IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 21, Issue 3 Ser.7 (March. 2022), PP 27-32
www.iosrjournals.org

Utility of CT guided core needle biopsies in primary lung carcinoma

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Abstract:
Background*: Non-specific clinico-radiological features often delay confirmatory diagnosis of lung cancer. With the availability of personalized treatment for various histological subtypes of primary lung carcinoma, obtaining pre-treatment tissue diagnosis has become mandatory in suspected lung cancer patients. Out of different methods to obtain sample from pulmonary nodule or mass lesion, CT guided core needle biopsy (CNB) has become the method of choice for diagnosis of lung cancer.*
Materials and Methods*: Total 205 CT guided CNBs performed in patients with suspected primary lung cancer on clinico-radiological basis, were analysed. WHO 2015 criteria and guidelines for interpretation of small biopsy of lung were followed for histological diagnosis.*
Results*: Conclusive tissue diagnosis with histological subtyping was possible on core biopsies of lung in 81% cases. Clinico-radiological and histopathological diagnosis concordance was 86.74%. In 92 % of Non-Small Cell Lung Cancers (NSCLCs) definitive subtyping was possible with use of selective immunohistochemistry (IHC) markers performed on the same core biopsy tissue. Complications associated with CT guided CNBs were minimal and managed conservatively.*
Conclusion*: CT guided CNBs can be employed as an efficient, safe and feasible method for histological subtyping of primary lung carcinoma with satisfactory diagnostic accuracy. Diagnosis based on histological and immunohistochemical examination of adequate CNB tissue was found to yield therapeutically meaningful outcome in primary lung cancer. The remaining CNB tissue can be utilised for various molecular studies, thus enabling the oncologist to institute targeted therapy.*
Key Words*: Diagnostic modalities, lung lesions, histopathological diagnosis, Histological subtyping of NSCLCs*

Date of Submission: 05-03-2022 Date of Acceptance: 21-03-2022

I. Introduction

According to the statistics by GLOBOCAN 2018, Lung cancer is now the most commonly diagnosed cancer occurring in 11.6% of the total cancer cases and the leading cause of cancer death in 18.4% of the total cancer deaths worldwide.[1] Most of these patients present in clinically advanced stages of lung cancer where surgery is not a feasible option. The goal in these patients is to establish the diagnosis and to confirm the disease stage with the least invasive technique possible so that personalized treatment can be instituted. Image-guided biopsy are the mainstay to obtain lung nodule specimen. CT has the highest accuracy for diagnosis as an imaging modality.[2] The value of clinico-radiological assessment of lung nodules and mass lesions lies in the feasibility of obtaining tissue for accurate diagnosis and to avoid under or over treatment of the patients. The aim of this study was to evaluate efficacy of CT guided lung biopsy in the diagnosis and histological subtyping of primary lung cancer at our tertiary care center.

II. Material And Methods

The present observational study was conducted over a period of three years from 2017 to 2019 at the Department of Pathology of a Tertiary Care Hospital and Medical Institute in central India.

Study Design: Observational study
Study Location: Department of Pathology of a Tertiary Care Hospital and Medical Institute in central India.
Study Duration: Three years (2017 to 2019)
Sample size: 205 patients.

Subjects & selection method: Elderly males who had presented to Respiratory Medicine Department with cough, dyspnoea and chest pain as chief complaints formed majority of cases in this study. On imaging studies these patients were detected to have pleuropulmonary nodules or mass lesions.

Inclusion criteria:

All patients clinically suspected of having neoplastic disease with radiological evidence of pulmonary nodules or mass lesions and undergoing evaluation by tissue diagnosis were included in the study.

Exclusion criteria:

Cases of known primary malignancy at other body sites with metastasis in the lung, on imaging, were not subjected to biopsy procedures.

Procedure methodology:

Ethical clearance was obtained from the Institutional Ethics Committee. Standard case proforma that included detailed clinical history and investigations performed was prepared for each patient in the study. After pre-procedural scan, Percutaneous Transthoracic CT guided Core Needle Biopsy from the pulmonary lesions were performed by the interventional radiologists with 20 G or 22 G coaxial automatic core biopsy needles with spring loaded mechanism. The procedure was repeated in same sitting, till adequate tissue cores of length more than 1cm were obtained. Lung CNBs were subjected to formalin fixation, routine paraffin sectioning and H&E staining.

All 205 consecutive lung biopsies were studied by two separate pathologists and divided into two groups:

1) Adequate where definitive diagnosis was possible
2) Inadequate when clinico-radiological diagnosis could not be confirmed or ruled out.

