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Clinicopathological profile and molecular characteristics in lung cancer patients in a tertiary care hospital

Authors

Gourab Arun[1], Nabakishore Sundaray[1], Soumya Surath Panda[2*], Srikant Kumar Dhar[1]

[1]Department of General Medicine, IMS and SUM hospital , Siksha O Anusandhan (Deemed to Be University), Kalinga nagar , Bhubaneswar, Odisha 751003, India.

[2]Department of Medical Oncology, IMS and SUM hospital , Siksha O Anusandhan (Deemed to Be University), Kalinga nagar , Bhubaneswar, Odisha 751003, India

*Corresponding Author

Soumya Surath Panda

Associate Professor, Department of Medical Oncology, IMS and SUM hospital , Siksha O Anusandhan (Deemed to Be University), Kalinga nagar , Bhubaneswar, Odisha 751003, India

Abstract

With rising frequency of different cancer, lung cancer being the commonest one, results in the greater part of the disease related passing over the globe. Malignant growth creates because of oncogene transformation bringing about either loss or gain of function in tumor silencer qualities. This study is useful as it attempts to investigate an area that seek optimum attention in cancer care. The main focus of the study is on the clinicopathological profile and molecular characteristics in patients with lung cancer. The results revealed that out of seven clinical features—lung mass, pleural effusion, cervical lymphadenopathy, bone metastasis, brain metastasis, pneumonia, and other metastasis (scrotum, adrenals)—of the patients, the most prominent one was lung mass (cough, haemoptysis, dysphagia, superior vena cava obstruction, wheezing and stridor, radiological evidence of lung mass with or without symptoms). Of three histopathological types—adenocarcinoma, squamous cell carcinoma, and large cell carcinoma—the most prevalent one was adenocarcinoma in the patients. The EGFR and ALK mutations were common in female patients and in non-smokers with adenocarcinoma. Majority of the patients of adenocarcinoma had lung mass as predominant clinical feature and they also had maximum number of EGFR and ALK mutations. Shortcomings and future directions were also discussed.

Keywords: *Malignant, oncogene, adenocarcinoma.*

Introduction

Malignancy as such influences the person's body, yet in addition his or her whole family—candidly just as monetarily. All things considered, WHO characterizes malignant growth as "a gathering of illnesses including unusual cell development with the possibility to attack or spread to different pieces of the body".[1,2] With rising rate of different malignancies, lung disease being the commonest one, results in the majority of the malignancy related passing over the globe. [3]. The incidence of lung carcinoma in India is on the rise. Non-small cell lung cancer (NSCLC) comprises 80-85% of lung carcinomas, whereas

adenocarcinoma is the most prevalent histologic type with men and women ratio of 1.7:1. [2, 3, 4]. The aetiology of lung cancer is manifold. There is a predominant role of genetic factors in lung cancer. Areas of genomic variation are identified in association with higher incidence of lung cancer. This is observed from the Genome Wide Association (GWA) studies. Tobacco consumption—oral and smoking—is one of the major behavioural risk factors for lung cancer. Environmental tobacco smoke (ETS) and exposures to asbestos, arsenic, nickel and polycyclic aromatic hydrocarbons are also found to be the causes of lung cancer. Cancer develops due to oncogene mutation resulting in either loss or gain of function in tumour suppressor genes. As the cell of origin for lung cancer has not been identified yet, it is very difficult to predict whether all histologic forms of lung cancer originate from one cell or not. However, type II epithelial cells can result in adenocarcinoma lung and cells of neuroendocrine origin act as precursors for SCLC. Adenocarcinoma of lung can arise when tumours express EGFR tyrosine kinase mutation. Some of the driver mutations in adenocarcinoma of lung are those involving the signalling molecules downstream of EGFR, e.g., the TK *HER2*, the GTPase, *BRAF*, *KRAS*, the lipid kinase, *PIK3CA*, the serine–threonine kinase. In 2007, other subsets of lung adenocarcinoma were found to be defined by the presence of specific translocations fusing tyrosine kinases such as ALK and ROS to aberrant upstream partners. Acquisition of one of these driver mutations e.g.; *EGFR*, *KRAS*, and *EML4-ALK* mutations is sufficient to promote tumorigenesis as these mutations are mutually exclusive. Thus far, potentially targetable driver mutations have mostly been identified in lung adenocarcinomas as opposed to lung cancers displaying other types of histologies. The inactive tumour-suppressor genes seen in lung cancer are *TP53*, *LKB1* (*STK11*), *RB1*, *CDKN2A/B*, *RASSF1A and FHIT*. Most of the tumour suppressor genes causing the development of lung cancer are found in chromosome 3p. This study is useful as it attempts to investigate an area that seek optimum attention in cancer care. The main focus of the study is on the clinicopathological profile and molecular characteristics in patients with lung cancer. The primary aim of the study is to study and correlate the clinical features, pathological profile, and molecular characteristics in lung cancer patients in a tertiary care centre.

