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CT Radiogenomics Of Non-Small Cell Lung Cancer

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Abstract

Background: Non-small cell lung cancer is one of the main causes of cancer-related mortality. Multiple molecular mutations have been implicated in its manifestation, which have a significant impact on the prognosis and probability of response to systemic therapies. It is hence of paramount importance to investigate their imaging features for early diagnosis and better prognostic outcomes.

Aim: To retrospectively identify the association between CT characteristics and EGFR, ALK and KRAS mutation status in lung biopsy specimens of NSCLC.

Materials and Methods: A comprehensive review of CT images of patients diagnosed with NSCLC during the period spanning January 2016 to January 2020 was conducted. The evaluated CT parameters included: tumour localization; dimensions; morphology; margin characteristics; air bronchogram; bubble-like lucency; pleural tail; pleural retraction; nodules in tumour lobe; nodules in non-tumour lobes; emphysema; fibrosis; pleural effusion; lymphadenopathy. Statistical analysis was done using Chi-square test and multivariate logistic regression to determine the independent factors for molecular mutation.

Results: Among the cohort of 97 NSCLC patients, 45 exhibited EGFR mutation, 23 had ALK-rearrangement, and 29 displayed KRAS mutation. Small size, peripheral location, air bronchograms, pleural retraction, female sex, and non-smokers were associated with EGFR mutation. ALK gene rearrangement was associated with young age, central location, pleural effusion, and absence of pleural tail. Smoking, round lesions, and tumour nodules in non-tumour lobe were associated with KRAS mutation.

Conclusion: This investigation has unveiled noteworthy associations between specific CT imaging features and EGFR, ALK, and KRAS mutations in NSCLC patients. These findings hold promise for enhancing our understanding of NSCLC heterogeneity and optimizing patient-specific treatment strategies.

Keywords: Anaplastic lymphoma kinase (ALK); Computed Tomography (CT); Epidermal growth factor receptor (EGFR), Kirsten rat sarcoma (KRAS); Non-small cell lung cancer (NSCLC); Radiogenomics

Introduction

Non-small cell lung cancer (NSCLC) is one of the most frequent cancers in the world, and is the leading cause of cancer-related death. Patients who present with early-stage disease undergo curative surgical resection. However, almost 30-60% of them present with recurrence. (1) The vast majority (~60%) of the patients have advanced metastatic disease that is not feasible for surgical resection. The standard treatment for such cases is platinum-based chemotherapy, whose response rate is ~30-40%. Resistance to platinum-based therapeutic drugs is seen in many patients, further bringing down the median survival

to about 8-10 months. (2) Hence, more effective treatments are needed for advanced or recurrent NSCLCs. Regulatory and genetic abnormalities that accelerate cell proliferation, inhibit cell death, and induce tumorigenesis have been discovered as a result of recent improvements in our understanding of cell signaling networks that control cell survival. (2) Introduction of innovative therapies targeting these signaling pathways have dramatically changed the treatment of NSCLC patients. According to new guidelines, people with NSCLC histology should now be tested for the most common targetable genetic abnormalities, including Epidermal Growth Factor Receptor (EGFR) gene mutations, Anaplastic Lymphoma Kinase (ALK) gene rearrangements, and non-targetable Kirsten rat sarcoma viral oncogene (KRAS). (2)

EGFR is a cell-surface tyrosine kinase receptor that can activate pathways associated with cell growth and proliferation when activated. (3) It is expressed in majority of NSCLC and has a significant role in regulation of the growth of tumour cells, including their differentiation, proliferation, motility and survival. (4) Mutation in the EGFR gene, increased number of EGFR genes and overexpression of the EGFR protein include some of the oncogenic mechanisms. (5) As they carry a better prognosis and are amenable to effective treatment with specific targeted therapies- Cetuximab (monoclonal antibodies) and Erlotinib and Geftinib (Tyrosine Kinase Inhibitors, TKI), (6) it would be ideal to start early treatment based on imaging features.

