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FREQUENCY AND PATTERN OF DISTANT METASTASES IN PATIENTS WITH NON-SMALL CELL LUNG CARCINOMA AT INITIAL PRESENTATION ON ^{18}F-FDG PET-CT

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Abstract

Non-small cell lung cancer (NSCLC) frequently presents with distant metastases, significantly impacting its prognosis and treatment options. The use of ^{18}F-FDG PET-CT proves to be an effective tool for the initial staging of NSCLC.

***Objective**: To evaluate the frequency and patterns of distant metastases in newly diagnosed NSCLC patients at initial presentation using ^{18}F-FDG PET-CT.*

***Methods:** Study included 62 biopsy proven NSCLC patients who underwent ^{18}F-FDG PET-CT at initial presentation between March 2024 to August 2024. Demographic data, histopathology, and sites of metastases were recorded and analyzed. Results were documented in designed pro-forma and collected data was evaluated by using SPSS 21.0 for statistical analysis. Age was presented as Mean ±SD. Data was stratified for age, gender and histological subtypes. Frequency and pattern of distant nodal excluding mediastinal (above and below diaphragm), visceral (Liver, Adrenal and other sites) and osseous lesions (axial and appendicular) were tabulated and shown by bar charts. Chi square test was used to determine the dependence between two categorical variables*

***Results:** Out of 62 patients, distant metastases were observed in 38 (61.2%) patients. Adenocarcinoma was more common (59.7%) than squamous cell carcinoma (40.3%) and was significantly associated with female gender (P=0.01). The mean age was 58.2 ±10.0 (Range 29-70) years. No significant association was noted between age and frequency of distant metastatic rate (P= 0.6). Regarding pattern of distant metastases, visceral metastases were most common (66%) including adrenal, liver and other sites including brain, muscles and pancreas, followed by osseous (57.8%) and distant nodal metastases (44.7%). Adenocarcinoma demonstrated comparable rates of distant nodal and visceral metastases but was more frequently associated with osseous involvement (64%) while*

squamous cell carcinoma showed higher prevalence of visceral involvement (85%).

***Conclusion**: ^{18}F-FDG PET-CT shows high efficacy in identifying distant metastases in NSCLC. Adenocarcinoma shows a broader metastatic distribution pattern as compared to squamous cell carcinoma. Employing ^{18}F-FDG PET-CT should be a standard practice for precise M staging at the time of initial diagnosis, aiding in treatment planning while minimizing the need for aggressive therapeutic approaches.*

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INTRODUCTION

Lung carcinoma (LC) is a major public health problem and is one of the leading causes of cancer-related deaths worldwide[1]. According to a cancer registry published data, Lung cancer is documented at the third most common diagnosed malignancy in Pakistan as more than ten thousands of cases were reported only in 2020 [2].

Among its histological subtypes, Non-Small Cell Lung Carcinoma (NSCLC) is the most common. Nearly one-third of NSCLC patients have distant metastases at the time of diagnosis. Locally advanced or metastatic disease (Stage 4) counts for more than 60% of the newly diagnosed cases thereby limiting the treatment options available [3]. Regarding the pattern of Lung cancer's spread, the most common sites are liver, bone, brain and adrenal glands[4]. Since Metastasis status (M) in the TNM staging has a direct impact on the treatment and prognosis of disease, early detection and staging of lung carcinoma is critical for determining the most appropriate management choice [5].

Diagnostic imaging plays a pivotal role in the detection and staging in a diagnosed case of Lung Cancer. Conventionally, Computed Tomography (CT) is commonly being used as modality of choice for screening and staging of lung cancers. With the recent introduction of hybrid molecular imaging, specially, radiotracer Fluroine-18 Flurodeoxygenase (^{18}F-FDG) incorporated Positron Emission Tomography (PET) combined with CT has revolutionized the detection and staging of LC and proves to be more beneficial and accurate in lung cancer staging and for evaluation of response to treatment [6].

