperative to investigate the lesions further with minimally invasive modality to differentiate between nonneoplastic, benign or malignant etiology.

Methods: Depending on clinico-radiological assessment, the most appropriate procedure for obtaining tissue was decided by team of clinicians and interventional radiologist in 215 patients. Percutaneous Transthoracic CT guided Core Needle Biopsy (CNB) was the most frequently used modality, followed by Transbronchial and Pleural biopsy to obtain tissue specimen from lung nodules and mass lesions. Video Assisted Thoracoscopic biopsy/surgery was used for diagnostic and therapeutic purposes in selected cases.

Results: In the present observational study, concordance of clinico-radiological findings with histopathological diagnosis was achieved in 88.1% cases. Diagnostic accuracy rate of 81.5% was achieved by CNB in the present study. Histopathological study of total 169 adequate cases of pleuropulmonary nodules and mass lesions showed maximum number of cases (84.6%) belonging to neoplastic category.

Conclusion: Diagnostic accuracy and adequacy rate were superior for percutaneous transthoracic Core Needle Biopsy (CNB) than Transbronchial Lung Biopsy (TBLB) or Pleural biopsy. CT guided CNB as a diagnostic modality was found to be effective and relatively safe method preferred by treating oncologist for confirmed tissue diagnosis especially of suspected primary lung cancers.

KEYWORDS

Clinico-radiological correlation, Diagnostic modalities, Specimen adequacy, Histopathological diagnosis

INTRODUCTION

Differential diagnoses of lung nodules and mass lesions range from various non-neoplastic, infective and neoplastic lesions. Neoplastic lesions include benign, malignant and metastatic nodules.[1,2] Overlap of imaging findings necessitates microscopic examination of sample obtained by guided biopsies for final diagnosis.[3]

Set guidelines and sampling protocols are recommended for evaluating pleuropulmonary lesions on the basis of occurrence of relevant symptoms and radiological features.[4]

This study was undertaken to know sample adequacy and efficacy of tissue obtained from different diagnostic modalities used in our center. A spectrum of pleuropulmonary nodules and mass lesions was studied in correlation to clinico-radiological findings.

MATERIALS AND METHODS

Present observational study was carried out over a span of two years from September 2017 to September 2019 at a Tertiary Care Hospital and Medical Institute in Central India. All patients included in the analysis were having radiological evidence of pleuropulmonary nodules or mass lesions and were undergoing evaluation by tissue diagnosis. Patients unwilling to give consent for the diagnostic procedure and patients unfit for undergoing invasive procedures were excluded from the study.

Ethical clearance was obtained for this study from the Institutional Ethics Committee. Detailed clinical history was obtained from each patient. Routine investigations included Complete Blood Count, Coagulation Profile, etc.

Radiological investigations including chest X-ray or CT scan were done for all the patients in the Department of Radiology of the Institute. Pleuropulmonary lesions less than 3cm were categorized as nodules and more than 3cm were termed mass lesions.[5] Lesion size, exact intrapulmonary site of lesion- central or peripheral, number of lesions - single or multiple, presence or absence of mediastinal lymphadenopathy and sites of metastasis in suspected lung cancers were assessed and noted. Depending on clinical and radiological assessment, provisional diagnosis was made in every case.

Methods for obtaining lung tissue specimen:

The most appropriate minimally invasive procedure for obtaining tissue was decided in each case by a team of clinicians, pulmonologists and interventional radiologists. One of the following procedures was performed -

1. Percutaneous Transthoracic CT guided Core Needle Biopsy (CNB)- 20 G or 22 G coaxial automatic core biopsy needles with spring loaded mechanism were used.
2. Transbronchial lung biopsy (TBLB) with a flexible fiber-optic bronchoscope
3. Pleural biopsy with an Abram's pleural biopsy needle
4. Video Assisted Thoracoscopic Surgery (VATS) by Standard three port method was used for diagnostic and therapeutic purposes in selected cases.

Tissue sample obtained was immediately put into formalin fixative bottle and sent to histopathology department. Routine paraffin processing and H&E staining was done initially for all samples. Special stains or selective immunohistochemical markers were utilized, when essential, in few cases.

RESULTS

In the present study, total 215 consecutive samples obtained from patients with pleuropulmonary nodules or mass lesions were analyzed and divided into two groups:

1) Adequate for definitive diagnosis- Specimen with sufficient material where definitive diagnosis could be given on microscopic examination.
2) Inadequate for definitive diagnosis- Specimen showing non-representative tissue including necrotic material, normal lung parenchyma and fibro-collagenous tissue. Clinico-radiological diagnosis could not be ruled out.