ALK gene rearrangement, most commonly with fusion to echinoderm microtubule-associated protein-like 4, is another common driver mutation with targetable treatment and is seen in approximately 7% of NSCLC. (7) They present in young people who have never smoked (8,9) with a higher rate of nodal metastases and lymphangitic carcinomatosis as compared to those with EGFR mutations, thus presenting with a worse prognosis. (10) Trials comparing ALK inhibition with chemotherapy in treatment-naive patients found that use of Crizotinib, first-generation ALK TKI, resulted in a longer progression-free survival time, and an increased response rate with a better quality of life. (11,12)

KRAS is seen in approximately 17% of NSCLC, and is associated with a positive smoking history. (13) Several studies (14–16) have shown that it is associated with tumours showing rapid growth and relatively higher rates of osseous, soft tissue and distant nodal metastases, hence associated with dismal prognosis and worse response to treatment. KRAS-positive NSCLC differs from other biomarker subtypes in that it has been difficult to treat, leading to it being labelled as "undruggable" for a long period. Chemotherapy has been the standard of treatment for patients with KRAS-positive NSCLC until recently. However, tremendous progress has been made, with a variety of medicines in various phases of research. Sotorasib is the only FDA-approved drug to target KRAS currently.

Molecular subtypes thus have an impact on prognosis and probability of response to systemic therapies. For those with activating alterations in the EGFR, ALK, and KRAS genes, targeted TKI therapy may significantly contribute to improved disease control, symptoms, and quality of life when compared to those who undergo standard platinum-based chemotherapy. Imaging-based NSCLC subtype data could aid thoracic surgeons in determining the best surgical resection procedures. Late-stage patients can benefit from an imaging-based subtyping strategy in the palliative situation. CT morphology can be used to track pattern changes during therapy as a result of clonal selection. Therefore, early description of the molecular subtype of lung cancer has important prognostic relevance and management implications. With increase in knowledge of the various biologic factors that affect prognosis and management of lung cancer, more attention is needed towards imaging to assess whether certain types of tumor biologic factors can be predicted by imaging.

Aims And Objectives:

Aim:

To retrospectively identify the relationship between CT characteristics and molecular mutation status in lung biopsy specimens in a cohort of Indian population.

Objectives:

1. Determine which CT features correlate best with molecular mutations.

2. Determine a combination of features which can predict the presence of EGFR, ALK, and KRAS mutation.

Materials And Methods:

This was a hospital-based retrospective observational single center study conducted between March 2020 to November 2021 in the Department of Radiodiagnosis and Imaging, at our institution. Institutional Ethics Committee approval was obtained (IEC No. 742/2019). Informed consent from patients was waivered due to retrospective nature of study. Data collection was done after obtaining consent from IEC and Medical Superintendent.

Sample Size: 97

Inclusion criteria:

1. Pre-treatment chest CT study of the primary tumour at our institution, a histopathological diagnosis of NSCLC, and data on molecular mutation status (EGFR / ALK / KRAS)

Exclusion criteria:

1. Unavailability of molecular mutation status
2. Subjects already on treatment (chemotherapy, radiotherapy) for NSCLC.

Study Subjects: Hospital numbers of those diagnosed with NSCLC based on CT findings and histopathological features between January 2016 to September 2019 were collected. This resulted in 176 cases. Molecular mutation status was available for 97 cases, whose CT images retrieved from PACS. Clinical data and molecular mutation status was retrieved from medical records.

Image Acquisition: The images were acquired using Philips Incisive 128-slice and Philips Brilliance Big Bore 16-slice CT machines in the Department of Radiodiagnosis and Imaging at our Institute. With patient in supine position, plain axial scan was taken with scan range extending from the apex of lungs to the dome of diaphragm. Iodinated contrast material, with at least 320 milligram Iodine per milliliter, was injected using a power injector at a rate of 5-6 ml/second followed by a saline chaser at the same rate, and axial post-contrast scan was taken with the same scan range. Determination of optimal contrast timing was done using a bolus trigger technique. 120 kVp and automatic tube current adjustment was used. Multiplanar reconstruction was done using thin sections into coronal and sagittal sections. Image reconstruction was done in 5 mm thick sections and images were stored in PACS.

Image Analysis: The Digital Imaging and Communications in Medicine (DICOM) images from CT studies were qualitatively analyzed in both lung and mediastinal windows by two radiologists with different degrees of experience in interpreting chest CT, who were blinded to the molecular mutation status. The first 10 cases were analyzed in consensus to standardize the reading. In case of difference in interpretation, the senior reader's decision was accepted. For each patient, date of CT examination, age, sex, and smoking status (positive for current or former smoking for at least 10 years) were extracted from the medical records. For each CT (each corresponding to a single patient), the following data **(Table 1)** was recorded on an Excel spreadsheet file (Microsoft Office Excel 2003, Richmond, VA, USA): 1) location of the lesion, indicated as central or peripheral; 2) maximum diameter of the lesion (in cm) evaluated on the multiplanar reconstructed (MPR) images in lung window; 3) margins, evaluated in lung window, and indicated as smooth, lobulated or spiculated; 4) presence or absence of air bronchograms; 5) presence or absence of bubble-like lucency; 6) presence or absence of pleural tail; 7) presence or absence of pleural retraction; 8) presence or absence of peripheral fibrosis; 9) presence or absence of peripheral emphysema ; 10) presence or absence of tumour nodules in the tumour lobe; 11) presence or absence of tumour nodules in the non-tumour lobes; 12) presence or absence of lymphadenopathy; 13) presence or absence of pleural effusion.