Material and Methods

Sample

Initially 64 patients admitted to IMS & SUM hospital during a period of two years with clinical and histopathological evidence of NSCLC were included in the study. At the time of data cleaning process, 11 cases were excluded because of missing data and the remaining 53 cases were considered for all analyses in the study (N = 53). Of these 53 cases, there were 23 (43.4%) women and 30 (56.6%) men with a mean age of 59.94 years (SD = 11.82, Range = 26–85 years).

Inclusion criteria

All the patients admitted to IMS & SUM hospital with clinical and histopathological evidence of NSCLC were included in this study.

Exclusion criteria

The patients who reported with small cell lung cancer were excluded from the purview of this study.

Study tools and technique

Before the conduct of the study, the protocol of the study was presented before the Institutional Ethics Committee (IEC) of the hospital. After the approval of the IEC vide Ref No. DMR/IMS-SH/SOA/160127, dated 02/12/2016, the study was conducted. All the patients enrolled in the study gave their informed consents. All the patients, who were diagnosed with NSCLC having clinical and histopathological evidence were included in this study considering the inclusion and exclusion criteria. The demographic features of the patients were collected from the medical records using a pre-defined case-record form. Each patient had undergone thorough physical examination and investigations including routine CBC, LFT, RFT,

imaging-Chest x-ray/contrast enhanced CT (CECT) of thorax/ whole body, bone scan, biopsy/immunohistochemistry, and tumor markers—carcino embyoigenic antigen (CEA) which were necessary at the first time of their visits or admissions to the hospitals.

Statistic

Except chronological age of the patients, all other data were in the form of nominal level of measurement (non-metric data). Therefore, the relationship between the clinicopathological profile and molecular characteristics in lung cancer patients was examined by means of frequency analysis, percentage analysis, and cross-tabulations as the main assumptions of Pearson's Chi-square ($\chi 2$) and Correspondence Analysis could not be met. Appropriate graphs in the form of Box Plot and Bar graphs were also used. For these analyses, IBM SPSS Statistics 22 software was used.

Results

The demographic characteristics and histopathology of patients are presented in Table 5.1. A total of 53 lung cancer patients were included in the study. From Table 5.1, it is observed that there were 23 (43.4%) women and 30 (56.6%) men with a mean age of 59.94 years (*SD* = 11.82, Range = 26–85 years). In the sample under study, smokers were (17, 32.1%) lesser compared to non-smokers (36, 67.9%). Of the 53 patients, 47 (88.7%) patients had adenocarcinoma, 2 (3.8%) patients had squamous cell carcinoma.

Table -1 Summary of patient demographic and histopathology (*N* = 53)

Characteristics	***n***	**%**
Mean age in years, *SD* (Range)	59.94	11.82 (26-85)
Age group		
Upto 40 years	3	5.7
41 to 60 years	28	52.8
Above 60 years	22	41.5
Gender		
Female	23	43.4
Male	30	56.6
Smoking habit		
Smoker	17	32.1
Non-smokers	36	67.9
Histopathology		
Adenocarcinoma	47	88.7
SCC	2	3.8
LCC	4	7.5

Note. "SCC = Squamous cell carcinoma, LCC = Large cell carcinoma".

Whereas 4 (7.5%) patients had large cell carcinoma. With a representation of 88.7%, adenocarcinoma was the most prominent histological subtype observed among the cases under study.

The distribution of the age across two genders of the patients has been represented in the form of Box. It is observed from the graph that the female patients were younger and more homogenous in age compared to male patients. Nevertheless, there was one male patient who was 26 years of age and shown as outlier with a serial number 39.

The percentages of cases falling across three age groups, two genders, two smoking habits, and three categories of histopathology are presented in the form of Bar graphs.