In this study, age range of 2 to 84 years with mean age 53.7 years was seen. Male to Female ratio was 1.8:1.

Table 1: showing frequency of use and adequacy of tissue samples in relation to sampling modalities used

Sampling modality	Used in number of cases (%)	Adequate for Histopathological diagnosis	Inadequate for definitive diagnosis
Core Needle Biopsy	173 (80%)	141(81.5%)	32(18.5%)
Transbronchial biopsy	19(9%)	8(42.1%)	11(57.9%)
Pleural biopsy	10(5%)	7(70%)	3(30%)
VATS	13(6%)	13(100%)	0(0%)
Total	**215 (100%)**	**169 (78.6%)**	**46 (21.4%)**

As seen from Table 1, out of total 215 specimens, definitive histopathological diagnosis was possible in 169 (78.6%) cases. While tissue slides from 46 (21.4%) cases showed either adjacent normal lung parenchyma, muscle, fat, fibro-collagenous tissue or necrotic tissue and were grouped under Inadequate for definitive diagnosis and excluded from further analysis.

CT guided Core Needle Biopsy (CNB) was the commonest minimally invasive sampling method used. Out of total 173 CT guided CNBs, definitive histological diagnosis could be obtained in 141 cases giving adequacy or a diagnostic success rate of 81.5%.

Video assisted thoracoscopic surgery (VATS) was used in 6% cases to obtain tissue from pleura and lung and as therapeutic measure. Lobectomy, cystectomy and pneumonectomy were the other specimens obtained by this method. Highest diagnostic success rate was achieved by VATS.

Most common complication was subcutaneous emphysema in 25% followed by pneumothorax 10% and pulmonary hemorrhage 5% cases. All complications were managed conservatively.

Correlation between clinico-radiological findings with histopathological diagnosis was obtained in 149 cases (88.1%), as shown in Table 2.

Chi square test was applied and p value of <0.001 was obtained. On the basis of imaging features, differentiation between neoplastic and non-neoplastic lesions was possible in statistically significant number of cases.

Table 2: showing histopathological and clinico-radiological correlation

		Histopathological diagnosis		
		Neoplastic	**Infective**	**Total**
Radiological diagnosis	**Neoplastic etiology**	**131**	5	136
	Infective etiology	4	**18**	22
	Neoplastic / Infective etiology	8	3	11
	Total	143	26	169

Discordance between radiological and histopathological diagnosis was found in nine cases. Five cases with histopathological diagnosis of non-neoplastic infective lesions were reported as neoplastic on radiology. Four neoplastic cases on histopathological examination were reported as non-neoplastic infective lesions on radiology.

In 11 cases the definite diagnosis on the nature of lesion was not possible on radiological imaging and was reported as either neoplastic or infective etiology. Out of these eleven cases, eight lesions were diagnosed as neoplastic and three lesions diagnosed as infective on the basis of histopathological examination.

The adequate biopsies were classified as neoplastic and non-neoplastic using standard criteria.[6,7] Neoplastic category was further classified as benign and malignant; malignant category included both primary and metastatic lesions. Primary lung malignancies were initially classified based on morphology alone as per the WHO 2015 criteria for the reporting of small biopsy of lung into Small Cell Carcinoma (SCC) and Non-Small Cell Carcinoma (NSCC) and further subtyping was made based on specific immunohistochemical markers.[8]

Majority of the cases (32%) presented with T3 tumor of more than 7cm in largest diameter closely followed by T2a tumors of size 3.1 to 5cm in 38 (29.4%) cases, T2b tumor of size 5.1 to 7cm in 34 (26.3%) cases and least commonly with T1 tumor size less than or equal to 3cm were found in 4 (3.1%) cases.

Four (3.1%) lung cancer cases presented with lung nodule with size less than or equal to 3cm and remaining 125 (96.9%) cases were designated as mass lesions with size more than 3cm on radiology.

Histopathological study of total 169 adequate cases of pleuropulmonary nodules and mass lesions, presented in Table 3, showed maximum number of cases belonged to malignant neoplastic category.

Table 3: showing histopathological diagnoses of 169 adequate cases.