As CT can reveal only the anatomical and morphological characteristics of a disease and is acquired only region wise, PET imaging has an additional benefit of detecting the metabolic properties of lesions and allowing a direct evaluation of the disease burden in a single setting of whole-body imaging. As a result, PET-CT appears to be more effective and less time-consuming diagnostic tool for staging of different malignancies. As the amount of the radiotracer FDG absorbed in tumor cells is proportional to the rate at which glucose is being metabolized therefore the amount of tracer avidity exhibited on PET-CT gives an accurate estimation of disease burden and its spread [7].

In comparison with conventional diagnostic imaging, PET-CT, categorically, has a higher diagnostic efficacy in detecting metastasis especially at the extra-thoracic, nodal, bone marrow and adrenal sites. With reference to published data, FDG PET-CT has an overall improved detection rate of extra-thoracic metastases in lung cancer, thus avoiding stage-inappropriate surgery in some cases [8]. Another study has shown that PET-CT turns out to be more beneficial in detecting liver and adrenal lesions at earlier stage with more accuracy than CT scan [5]. PET-CT improves the ability to diagnose distant metastases in potentially curable NSCLC. After a negative conventional staging, unknown metastases were first found on PET-CT in 5% to 29% of the patients [9]. A retrospective study by Choi et al. found that ^{18}F-FDG PET-CT had a better sensitivity and specificity in detecting metastatic lesions in NSCLC. Additionally, it demonstrated utility in distinguishing between benign and malignant adrenal lesions, a common site for metastases where CT may fall short due to overlap in morphological appearance [10]. These findings underline the integral role of PET-CT in comprehensive staging.

This study aims to analyze the frequency and distribution of distant metastases in patients with newly diagnosed NSCLC using ^{18}F-FDG PET-CT, while also assessing the variation in metastatic patterns between histologic subtypes and gender. The findings provide local evidence supporting the integration of PET-CT in the routine staging workup for lung cancer patients and its early detection can avoid patients to undergo radical treatment options.

MATERIALS AND METHODS

This observational cross-sectional study was conducted at the Institute of Nuclear Medicine and Oncology Lahore (INMOL) over a six-month period following ethical approval. Of the 1160 patients referred for ^{18}F-FDG PET-CT between May to October 2024, 62 biopsy-proven cases of non-small cell lung carcinoma (NSCLC) aged 25–70 years were included based on defined inclusion and exclusion criteria. All patients underwent standard PET-CT preparation, including fasting, hydration, and rest. Scanning was performed 45–60 minutes post-injection of 5–7 MBq/kg of ^{18}F-FDG using a PET-CT system. CT acquisition preceded PET (3.8 mm slice thickness, 100 kV, 50 mA). Qualitative analysis assessed non-physiological FDG uptake relative to background tissues, while quantitative evaluation utilized SUV_{max} with uptake >2.5 considered suspicious for malignancy. Inclusion and Exclusion criteria are given in **Figure 1.**