Clinical features

Clinical features of the patients under study were classified under seven-lung mass, pleural effusion, cervical lymphadenopathy, bone metastasis, brain metastasis, pneumonia, and other metastasis, like scrotum, adrenals. Of these, except lung mass others six are individual clinical features, whereas lung mass includes cough, haemoptysis,

dysphagia, superior vena cava obstruction, wheezing and stridor, radiological evidence of lung mass with or without symptoms.

These seven clinical features are presented. From Table 2 , it is evident that the presence of lung mass was most dominant (90.6%) among all clinical features. Next to lung mass, pleural effusion was observed to be higher (20.8%) in selected cases. In only one patient (1.9%), brain metastasis was observed, whereas bone metastasis was found in 2 (3.8%) cases. Other metastasis (Scrotum, adrenals) was seen in 3 (5.7%) cases. Cervical lymphadenopathy and pneumonia were evident in 8 (15.1%) and 7 (13.2%) patients respectively.

Table 2: Clinical features (*N* = 53)

Clinical features	Present (%)	Absent (%)
Lung mass*	48 (90.6)	5 (9.4%)
Pleural effusion	11 (20.8)	42 (79.2)
Cervical lymphadenopathy	8 (15.1)	45 (84.9)
Bone metastasis	2 (3.8)	51 (96.2)
Brain metastasis	1 (1.9)	52 (98.1)
Pneumonia	7 (13.2)	46 (86.8)
Other metastasis**	3 (5.7)	50 (94.3)

Note. *Lung mass includes cough, haemoptysis, dysphagia, superior vena cava obstruction, wheezing and stridor, radiological evidence of lung mass with or without symptoms

**Other metastasis (scrotum, adrenals)

Relationship between gender and clinical features

The results of cross-tabulation between gender and clinical features are presented in Table 3. From Table 3, it is evident that in males 27 (50.9%) cases had lung mass, 5 (9.4%) cases had pleural effusion, 7 (13.2%) cases had cervical lymphadenopathy, 2 (3.8%) case had bone metastasis, 1 (1.9%) case had brain metastasis, 5 (9.4%) cases have pneumonia and 1 (1.9%) cases had other metastasis (like scrotum or adrenal).

Relationship between EGFR and clinical features

The results of cross-tabulation between EGFR positive cases and clinical features are presented in Table 3. From Table 3, it is observed that 15 (28.3%) cases had lung mass as predominant feature followed by pneumonia 5 (9.4%) and pleural effusion 4 (97.5%), whereas 2 (3.8%) cases had cervical lymphadenopathy, 1 (1.9%) case had bone metastasis and 2 (3.8%) cases had other metastasis (like scrotum or adrenal).

Table 3 Association of each of the individual factor vis-à-vis clinical features (*N* = 53)

Category	LM* *n* (%)	PE *n* (%)	CL *n* (%)	BM *n* (%)	BrM *n* (%)	PN *n* (%)	OM *n* (%)
Age group							
Upto 40 years	3 (5.7)	0(0)	0(0)	0(0)	1(1.9)	0(0)	0(0)
41 to 60 years	24(45.3)	7(13.2)	5(9.4)	1(1.9)	0(0)	4(7.5)	2(3.8)
Above 60 years	21(39.6)	4(7.5)	3(5.7)	1(1.9)	0(0)	3(5.7)	1(1.9)
Gender							
Female	21(39.6)	6(11.3)	1(1.9)	0(0)	0(0)	2(3.8)	2(3.8)
Male	27(50.9)	5(9.4)	7(13.2)	2(3.8)	1(1.9)	5(9.4)	1(1.9)
Smoking habit							
Smoker	16(30.2)	2(3.8)	4(7.5)	1(1.9)	0(0)	3(5.7)	0(0)
Non-smokers	32(60.4)	9(17.0)	4(7.5)	1(1.9)	1(1.9)	4(7.5)	3(5.7)
Histopathology							
Adenocarcinoma	42(79.2)	10(18.9)	7(13.2)	2(3.8)	1(1.9)	6(11.3)	2(3.8)
SCC	2(3.8)	0(0)	0(0)	0(0)	0(0)	1(1.9)	0(0)
LCC	4(7.5)	1(1.9)	1(1.9)	0(0)	0(0)	0(0)	1(1.9)
EGFR	**15(28.3)**	**4(7.5)**	**2(3.8)**	**1(1.9)**	**0(0)**	**5(9.4)**	**2(3.8)**
ALK	**6(11.3)**	**2(3.8)**	**0(0)**	**0(0)**	**0(0)**	**0(0)**	**0(0)**

Note." LM = lung mass, PE = pleural effusion, CL = cervical lymphadenopathy, BM = bone metastasis, BrM = brain metastasis, PN = pneumonia, OM = other metastasis (scrotum, adrenals)".