Table 1 : Features of tumour assessed on CT images

1. Location	Central	Located in segmental or more proximal bronchi

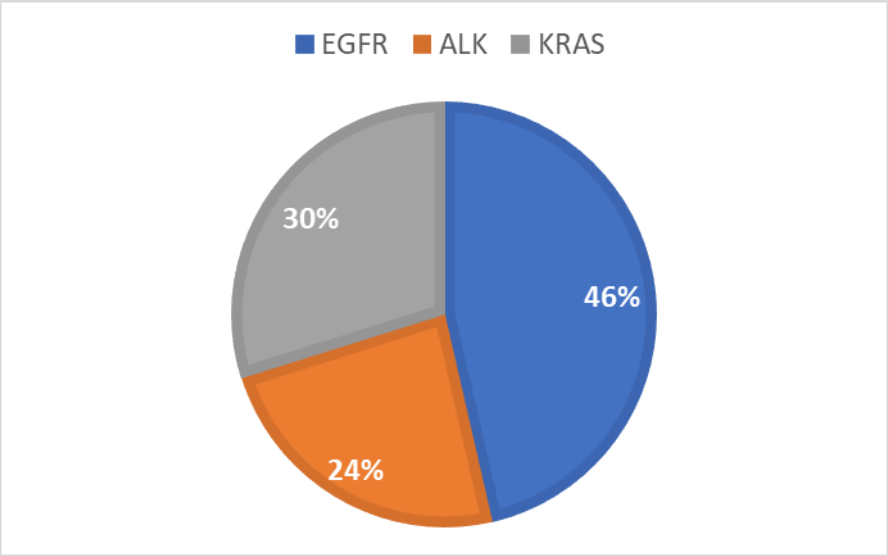
	Peripheral	Located in subsegmental bronchi or more distal airway
2. Size	< 3cm	Maximum diameter of the lesion in lung window setting (WL: -500, WW: 1500)
	>3 cm	
3. Margins	Smooth	Evaluated in lung window setting (WL : -500, WW: 1500)
	Lobulated	
	Spiculated	
4. Air bronchograms	Present / Absent	Branched air structure within the tumour
5. Bubble-like lucency	Present / Absent	Presence of air within tumour at the time of diagnosis before the biopsy
6. Pleural tail	Present / Absent	Slender soft tissue extending between tumour and the pleura
7. Pleural retraction	Present / Absent	Retraction of pleura towards the tumour
8. Peripheral fibrosis	Present /Absent	Either caused by tumour or pre-existing
9. Peripheral emphysema	Present/ Absent	Either caused by tumour or pre-existing
10. Tumour nodules in tumour lobe	Present/ Absent	Any non-calcified nodules suspected to be malignant or indeterminate Both solid and ground glass opacification nodules
11. Tumour nodules in non- tumour lobe	Present/ Absent	Any non-calcified nodules suspected to be malignant or indeterminate Both solid and ground glass opacification nodules
12. Lymphadenopathy	Present/ Absent	Hilar or mediastinal lymph nodes with short axis diameter more than 10 mm
13. Pleural effusion	Present/ Absent	On tumour side or non-tumour side of thoracic cavity

Statistical Analysis: Data was analyzed to determine which CT features correlate best with molecular mutations and to determine a combination of features which can predict presence of EGFR / KRAS / ALK mutation. Data was entered into Microsoft Excel Data Sheet and analyzed using SPSS 22 version software. Categorical data was represented in the form of Frequencies and proportions. Univariate variate analysis was done by using Chi-square test as test of significance for qualitative data. p value of <0.05 was considered as statistically significant after assuming all the rules of statistical tests. Multivariate logistic regression was done for features that showed p value < 0.05 in univariate analysis, to determine the independent factors for molecular type of NSCLC.