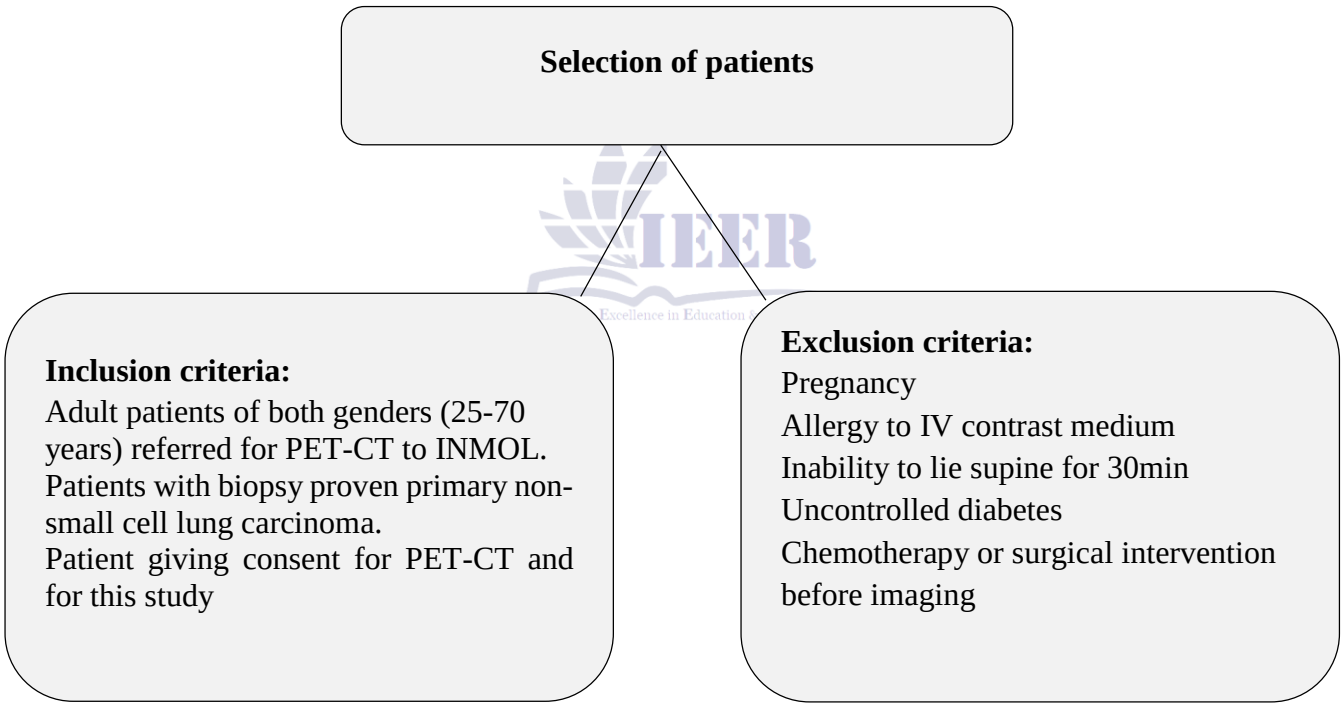

Figure 1: Eligibility criteria for patient selection

STATISTICAL ANALYSIS

Results were documented in designed pro-forma. Collected data was evaluated by using SPSS 21.0 for statistical analysis. Gender, Frequency and pattern of distant metastases including distant nodal excluding mediastinal groups, Visceral (liver, adrenal gland and other sites) and bones (axial & appendicular skeleton involvement) were exhibited as percentage of total number of cases. Age was presented as Mean ±SD. Data was stratified for age, gender and histological subtypes. Frequency and pattern of distant nodal (above and below diaphragm) excluding mediastinal

groups, visceral (Liver, Adrenal and other sites) and osseous lesions (axial and appendicular) were tabulated and shown by bar charts. Chi square test was used to determine the dependence between two categorical variables.

RESULTS

A total of 62 patients with histologically confirmed NSCLC underwent ^{18}F-FDG PET-CT for initial staging. Among them, 47 were male (76%) and 15 were female (24%). Adenocarcinoma was identified in 37 patients (59.7%) and was more common in females (13/15), whereas squamous cell carcinoma was observed in 25 patients (40.3%), predominantly in males (23/25) *(P=0.014)*. The mean age was 58.2 ± 10.0 (Range 29-70) years. Moreover, 47 patients were above 50 years while 15 were aged below 50 years of age.

Out of the 62 patients, distant metastases were detected in 38 (61.3%) cases at initial presentation presentation, while 24 (38.7%) patients had no evidence of distant spread. Patients aged <50 showed slightly higher incidence of distant metastases (66%) at initial presentation as compared to the ones aged >50 years (60%) exhibiting no significant association between age and frequency of distant metastases *(P= 0.6)*. Out of 37 patients with adenocarcinoma, 25 patients (67%) had distant metastases while among 25 patients with squamous cell carcinoma, only 13 patients (52%) were found to have metastatic spread. Visceral metastases were the most common, observed in 25 patients (65.7%). Within this category, metastases were noted in adrenal (36%), liver (28%) and other visceral sites (68%) including brain, thyroid and muscular deposits. Bone metastases were detected in 26 patients (58%), with a predominant involvement of the axial skeleton (91%) and less frequent involvement of the appendicular skeleton (36%). Distant nodal metastases were observed in 17 patients (44.7%), predominantly above the diaphragm as shown in **Figure 2.** The demographics details along with frequency and pattern of distant metastases are summarized in **Table I.**