"SCC = Squamous cell carcinoma, LCC = Large cell carcinoma, EGFR = Epidermal growth factor receptor, ALK = anaplastic lymphoma kinase".

*LM (Lung mass) includes cough, haemoptysis, dysphagia, superior vena cava obstruction, wheezing and stridor, radiological evidence of lung mass with or without symptoms

Relationship between EGFR and clinical features

The results of cross-tabulation between EGFR positive cases and clinical features are presented in Table 3. From Table 3, it is observed that 15 (28.3%) cases had lung mass as predominant feature followed by pneumonia 5 (9.4%) and pleural effusion 4 (97.5%), whereas 2 (3.8%) cases had cervical lymphadenopathy, 1 (1.9%) case had bone metastasis and 2 (3.8%) cases had other metastasis (like scrotum or adrenal).

The percentages of cases falling across EGFR positivity and seven clinical features are presented in the form of Bar graph in Figure 1.

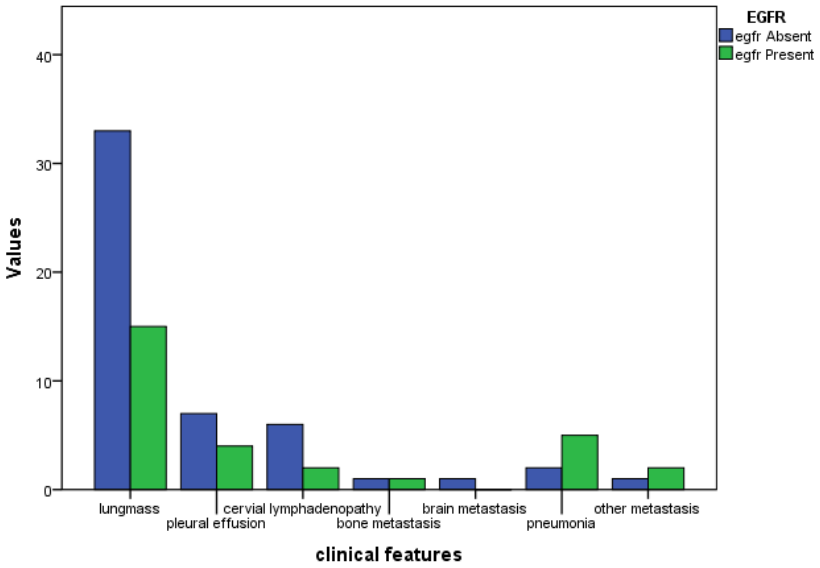

Figure 1 Bar graph showing percentage of seven clinical features in EGFR positive and negative cases

Relationship between ALK and clinical features

The results of cross-tabulation between ALK positive cases and clinical features are presented in Table 5.3. From Table 5.3, it is observed that 6 (11.3%) cases had lung mass which is the more prominent than pleural effusion with 2 (3.8%) cases.

The percentages of cases falling across ALK positivity and seven clinical features are presented in the form of Bar graph in Figure 2.

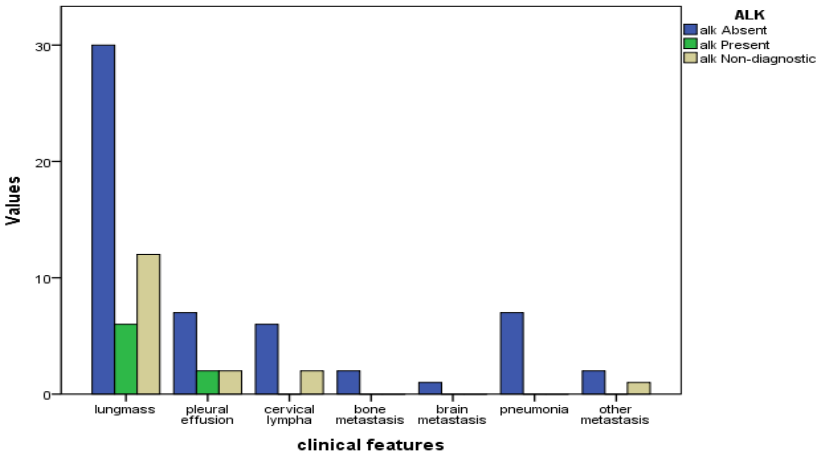

Figure 2 Bar graph showing percentage of seven clinical features in ALK positive and negative and non-diagnostic cases