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), Non-Small Cell Carcinoma (NSCC) and Others. Standard morphologic criteria for the reporting of NSCC were followed and subtyped into Adenocarcinoma, Squamous cell carcinoma and NSCC Unclassifiable categories. NSCC Unclassifiable cases were subjected to further subtyping based on the use of specific immunohistochemical markers.[3]

III. Result

Beginning in 2017, an upsurge in the utilization of CT guided core needle biopsy as the primary modality of choice for the evaluation of lung lesions was observed. In the year 2017, 43 CNBs were performed with adequacy rate of 79% (n=34). While 81 CNBs each were performed in the year 2018 and 2019, with adequacy rate of 82.7% (n=67) and 80.2% (n=65) respectively. In the present study, total 205 consecutive CT guided CNBs from radiologically evident lung lesions were studied to give tissue diagnosis.

Table 1: Definitive histological diagnosis could be obtained in 166 cases. The diagnostic accuracy rate for CT guided CNBs in the interpretation of lung lesions was 81%. Among the adequate biopsies, majority of CNB specimen (89.15%) yielded a diagnosis of neoplastic lesion on histopathological examination. Primary lung malignancy formed the major bulk of the malignant cases comprising predominantly of Non Small Cell Carcinoma (NSCC). Out of three cases in Others category, two cases of lymphoma and one case of adenoid cystic carcinoma were diagnosed. Seven malignant cases metastatic to the lungs could be identified based on the evaluation of past history and previous health records along with the characteristic histological features of the present biopsies. Three benign lesions could be accurately diagnosed on material obtained from CT guided CNBs. The diagnosis was confirmed after complete excision and IHC studies. Excision of the lesions resulted in complete cure with no evidence of disease spread or recurrence on follow-up.

Table no. 1: Shows histopathological diagnosis of all 205 CT guided CNBs

HPE diagnosis	**No. of cases (n)**	**Percentage**
Adequate	**166**	**81%**
Neoplastic	148	89.15%
• Benign	• 3	• 1.8%
- Adenoma	- 1	- 0.6%
- Benign mesenchymal tumour	- 2	- 1.2%
• Malignant	• 145	• 87.34%
- Primary	- 138	- 83.13%

▪ Small cell carcinoma ▪ Non Small Cell Carcinoma ▪ Others - Metastatic	▪ 10 ▪ 125 ▪ 3 - 7	▪ 7.2% ▪ 90.6% ▪ 2.2% - 4.2%
Non neoplastic	18	10.85%
• Granuloma formation • Changes of pneumonia	• 10 • 8	• 6% • 4.8%
Inadequate	**39**	**19%**
TOTAL	**205**	**100%**

Table 2: In the present study, 73.6% (n=92) of NSCC cases could be diagnosed and subtyped based on characteristic histopathological features alone. Immunohistochemical studies were done for remaining 33 Non-Small Cell Carcinoma- unclassifiable cases. Twelve cases showed positivity for TTF-1 and were reassigned as Adenocarcinoma, while eleven cases showed positivity for p40 and were included in Squamous cell carcinoma category. Three cases that showed positivity for both TTF-1 and p40 and were reported as 'Non-Small Cell Carcinoma Not Otherwise Specified (NSCC NOS) showing features of both squamous cell carcinoma and adenocarcinoma' as recommended by the WHO 2015 criteria for reporting of small biopsy and cytology of lung cancer.[3] Remaining seven cases could not be further assessed and were designated Non-Small Cell Carcinoma-Not Otherwise Specified (NSCC NOS). Adenocarcinoma was found to be the predominant primary lung cancer subtype (50.4%) followed by Squamous cell carcinoma (41.6%). Based on the histopathological and IHC studies, accurate histological subtyping could be done in 92% (n=115) cases of total NSCC.

Table no. 2: Subtyping of Non Small Cell Carcinoma based on histological features and IHC

Diagnosis	**Subtyping on histopathology**	**Subtyping of NSCC-unclassifiable cases using IHC**	**Total**
Adenocarcinoma	51	12	63
Squamous cell carcinoma	41	11	52
• NSCC NOS showing features of both adenocarcinoma and squamous cell carcinoma • NSCC NOS		• 3 • 7	10
Total	**92 (73.6%)**	**33 (26.4%)**	**125**

Table 3: On radiology, five (3.7%) primary lung cancer cases presented with lung nodule with size less than or equal to 3cm and remaining 125 (96.3%) cases were designated as mass lesions with size more than 3cm. Out of total 138 cases of primary lung cancer, 56% (n=73) cases showed metastasis to distant organs. Contralateral lungs and skeletal system were the most common sites of metastasis for all subtypes of NSCC, while SCC showed predominantly hepatic metastasis.