The pattern of metastatic involvement varied by histological subtype. Adenocarcinoma was more frequently associated with bone metastases (64%) followed by visceral and distant nodal metastases, whereas squamous cell carcinoma more often showed visceral involvement (85%). The frequency and pattern of distant metastases varied by histological subtypes are summarized in **Table II.**

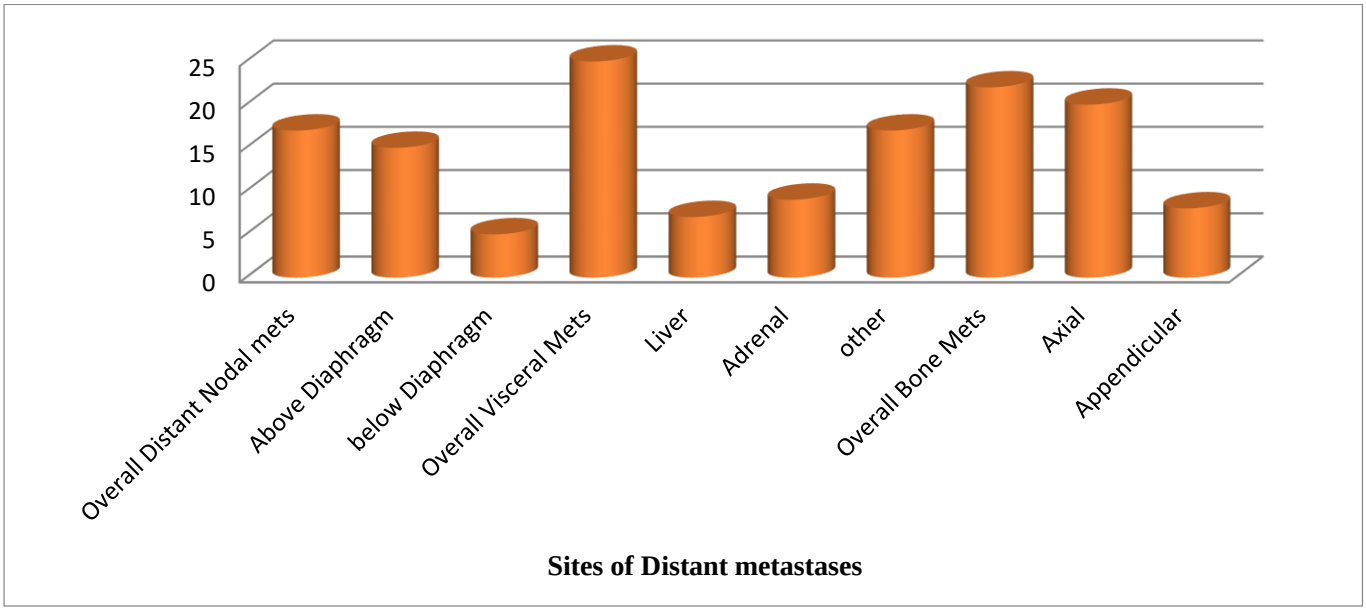

Figure 2: Distribution of distant metastases in NSCLC patients (n=62)

Table. I Demographics, Frequency and pattern of distant metastases in patients of NSCLC		
	No of Patients (n=62)	**Percentage (%)**
Gender Male Female	 47 15	 75.8 24.2
Age <50 >50	 15 47	 24.2 75.8
Histological Subtypes Adenocarcinoma Squamous cell carcinoma	 37 25	 59.7 40.3
Frequency of Metastases		
Distant Metastases Present	38	61.29
No Distant Metastases	24	38.71
Pattern of Distant Metastases		
Distant Nodal Metastases	17	44.74
• Above Diaphragm	15	88.24
• Below Diaphragm	5	29.41
Overall Visceral Metastases	25	65.79
• Liver	7	28.00
• Adrenal	9	36.00
• Other Visceral Sites	17	68.00
Overall Bone Metastases	22	57.89
• Axial Skeleton	20	90.91
• Appendicular Skeleton	8	36.36