HPE diagnosis	**Percentage (%)**	**Cases (n)**
Neoplastic	84.6%	143
Malignant	83.4%	141
• Adenocarcinoma	35.5%	60
• Squamous cell carcinoma	31.4%	53
• NSCC NOS*	2.9%	5
• Adenoid cystic carcinoma	0.6%	1
• Small cell carcinoma	6.5%	11
• Malignant mesothelioma	2.4%	4
• T cell lymphoblastic lymphoma	0.6%	1
• Metastatic	3.5%	6
Benign	1.2%	2
• Mucous gland adenoma	0.6%	1
• Solitary fibrous tumor	0.6%	1
Non neoplastic	15.4%	26
Inflammatory- Pneumonia	2.9%	5
Granuloma	2.9%	5
Tuberculosis	1.2%	2
Non-specific pleuritis	1.8%	3
Non-specific infective lesion	2.4%	4
Cysts - Hydatid cyst	2.4%	4
Inflammatory/Infective cystic lesion	1.2%	2
Other - Pulmonary alveolar microlithiasis	0.6%	1
TOTAL	**100%**	**169**

*NSCC NOS-Non-Small Cell Carcinoma Not Otherwise Specified

Adenocarcinoma (35.5%) was the most common primary malignant tumor of the lung closely followed by squamous cell carcinoma (31.4%). Small cell carcinoma (6.5%), Non-Small Cell Cancer Not Otherwise Specified (2.9%) and malignant mesothelioma (2.4%) were the other less frequently occurring lesions.

Out of total 118 Non-Small cell carcinomas, 48 cases of adenocarcinoma and 42 cases of squamous cell carcinoma were diagnosed based solely on the morphological features. Remaining 28 cases were labelled as Non-Small Cell Carcinoma Not Otherwise Specified (NSCC NOS). These NSCC NOS biopsies were then subjected to Immunohistochemical examination and further subtyped. One case of primary salivary gland carcinoma of lung was diagnosed as adenoid cystic carcinoma (0.6%). Extensive search for primary salivary gland lesion was done by CT scan of the Head and Neck region, in the absence of which it was labelled as primary salivary gland tumor of the lung.

In three cases, diagnosis of mesothelioma was suggested on microscopic features in pleural biopsy material. One case was suggested as mesothelioma on material obtained by VATS. A single case of lymphoma (0.6%) was obtained. Further work-up was done by FNAC from the mediastinal lymph nodes and diagnosis confirmed by Flow cytometry.

There were six cases (3.5%) of metastasis to the lung. Attempt to identify the primary was done based on presenting complaints, past history, thorough clinical and physical examination and other radiological findings in these cases.

A case of Solitary Fibrous Tumor of pleura (SFT) was diagnosed on CNB material. Solitary well-defined soft tissue mass on radiology along with characteristic microscopic features clinched the diagnosis.

Among the non-neoplastic lesions, non-caseating granulomas (2.9%) and pneumonia (2.9%) were the most common diagnosis followed by non-specific infective lesion (2.4%) and hydatid disease (2.4%). All the cases of Hydatid cyst were diagnosed and treated by VATS.

Two cases of pulmonary tuberculosis (1.2%) showing caseating granulomas with positive AFB stain were obtained; one each by pleural biopsy and VATS. A rare case of Pulmonary Alveolar Microlithiasis (PAM) (0.6%) was obtained by Transbronchial lung biopsy.

DISCUSSION

The value of clinico-radiological assessment of lung lesions lies in the

feasibility of obtaining tissue for accurate diagnosis and to avoid under- or over-treatment of such patients.[9]

According to the glossary of terms for chest imaging proposed by the Fleischner Society, a lung nodule is defined as an approximately rounded opacity more or less well-defined measuring up to 3 cm in diameter. Rounded lesions measuring more than 3 cm in diameter are termed lung masses and should be considered indicative of lung cancer until histologically proven otherwise.[5]

In our setting, patients presenting with pleuropulmonary nodules and mass lesions initially undergo non-invasive ancillary investigations-examination of sputum, bronchoalveolar lavage, bronchial washings and radiological investigations to evaluate the cause of presenting respiratory symptoms. The pleuropulmonary nodules and mass lesions that are diagnosed as non-neoplastic or infective lesions undergo treatment with disease-specific antibiotic courses and observed for relief of symptoms. These non-resolving infective lesions and suspected malignant lesions were subjected to minimally invasive procedures for obtaining tissue for definitive diagnosis. Similar approach is recommended in the studies by Erasmus et al (2000), Leef et al (2002) and Khan et al (2010); for radiological differential diagnosis of pleuropulmonary lesions.[1,3,9]