Table no. 3: Histopathological subtypes of primary lung cancers in relation to radiological profile

Radiological parameters	**Squamous cell carcinoma**	**Adeno-carcinoma**	**NSCC NOS**	**Small cell carcinoma**	**Total**
Site					
• Central	11	12	2	5	30 (22.22%)
• Peripheral	41	51	8	5	105 (77.77%)
Size					
• Tx (could not be assessed)	5	8	2	2	17 (12.6%)
• T1 (≤ 3cm)	0	4	0	1	5 (3.7%)
• T2 (>3 to ≤ 5cm)	13	20	2	1	36 (26.66%)
• T3 (>5 to ≤ 7cm)	13	16	2	2	33 (24.44%)
• T4 (>7cm)	21	15	4	4	44 (32.6%)
Pleural effusion					
• Present	17	40	6	6	69 (51.11%)
• Absent	35	23	4	4	66 (48.88%)
Mediastinal LAP					
• Present	34	49	9	8	100 (74%)
• Absent	18	14	1	2	35 (26%)
Number of lesions					
• Single	36	30	6	10	82 (60.74%)
• Multiple	16	33	4	0	53 (39.26%)

A provisional diagnosis based on clinical history, physical examination and radiological features was compared with the final histopathological diagnosis made on the biopsy material obtained under CT guidance and showed concordance in 144 cases. Thus, clinico-radiological correlation with the histopathological diagnosis was obtained in 86.74% cases.

Table 4: All complications could be managed conservatively.

Table no. 4: shows complications associated with CT guided CNBs of lung lesions

Complication	Number of cases	Percentage
No complication	123	60%
Subcutaneous emphysema	51	25%
Pneumothorax	21	10%
Pulmonary haemorrhage	10	5%
Total	**205**	**100%**

Out of total 145 malignant cases diagnosed on histopathology, 50 patients registered at the Radiotherapy and Medical Oncology Department of the Institute. 52.89% of the malignant cases were in advanced stage of lung cancer. All the paraffin blocks with tumour tissue were made available to the treating oncologist for additional immunohistochemical and molecular studies. Molecular studies were done on the tissue blocks of 15 cases of primary lung malignancy. Epidermal Growth Factor Receptor (EGFR) mutation was detected in 7 out of 15 cases. Three cases of adenocarcinoma and two cases of squamous cell carcinoma showed exon 19 deletion in EGFR gene. Exon 21 (L585R) substitution in the EGFR gene was detected in the remaining two cases of adenocarcinoma subjected to molecular testing. ALK and ROS1 mutations were not detected in any of the 15 cases. One case was subjected to detection of PDL1 mutation and was found negative for it. Personalized treatment could be administered to these patients.

IV. Discussion

CT scan guided lung biopsy, using semiautomated or fully automated biopsy needles, has presently been accepted in many centers as the principal method of evaluation of lung nodules and mass lesions.[4] The utility of the sample thus obtained can be analyzed further for histological subtyping of primary lung cancer for triaging patients and instituting targeted therapy. Using this method in our Institute for the first time and following WHO guidelines, we could achieve acceptable diagnostic accuracy for evaluation of lung cancers.

In the present study, adenocarcinoma (n=63) was the most common histological subtype followed closely by squamous cell carcinoma (n=52). Recent data about the prevalence of lung cancer show evolving trends with increasing incidence of adenocarcinoma and decrease in the incidence of squamous cell carcinoma worldwide.[5] In most of the Western studies and majority of the Asian studies, adenocarcinoma has surpassed squamous cell carcinoma as the most common histological subtype.[6] Various Indian studies show a wide variation in the percentage of predominant histological subtype of primary lung cancer. Findings of Indian studies appear to be in the transition phase with some studies still showing squamous cell carcinoma as the prevalent subtype.[7,8] Changing trend of predominance of adenocarcinoma subtype in primary lung cancer is reflected by Indian studies of Noronha et al, Krishnamurthy et al, Bala et al and Das et al.[9-12]

WHO 2015 recommended limited use of immunohistochemical and/or mucin stains for NSCLC-NOS cases that cannot be recognized as adenocarcinoma or squamous cell carcinoma definitively by light microscopy. To preserve as much tissue as possible for molecular testing in small biopsies, they suggested initial evaluation using only one adenocarcinoma marker- TTF-1 and one squamous marker- p40.[3] This protocol was followed in the present study and by using immunohistochemistry, 70% of the NSCC-unclassifiable cases could be subtyped into therapeutically meaningful categories. The findings were in concordance with the studies by Loo et al and Savithamol et al.[13,14] WHO 2015 also recommended that the diagnosis of NSCC- NOS should not exceed more than 10% cases and the terminology of NSCC NOS to be used only when a more specific diagnosis cannot be made based on morphology and/or special staining.[3] Our percentage of NSCC NOS cases 8% were in accord with the WHO 2015 guidelines.