Table II Frequency and Pattern of distant metastases by histological subtypes		
Frequency of Metastases	**Distant metastases**	**No distant metastases**
Adenocarcinoma (n=37) Squamous cell carcinoma (n=25)	25 (67%) 13 (52%)	12 12
Site of Metastases	**Squamous Carcinoma (n=13)**	**Adenocarcinoma (n=25)**
Visceral Metastases	11 (84.6%)	14 (56.0%)
• Liver	3 (27.3%)	4 (28.6%)
• Adrenal	3 (27.3%)	6 (42.9%)
• Other Visceral Sites	8 (72.7%)	10 (71.4%)
Bone Metastases	6 (46.2%)	16 (64.0%)
• Axial Skeleton	6 (100%)	14 (87.5%)
• Appendicular Skeleton	2 (33.3%)	6 (37.5%)
Distant Nodal Metastases	3 (23.1%)	14 (56.0%)
• Above Diaphragm	3 (100%)	12 (85.7%)
• Below Diaphragm	0 (0%)	5 (35.7%)

DISCUSSION

This study highlights the essential role of ^{18}F-FDG PET-CT in the non-small cell lung cancer (NSCLC) workup, especially in detecting distant metastases that impact the stage, prognosis, and treatment strategies. A considerable number of our patients were found to have distant metastases at initial presentation, supporting other studies and illustrating the ongoing problems of late diagnosis. Contributing factors include the vague nature of the presenting symptoms and lack of availability of diagnostic imaging in some parts of the world. For example, Hellwig et al. reported that PET-CT altered the intended management plan in about 29% of patients diagnosed with NSCLC because they had unexpected distant metastases [11]. Although our study does not support age group having a significant association with frequency of distant metastases, patients less than 50 years old displayed somewhat higher distant metastatic rate at initial diagnosis which supports published literature [12].

The high prevalence of metastatic disease in our sample reflects the aggressive biological behavior of NSCLC and further supports the utility of ^{18}F-FDG PET-CT as a comprehensive imaging modality. Distant nodal metastases (excluding mediastinal stations) were identified in 44.7% of patients, with notable prevalence in supraclavicular and cervical nodal groups. This distribution is anatomically consistent with known lymphatic drainage pathways from the thoracic cavity. Although below diaphragmatic nodal involvement was less common, its presence reinforces the necessity of whole-body PET-CT imaging. These findings align with prior reports, including Fischer et al., who emphasized the prognostic significance of distant nodal involvement, despite its lower incidence compared to visceral spread [13].

Visceral metastases were observed in 65.8% of metastatic patients, with the adrenal glands and liver being the most frequently affected organs. These results are consistent with prior literature, such as the multicenter analysis by Silvestri et al., which attributed the frequent involvement of the adrenal glands to their rich sinusoidal vascular network and dual arterial supply [14]. Additionally, our findings illustrate PET-CT's sensitivity in detecting metastases in atypical visceral locations including the brain, thyroid, pancreas, and skeletal muscles which are often overlooked on conventional imaging techniques. This supports prior observations by Ghosh et al., who reported that PET-CT often identifies small, metabolically active lesions in unusual sites which can impact staging and management options [15].

Bone metastases were found in 57.9% of skeletal metastases with the strong predominance of involvement of the vertebrae, pelvis, and ribs which are rich in red marrow and favored by hematogenous tumor spread. Involvement of appendicular skeleton was also common, occurring in 36% patients. Bone involvement has crucial implications not only for prognosis but also for the requirement for palliative interventions such as radiotherapy or bisphosphonate therapy.