Criteria for non-diagnostic results were similar to those used in a study by Lee et al (2019).[10] Comparative studies for choice of diagnostic modality have stated that CNB samples are preferable over Guided FNAC samples.[11-15] Erasmus et al (2000) emphasized the overlap of clinic-radiological findings, importance of distinguishing malignant from benign solitary pulmonary nodules and concluded that transthoracic needle aspiration biopsy can be useful for the final diagnosis.[1]

With the advent of advancement in various imaging modalities, percutaneous transthoracic biopsies are being performed more efficiently, with lesser complications and with increased diagnostic accuracy.[16] CT scan guided lung biopsy has presently been universally accepted as the principal method of evaluating lung nodules and mass lesions, especially in suspected lung cancers.[17-20] Core Needle Biopsy have gained a favorable response and are being preferred for the diagnosis of peripherally located nodule or mass lesions of lung.[16,21] Histopathological examination of the biopsy tissue was preferred over cytology sample for final diagnosis of pleuropulmonary lesions by our team of experts.

Sample adequacy and diagnostic accuracy of CNBs in the present study are comparable to studies by Tsukada et al (2000) and Tian et al (2017).[21,22]

Transbronchial Lung biopsy (TBLB) resulted in least satisfactory sample adequacy rate in our study although all the lesions were located in the perihilar region. Mazzone et al (2002) have stated that diagnostic yield for bronchial biopsy is higher for exophytic endobronchial lesions than for submucosal or peri-bronchial lesions.[23,24]

Pleural biopsies were tried in limited number of cases having massive pleural effusion. Mesothelioma have characteristic radiological findings; however, biopsy and pleural effusion cytology are needed for differentiation from pleural metastasis of adenocarcinoma.[25]

VATs proved to be a very efficient diagnostic and therapeutic modality with comparable diagnostic accuracy in the studies by Rena et al (1999) and Luo et al (2013).[26,27] Advantages of the technique have been reported in different types of lung lesions.[28,29] The small number of cases in our study was the limitation.

Clinico-radiological correlation in the present study was acceptable. Radiological imaging features are able to differentiate between majority of the malignant lesions from the benign ones and can even give clue to the cancer cell types in few lesions. Being aware of certain overlapping features on radiology, histopathological diagnosis is imperative for the final diagnosis in some cases.

As seen from Table 3, definitive diagnosis of various non-neoplastic as well as neoplastic pleuropulmonary lesions was possible. Loverdos et al (2019) have given a comprehensive list of differential diagnoses of pulmonary nodules and advocated novel diagnostic modalities to be included in management decisions for the patients.[5] CNBs are effective for all pleuropulmonary nodules and mass lesions according to studies by Kocijancic et al (2007), Liang et al (2014) and Anzidei et al (2017).[18-20] Results of the present study are in concordance.

Maximum 84.6% of cases belonged to neoplastic category and lung cancer was the most frequent diagnosis obtained in our study.

The goal in lung cancer patients is to establish the diagnosis and to confirm the disease stage with the least invasive technique possible. Most of the times, only cytology and/or small biopsy specimens are available for diagnosis.[16] WHO 2015 has given separate guidelines for interpretation of small tissue biopsy.[8] It is a challenge for the present-day pathologists to give therapeutically meaningful report based on the limited tissue obtained.

With the discovery of several therapeutic options that are only approved for treatment of patients with specific histologic types, limited diagnostic work-up can assist in accurate histological categorization. Remaining tissue in the paraffin block can be used for immunohistochemistry and molecular studies for subtyping of Not Otherwise Specified (NOS) category of Non-Small Cell Carcinoma (NSCC). Molecular studies in the form of EGFR testing is recommended for personalized treatment of selected lung cancer cases.

CONCLUSION

CT guided CNB as a minimally invasive diagnostic modality was found to be effective and relatively safe method for evaluation of pleuropulmonary nodules and mass lesions. CNB was preferred by treating oncologist for tissue diagnosis especially of primary lung cancers.

It is a challenge for the pathologist to accurately diagnose and classify lung cancers in small biopsy specimen obtained via minimally invasive procedures. Although most cases of lung cancer can be classified based on morphology, selective use of Immunohistochemistry in problematic cases enhances diagnostic accuracy.

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