Apart from the predominant number of primary lung malignancies diagnosed on CT guided CNBs from lung nodules and mass lesions, the diagnoses in our cases revealed various non-neoplastic, infective and benign and malignant metastatic neoplastic conditions. In most cases of known primary malignancy at other sites presenting with lung metastasis on imaging, biopsy was not done, as per the protocol by the treating oncologist. This practice and protocol followed explains the low number of metastatic lesions in the present study.

Cases diagnosed as non-neoplastic pulmonary lesion on clinico-radiological findings are usually empirically treated with antibiotics and other medications. Patients with non-resolving lesions showing increase in the size of the lesion or patients showing worsening of symptoms are then subjected to invasive sampling modalities. Thanos L et al found that specific diagnosis for pneumonia and pneumonia mimics was possible in 87.5% of CNBs obtained by using an automated biopsy gun.[15]

WHO 2015 states that Lung cancer can occur anywhere in the lungs, but is more common in the periphery of the lungs than in the hilar region and more common in the upper lobes than in other lobes which was precisely reflected in our findings which showed 77.77% of primary lung cancers located in peripheral lung parenchyma.[3] Wang Y et al found that CT guided percutaneous transthoracic needle biopsy has high diagnostic accuracy of 95.4% for paramediastinal lesions and 94.7% for non-paramediastinal lung lesions.[16]

By definition, a lung nodule is a rounded or irregular opacity, which may be well or poorly defined, measuring ⩽3 cm in diameter, surrounded by aerated lung on radiological imaging. Opacities more than 3cm are termed as mass lesions.[17] Majority of the cases (96.3%) in the present study were designated as mass lesions with size more than 3cm on radiology. High diagnostic yield of small pulmonary nodules can be obtained using CT guided CNB and these specimens provide adequate tissue for molecular testing as shown in studies by Tian P et al and Li et al.[18,19]

Although mediastinal lymphadenopathy was found in 74% of cases of primary lung malignancy on radiological imaging, histopathological staging of mediastinal lymph nodes was beyond the scope of the present study. Multiple lung lesions were seen in 39.26% of primary lung cancers. Differentiation from metastatic lesions is difficult in these cases and makes histopathological diagnosis mandatory. High rate of multiple lesions in primary adenocarcinoma lung is explained by the aerogenous tumour cells spread through air spaces (STAS) surrounding the outer edge of the primary tumour. STAS is an increasingly recognised pattern of invasion seen exclusively in adenocarcinomas.[3]

Metastasis to distant organs was seen in 56% cases of primary lung cancer with majority showing metastasis to contralateral lung similar to study by Lakshmaiah et al.[20] These cases were grouped under M1 of the 8th TNM classification of lung cancer.[21] This finding indicates that more than half of the lung cancer patients in the present study belonged to Stage IV (Advanced stage) of the disease and were clinically unresectable on presentation. Minimally invasive technique of CT guided CNB was indispensable for obtaining tissue specimen for diagnosis and prognosis in these cases.

Higher rate of post-procedure pneumothorax was found in the studies by Manhire et al and Wu et al. They have mentioned various risk factors for the development of biopsy-related pneumothorax including the presence of chronic obstructive pulmonary disease (COPD), small lesion size, a long needle path, and repeated pleural puncture.[22,23]

Until the past decade, there have been no therapeutic implications to classify the Non-Small Cell Lung Cancers (NSCLC) further. Little attention was given to the distinction of adenocarcinoma and squamous cell carcinoma in small tissue samples. The situation changed dramatically with the discovery of several therapeutic options that are only approved for treatment of patients with specific histologic subtypes.[24,25] This necessitated acquiring adequate tumour tissue specimen using minimally invasive technique having high yield with low complication rates.[6]

V. Conclusion

Present study found CT guided CNBs to have acceptable diagnostic accuracy, lesser rate of complications and feasibility to obtain adequate tissue for ancillary testing. Limited diagnostic work-up that makes judicious use of IHC can assist in accurate histological categorization and therapy guidance of primary lung carcinoma.

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Nadia Ilyas, et. al. "Utility of CT guided core needle biopsies in primary lung carcinoma." *IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)*, 21(03), 2022, pp. 27-32.