Results:

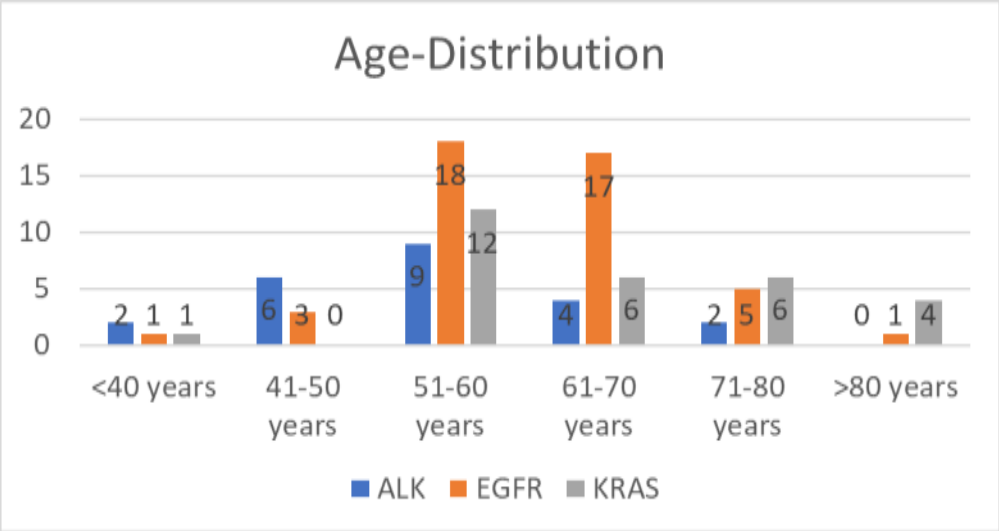
In the study 23 (24%) had ALK type, 45 (47%) had EGFR type and 29 (30%) had KRAS type.

Chart 1: Distribution of molecular mutations in study subjects



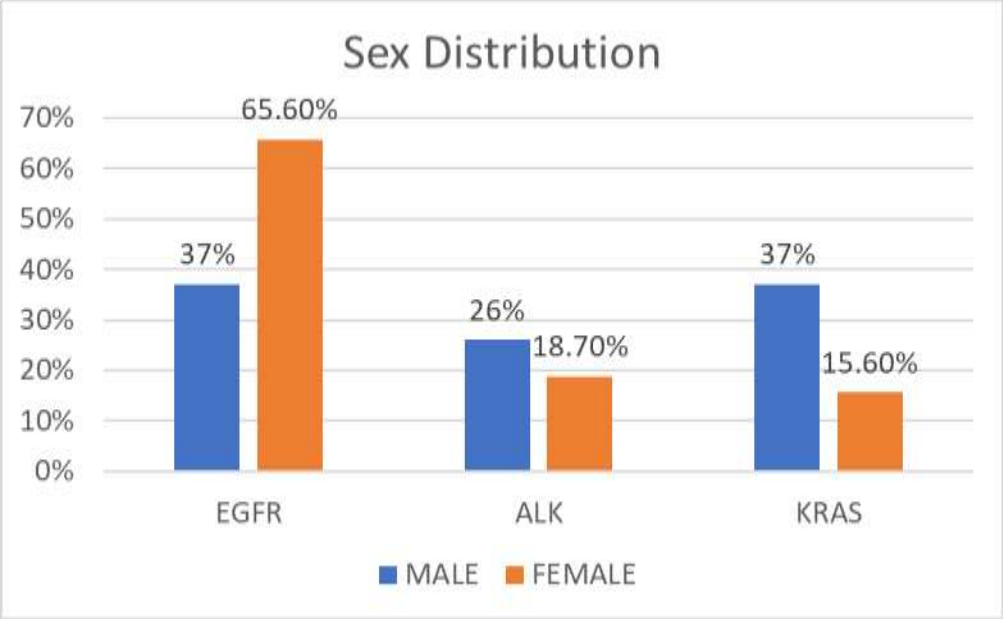
Majority of subjects were in the age groups 51 to 60 years (40.2%) and 61-70 years (27.8%).