When comparing our findings to existing literature on histological subtypes, some patterns aligned while others diverged. As established in prior studies, adenocarcinoma was the most common subtype, particularly among female patients, a trend associated with non-smoking status and female gender globally [16, 17]. This is clinically relevant, as adenocarcinomas are more likely to harbor actionable mutations (e.g., EGFR, ALK) which respond well to targeted therapies. Interestingly, while literature typically associates adenocarcinoma with visceral metastases, especially to the adrenal glands, liver, and brain [18, 19], our results depicted a higher frequency of bone metastases, with nodal and visceral spread being more evenly distributed. This discrepancy may point to underlying regional, biological, or demographic variations in metastatic behavior.

Squamous cell carcinoma (SCC), in contrast, is typically regarded as more locally advanced with bone and lymphatic metastatic involvement [20]. Our study identified a greater-than-expected incidence (85%) of visceral metastases in SCC cases. Proximal axial skeleton bone involvement remained prominent, but distal nodal involvement was relatively sparse. This difference may be due to either a more aggressive disease phenotype in our population or the heightened sensitivity of ^{18}F-FDG PET-CT in detecting early metastatic spread not visible on conventional imaging [21].

Our study highlights the whole-body ^{18}F-FDG PET-CT scan's clinical usefulness not only regarding precise

staging but also its impact on treatment strategies, particularly for differentiating candidates for curative-intent therapy from those who require systemic or palliative therapies. Van Tinteren et al. demonstrated that the incorporation of ^{18}F-FDG PET into the diagnostic workup eliminated a considerable number of futile thoracotomies [22]. Current international recommendations issued by the NCCN and ESMO now incorporate the use of PET-CT imaging as baseline staging for reserves-for-surgery NSCLC patients [23, 24]. In addition, accurate and timely detection of distant metastatic disease is fundamental to determining eligibility for some of the newer treatment options, such as immunotherapy and Stereotactic Body Radiation Therapy (SBRT).

Overall, while past literature often categorizes metastatic patterns based on histological subtypes, our findings suggest more overlap and variability than traditionally recognized patterns. Adenocarcinoma, for instance, demonstrated a surprisingly high rate of bone metastases, while SCC showed a broader visceral spread. These differences emphasize the need for individualized imaging strategies and support the continued integration of PET-CT into routine NSCLC workups.

LIMITATIONS

This study has certain limitations. It was single-center study, which may introduce selection bias. Additionally, not all metastatic sites were histologically confirmed, and the correlation between PET findings and clinical outcomes was not evaluated. Future multicenter studies with larger sample sizes and long-term follow-up would provide more robust evidence.

CONCLUSION

The findings from this study underscore the indispensable role of ^{18}F-FDG PET-CT in the initial staging of NSCLC. By revealing the true extent of metastatic disease, PET-CT can significantly alter the staging and prevent futile surgical interventions & helps in determining the most appropriate treatment modality including systemic therapy, targeted agents, radiotherapy, or palliative care. Moreover, the detection of multiple site involvement or unexpected metastases allows for a better prognostic assessment and more personalized patient management. In addition, our study demonstrates that age has no significant association with development of distant metastases so regardless of patient's age, routine use of ^{18}F-FDG PET-CT in the initial workup of NSCLC should be considered. It reveals a high burden of metastatic disease at presentation, with significant variation by histologic subtype. The results support policy changes that require unrestricted access to PET-CT scanners for all patients with clinically confirmed advanced lung cancer, particularly in areas with high disease prevalence and scarce resources for diagnostic imaging.

Declarations

Data Availability statement

All data generated or analyzed during the study are included in the manuscript.

Ethics approval and consent to participate

Approved by the department concerned (IRB/INMOL-24-18)

Consent for publication

Approved

Funding

Not applicable

Conflict of interest

The authors declared the absence of a conflict of interest.

Author Contribution

Dr Farooq Hassan Shahid (Resident Nuclear Medicine) - Manuscript drafting, Study Design, Data entry, Data analysis, Literature review.

Dr. Huma Imtiaz (Resident Paediatric surgery)- Data entry, Data Analysis, Literature review

Dr. Muhammad Numair Younis (Consultant Nuclear Physician) - Conception of study, Manuscript review, Critical input

All authors reviewed the results and approved the final version of the manuscript. They are also accountable for the integrity of the study

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