Relationship between each of the individual factor and EGFR

The results of cross-tabulation between each of the individual factor and EGFR (*N* = 53) are presented in Table 4. From Table 5.5 it is observed that EGFR mutation was more common in the age group of 40 to 60 years (*n* = 9, 17%) compared to other two age groups. Compared to male patients, more female patients (*n* = 9, 17%) had EGFR mutation. The number of non-smokers having EGFR mutation was higher (n = 14, 26.4%) compared to smokers. Likewise, compared to number of patients with squamous cell carcinoma and large cell carcinoma, the number of patients with adenocarcinoma having EGFR mutation was higher (*n* = 15, 28.3%).

Table 4 Association of each of the individual factor vis-à-vis EGFR (*N* = 53)

Category	EGFR Positive *n* (%)	EGFR Negative *n* (%)	Total *n* (%)
Age group			
Upto 40 years	0(0)	3(5.7)	3(5.7)
41to 60 years	9(17.0)	19(35.8)	28(52.8)
Above 60 years	8(15.1)	14(26.4)	22(41.5)
Gender			
Female	9(17.0)	14(26.4)	23(43.4)
Male	8(15.1)	22(41.5)	30(56.6)
Smoking habit			
Smokers	3(5.7)	14(26.4.5)	17(32.1)
Non-smokers	14(26.4)	22(41.5)	36(67.9)
Histopathology			
Adenocarcinoma	15(28.3)	32(60.4)	47(88.7)
SCC	1(1.9)	1(1.9)	2(3.8)
LCC	1(1.9)	3(5.7)	4(7.5)

Note. "SCC = Squamous cell carcinoma", LCC = Large cell carcinoma, EGFR = Epidermal growth factor receptor".

Discussion

It is seen in this investigation that the EGFR and ALK transformation have been discovered most prevalently in adenocarcinoma pursued by LCC with cases SCC. This finding has been upheld by a few examinations. A vast report has been directed crosswise over 129 organizations in Spain from April 2005 to November 2008, where 350 (16.6%) out of 2105 lung malignant growth patients demonstrated EGFR transformation and it was progressively visit in ladies (69.7%), in patients with adenocarcinomas (80.9%), and in non-smokers (66.6%). In Asian populaces, the EGFR transformations are seen in up to 62 percent[8].

Another investigation led in a tertiary consideration therapeutic focus in South India for multiyear length from 2006 to 2011 has discovered that out of the 84 instances of NSCLC, 46 cases (55%) are adenocarcinoma of the lung and EGFR transformation is sure in 89% of adenocarcinoma and negative in 11% of the cases.

Another review investigation of NSCLC patients in a tertiary consideration medical clinic arranged in Hyderabad for a time of three years from January 2011 to December 2013 has uncovered that out of 111 patients, EGFR change has been distinguished with a recurrence of 30.6%. The most widely recognized EGFR initiating changes watched are cancellations in exon-19 (71%) and a missense transformation L858R in exon-21 (25%). Generally female patients have had more EGFR changes when contrasted with their male partners (44% versus 19.6%) and non-smokers have had higher number of changes than smokers (41% versus 12%).

A review examination of 186 patients of North Indian inception were tried for EGFR change for a time of 3 years (i.e., 2012– 2014). EGFR transformations have been identified in 26 patients (16.6%) and the most well-known EGFR change among them is exon-19 erasure (12.1%) trailed by exon-21 transformation (3.8%). Among the 88 patients who have been tried for ALK quality

improvement, just two patients (2.3%) have been seen to have positive outcomes.

Conclusion

The consequences of this investigation propose that the commonness of EGFR is like that announced among Caucasians, among South Indians and North Indians that nearness of EGFR is a positive prognostic marker in NSCLC with adenocarcinoma. Adenocarcinoma was more typical than squamous cell carcinoma and extensive cell carcinoma in our investigation. In our examination, 28.3% of the adenocarcinomas have indicated EGFR inspiration and 60.4% have appeared negative. The predominance of enacting EGFR and ALK changes in youthful populace, non-smokers, female patients and their clinical relationships in our examination are tantamount to those recently led investigations on Indian patients from different geographic territories. One of the major shortcomings of the study is its small sample in a tertiary care centre. Future studies should include a large pool of sample from various hospitals across India.

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