Chart 2: Age distribution with molecular mutations of study subjects



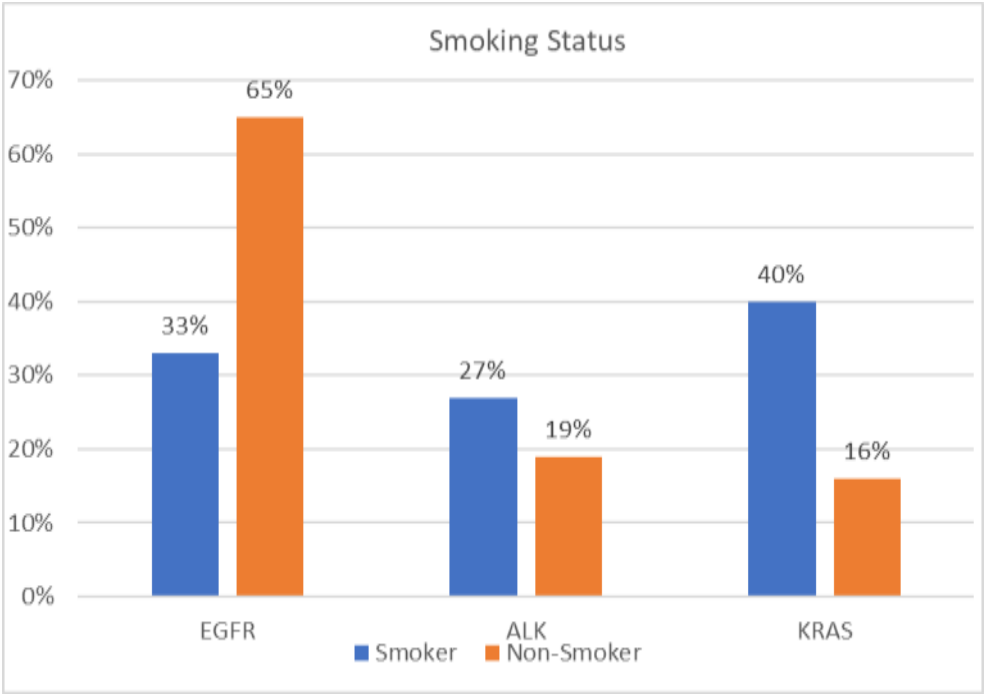
In the study 67% (65/97) were males and 33% (32/97) were females. Most of the females (65.6%) had EGFR mutation while EGFR and KRAS mutations were almost equally distributed among the males (37%).

Chart 3: Sex distribution with molecular mutations of study subjects



56% (55/97) of the subjects were smokers while 44% (42/97) were non-smokers.

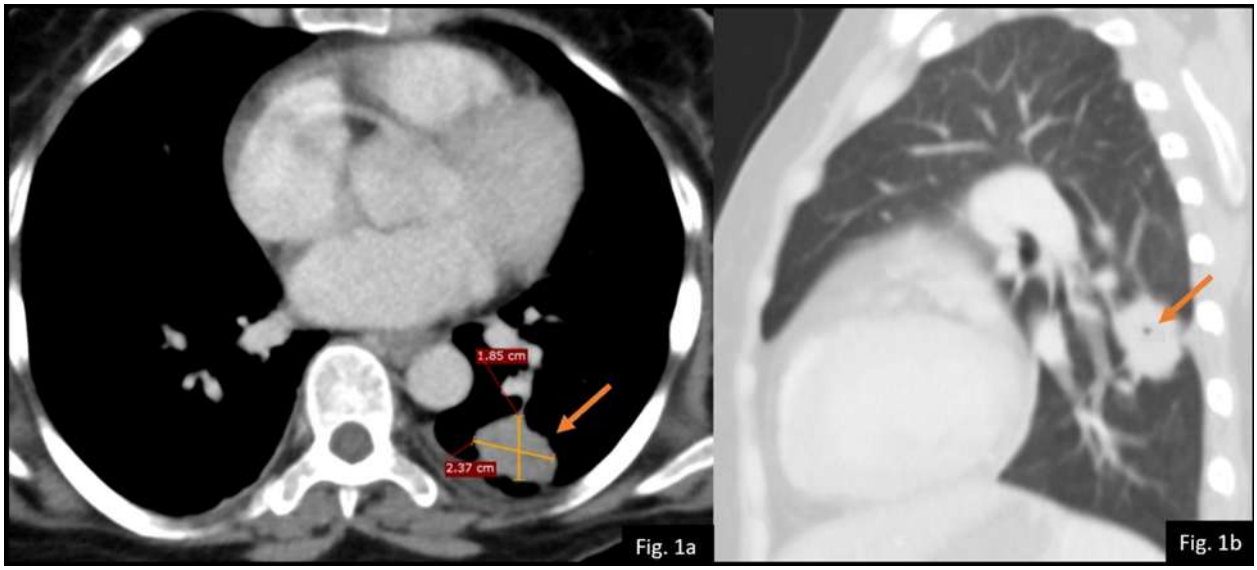
Chart 4: Smoking status with molecular mutations of study subjects



After using multivariate analysis, statistically significant correlation ($p<0.05$) with molecular subtype was seen with location, size, shape, air bronchogram, pleural tail, pleural retraction, tumour nodules in non-tumour lobes and pleural effusion.

A small peripherally located lesion in a non-smoker female is highly likely to harbor **EGFR mutation**. Presence of air bronchograms and pleural retraction increased the odds by 1.5 times for the same **(Figure 1) (Table 2).**

Figure 1: EGFR subtype



1a. Post-contrast axial CT section of thorax showing small peripherally located spherical lesion (arrow)

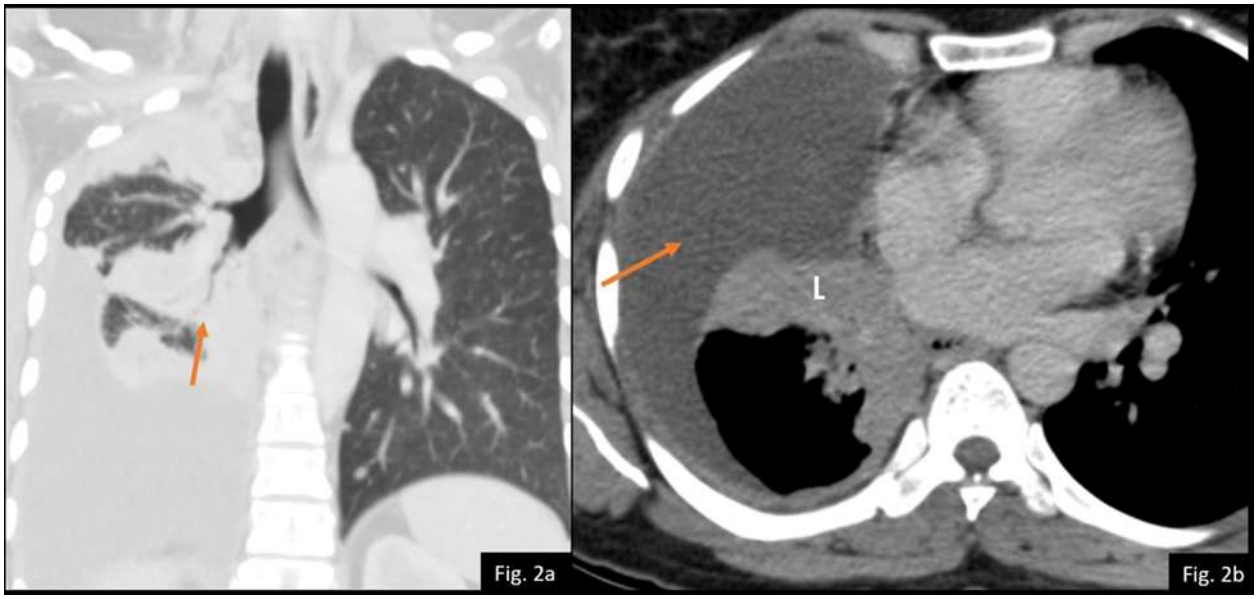
1b. Plain sagittal CT section of thorax showing lesion (arrow) associated with pleural retraction

Table 2 : Factors associated with EGFR mutation

		EGFR+ N=45	EGFR– N=52	p-value	Adjusted odds ratio
Size	< 3cm	25	9	0.01	3.822
	>3cm	20	43		
Sex	Female	23	11	0.045	3.261
	Male	22	41		
Air bronchogram	Present	26	21	0.04	1.534
	Absent	19	32		
Pleural retraction	Present	27	18	0.03	1.527
	Absent	18	34		
Location	Central	12	30	0.016	0.267
Smoking status	Smoker	18	37	0.023	0.270
	Non-smoker	27	16		

A significant association of ALK subtype was seen with a centrally located tumour and presence of pleural effusion in a subject with age less than 60 years. Absence of pleural tail increased the probability of ALK + subtype by 76% **(Figure 2) (Table 3).**

Figure 2: ALK subtype



2a. Plain coronal CT section of thorax showing centrally located lesion (arrow)

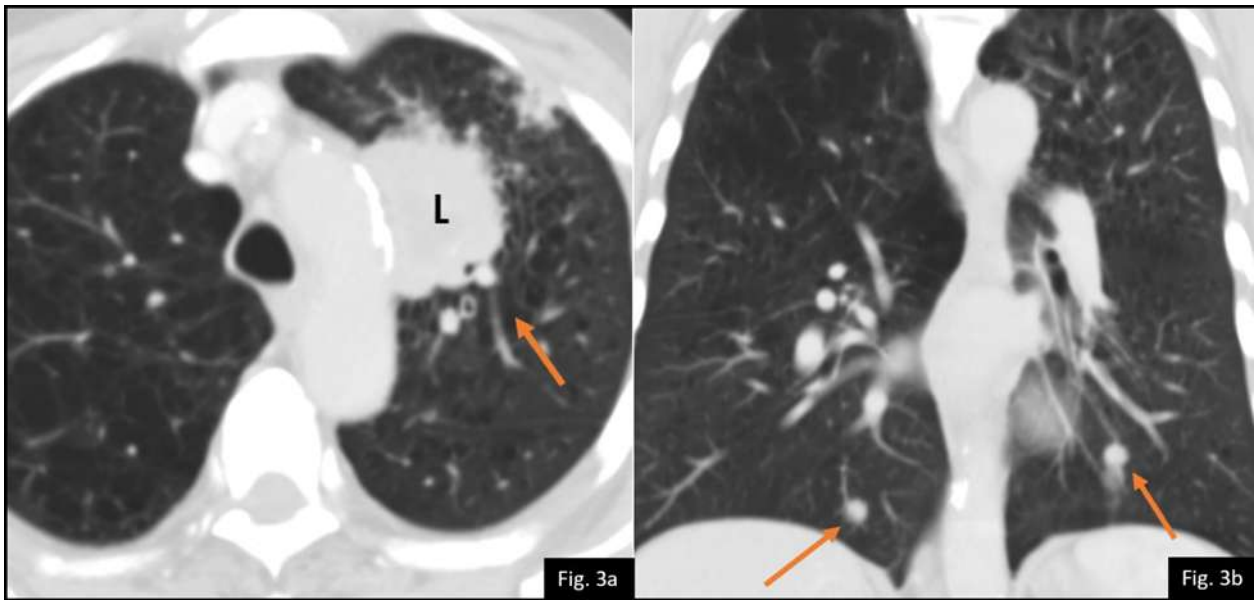
2b. Axial post-contrast CT section of thorax showing lesion (L) with pleural effusion (arrow)

Table 3 : Factors associated with ALK gene rearrangement

		ALK+ N=23	ALK– N=74	p-value	Adjusted odds ratio
Pleural effusion	Present	19	30	0.002	6.966
	Absent	4	44		
Location	Central	17	25	0.01	5.55
	Peripheral	6	49		
Age	<60 years	17	35	0.021	3.157
	>60 years	6	39		
Pleural tail	Present	4	41	0.03	0.247
	Absent	19	33		

Tumours showing **KRAS gene mutation** are more likely to be spherical in shape associated with presence of nodules in non-tumour lobes. A smoker is 2.5 times more likely to have KRAS+ subtype **(Figure 3) (Table 4).**

Figure 3: KRAS subtype



3a. Plain axial CT section of thorax showing centrally located spherical lesion (L) with adjacent emphysematous changes (arrow)

3b. Plain coronal CT section of thorax showing nodules (arrows) in non-tumour lobes.

Table 4 : Factors associated with KRAS mutation

		KRAS+ N=29	KRAS– N=68	p-value	Adjusted odds ratio
Nodules in non-tumour lobes	Present	25	31	0.001	7.459
	Absent	4	37		
Shape	Spherical	24	30	0.002	6.080
	Non-spherical	5	38		
Smoking status	Smoker	22	33	0.03	2.560
	Non-smoker	7	35		

Table 5: Comparison of imaging features of molecular subtypes of NSCLC with other studies

Molecular subtype	Feature	Rizzo et al p-value	Park et al p-value	Our study p-value
ALK	Pleural effusion	0.021	0.03	0.002
	Central location	0.03	N/A	0.01
	Absent pleural tail	0.048	0.02	0.03
EGFR	Small size	0.017	0.05	0.01

	Air bronchograms	0.05	0.04	0.04
KRAS	Nodules in non-tumour lobes	0.024	0.04	0.002
	Spherical shape	0.003	0.03	0.03

Discussion:

Among the various molecular mutations of NSCLC, EGFR gene mutation has a better prognosis with multitude of targeted drugs available for treatment, while on the other hand, KRAS mutation is the most aggressive type, carrying the worst prognosis of all with a dearth of available targeted treatment. If imaging characteristics can be linked to treatment-response gene expression patterns, routine imaging studies could predict the likely response to specific chemotherapeutics and help create an optimal personalized treatment that is based on genetics.

Our study has confirmed the association between higher risk of EGFR mutation and female sex and non-smokers. Tumours with this mutation carry a better prognosis as they are more likely to be small in size (16,17) when compared to those with other mutations. On histology, EGFR+ tumours more commonly show a predominant lepidic type of growth, where the cells proliferate along the alveolar wall surface, showing no evidence of bronchial, vascular or stromal invasion. This explains the significant correlation of EGFR + subtype with presence of air bronchograms, as seen in previous studies. (16)(18). Pleural retraction associated with EGFR mutation (16,17) is a vital characteristic for tumour resection, as it implies visceral pleural invasion, thereby upstaging the tumour. Previous studies (16,17) have shown a significant correlation between EGFR+ NSCLC and absence of fibrosis, which could be explained by the predominance of EGFR+ tumours in non-smokers. However, our study could not confirm this correlation. We attributed it to the endemicity of tuberculosis in India, which resulted in a significantly high proportion of subjects presenting with pre-existing fibrosis. Studies (2,4,5) have shown that TKIs have significantly improved the disease-free survival and quality of life in patients with EGFR mutated advanced lung adenocarcinoma. Early suspicion of the mutation via imaging may help reduce the time for treatment.

Tumours with ALK gene rearrangement are seen more commonly in younger patients with advanced lung carcinoma (16,17), which was confirmed in our study. A high frequency of centrally located ALK+ tumors was seen in our study, which is responsible for the lack of resectability of these tumors, thus contributing to their poor prognosis, as seen by Yamamoto et al. (18) The lack of pleural tail in ALK positive tumour could be attributed to the predominance of central location of the lesion. Statistically significant association was noted between the presence of pleural effusion and ALK rearrangement in concordance with previous studies , (16–18) suggesting pleural invasion, which correlates with the poor prognosis of patients with ALK positive NSCLC. However, a significant correlation with lymphadenopathy was noted by Park et al, (17) which was not seen in our study. ALK rearrangement tumours are rare and associated with a poor prognosis. If its presence can be predicted by CT findings prior to treatment, it may shorten the time for oncologists to consider the use of the few available targeted drugs.

KRAS proto-oncogene is reported as a negative prognostic sign (13) due to its highly aggressive nature. When tumour growth is obstructed by the growth of vessels, bronchi, and lymphatic tissues, and immune system of the normal lung, an ellipsoid shape is seen. However, due to invasive nature of KRAS tumours, a round shape is most commonly seen. The presence of tumour nodules in non-tumor lobes indicates that the tumour has disseminated hematogenously, which is related to the aggressive nature of these tumours. Previous research has found a link between KRAS + tumours and smoking, which was verified in our investigation. Rizzo et al (16) found a substantial relationship between emphysema and KRAS mutant tumours, which they attribute to the association with smokers. The lack of this link in our study could be due to the high number of smokers, which resulted in a higher frequency of emphysema, which was nearly evenly distributed across the subjects. **(Table 5)**

Radiogenomics thus has the ability to influence therapy methods by analyzing the likelihood of response to treatment. CT scan may be used to have a quick preliminary diagnosis, thus potentially shorting waiting time for diagnosis, thereby allowing more time for clinicians, patients, and their families to prepare for future treatments.

Limitations

1. The retrospective design introduced selection bias that may have influenced the final overall effect.
2. It is a discovery-phase study, without validation of our findings.
3. With regard to the genomic findings, our data were recorded as presence or absence of mutations/rearrangements, and not the different types of mutations.

Declarations

1. This study was not funded.
2. Ethical approval: Obtained. IEC (IEC No. 742/2019)
3. No conflict of interest.

Conclusions

1. Statistically significant correlation with molecular subtype was seen with lesion location, size, and shape, and air bronchogram, pleural tail, pleural retraction, tumour nodules in non-tumour lobes, and pleural effusion.
2. Presence of a small peripherally located lesion in a non-smoker female with air bronchograms and pleural retraction correlated with EGFR gene mutation.
3. Presence of pleural effusion with a centrally located lesion in a younger age group with absence of pleural tail correlated with ALK gene rearrangement.
4. Presence of nodules in non-tumour lobes with a spherical lesion in a smoker correlated with KRAS gene mutation.

List of abbreviations:

CT- Computed Tomography

NSCLC- Non-small cell lung cancer

EGFR - Epidermal Growth Factor Receptor

ALK- Anaplastic Lymphoma Kinase

KRAS- Kirsten Rat Sarcoma viral oncogene

TKI- Tyrosine Kinase Inhibitors

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