

Lung Cancer

Delays in Lung Cancer Diagnosis: Observations from a Tertiary Care Centre in Kerala, India

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South Asian J Cancer 2023;12(3):266–273.

Abstract



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Keywords

- delays
- diagnosis
- lung cancer

Introduction Timely diagnosis of lung cancer is critical because treatment outcomes correspond to the stage of disease. This study identified patient and physician determined reasons for diagnostic delays.

Materials and Methods This was an observational cross-sectional study, conducted at a tertiary care institution in South India, for 12 months. From 207 consecutively selected patients, with a presumptive lung cancer diagnosis, 150 were enrolled utilizing a prefixed questionnaire. The time intervals from appreciation of initial respiratory symptoms to a final tissue diagnosis were defined sequentially as approach interval, referral interval, and diagnostic interval and factors causing delay in each interval were identified.

Results In a state with 100% literacy, the mean time to approach a doctor was 8 weeks (range: 0–336 days; SD: 7.95) with a delay seen in 52% of the study group. Referring a suspect lung cancer diagnosis to a specialist, took an average of 4.98 weeks (range: 1–26 weeks; SD: 5.64) with referral delays in 47.3% of patients. The mean diagnostic interval was 9.21 days (range: 3–41 days; SD: 7.18) and 16.7% of cases had diagnostic delays in spite of a definite procedure.

Conclusion In a tuberculosis endemic location, empirical treatment with anti-tuberculosis therapy and prolonged antibiotic courses without serially monitoring the course of disease are responsible for referral delays. Also, 88.2% of the total females studied, presented late due to family and work pressures, fear of being stigmatized and being on prolonged home remedies. A wider dissemination and awareness on lung cancer are needed especially among females. A low threshold to reinvestigate and an early referral to a pulmonary or lung cancer specialist, when expected clinicoradiological improvement is lacking, in microbiologically negative tuberculosis should be highlighted.

DOI <https://doi.org/10.1055/s-0043-1762597> ISSN 2278-330X

How to cite this article: Yohannan M, Narayan KV, Venugopal KP, et al. Delays in Lung Cancer Diagnosis: Observations from a Tertiary Care Centre in Kerala, India. South Asian J Cancer 2023; 2023;12(3):266–273.

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Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

Introduction

Lung cancer, the most commonly diagnosed cancer in the world (2.09 million, 11.6% of the total) is the 'Captain of men of all deaths' in terms of cancer mortality worldwide.¹ A similar pattern is seen in our country, with lung cancer accounting for around 6.9% of all newly diagnosed cancer cases and 9.3% of all cancer related mortality in all sexes.² The hospital-based and population-based cancer registries from various locations in our state have reported the incidence of lung cancer in men during 2012–2014 as 13% and 18.2%, respectively, which is higher than the values of the country and globally.^{1,3,4}

Timely diagnosis is critical in lung cancer because the treatment outcomes correspond to the stage at diagnosis.^{5,6} However, data suggest that the majority of lung cancer patients are diagnosed at an advanced stage with distant metastasis, resulting in poor prognosis.^{7,8} The delays could be at multiple levels. Patients often ignore the symptoms and delay seeking healthcare because of a lack of perception, awareness or ignorance, resulting in approach delays. It could also occur when there are inadequate or inaccessible health care facilities. The delays can occur from physicians because of an alternate diagnosis and delayed referral to specialists.

Our institution is a tertiary care teaching hospital in South India catering to a population of about 10 million from 5 adjacent districts and the Pulmonology Department attends to about 200 cases of lung cancer annually. However, hardly 5% of our patients can be taken up for a curative treatment because we get to diagnose the majority, at a late stage of the disease. There are limited data on the factors responsible for a delay in diagnosis from this part of the world. This study focused on the factors contributing to a delay in the diagnosis of lung cancer. Identification of these factors can contribute to the formulation of strategies for early diagnosis of lung cancer, including but not confined to cancer screening plans and patient awareness programs.

Materials and Methods

We conducted an observational cross-sectional study in the Department of Pulmonary Medicine, at a tertiary care institution for 12 months. (October 1, 2018 to September 30, 2019). The Institute's Ethics and Research Committee approved the study as per reference no. GMCK/KTM/IEC/31/2018 dated September 19, 2018.

Objectives

Identify factors from both patient's and physician's side contributing to delays in the diagnosis of lung cancer

Study Population

Inclusion Criteria

All consecutive patients aged 16 years or above with a presumptive diagnosis of lung cancer and malignant pleural effusion based on the following clinic-radiological and sono-

logical findings in isolation or a combination, who consented to the study were included:

- Unexplained hemoptysis or a persistent cough with radiological chest X-ray findings as described below.
- Chest x-ray or a CT-thorax showing a nonresolving consolidation/persistent nodule/mass lesion/obstructive collapse/massive pleural effusion with need for repeated thoracentesis.
- Hoarseness of voice with or without accompanying dysphagia
- Firm to hard significant cervical or supraclavicular lymph node enlargement
- Superior vena-caval syndrome
- Diaphragmatic pleural nodules on a thoracic ultrasound.

Exclusion Criteria

- Patients with microbiologically or clinically diagnosed active pulmonary or extra-pulmonary tuberculosis as per the national guidelines.⁹
- Diagnosed extra-thoracic malignancy with lung metastasis
- Histopathology and tissue immunohistochemistry which confirmed an extra-thoracic source of malignancy.

Questionnaire and Data Collection

We collected details based on a face-to-face interview and also referenced previous medical records with a questionnaire. We collected details based on a face-to-face interview and also referenced previous medical records with a questionnaire ([Supplementary Material S1](#), available in the online version). The questionnaire was prepared in an exhaustive, clinically relevant manner and content validated with the help of inputs from the senior consultants (over 10 years' experience working with lung cancer) of the department.

The different time intervals from appreciation of initial symptoms to the final tissue diagnosis were segregated and calculated as follows ([~Fig. 1](#)).

Approach interval—from the date of onset of initial symptoms to the date of first visit to a doctor for a specific complaint.

Referral interval—from the first doctor visit to arrival at a specialist tertiary care center for probable lung cancer diagnosis.

Diagnostic interval—from the date of first visit to the specialist center to the date of receiving a definite histopathology report of Lung cancer.

Time delays at each interval were classified on the basis of literature available at the time of study as follows:

1. *Approach delay*—defined when the approach interval was 30 days or more

Based on a study by Chatterjee et al on time intervals in lung cancer diagnosis, the approach interval from symptom onset to first doctor visit was about 60 days.¹⁰ All patients with cough lasting for more than 2 weeks are considered presumptive pulmonary tuberculosis (PTB) as per the national policy, and because 60 days is a long time delay, we opted 1 month or more as an approach delay.⁹ The factors studied included age, sex, education level, urban versus rural residence, occupation,

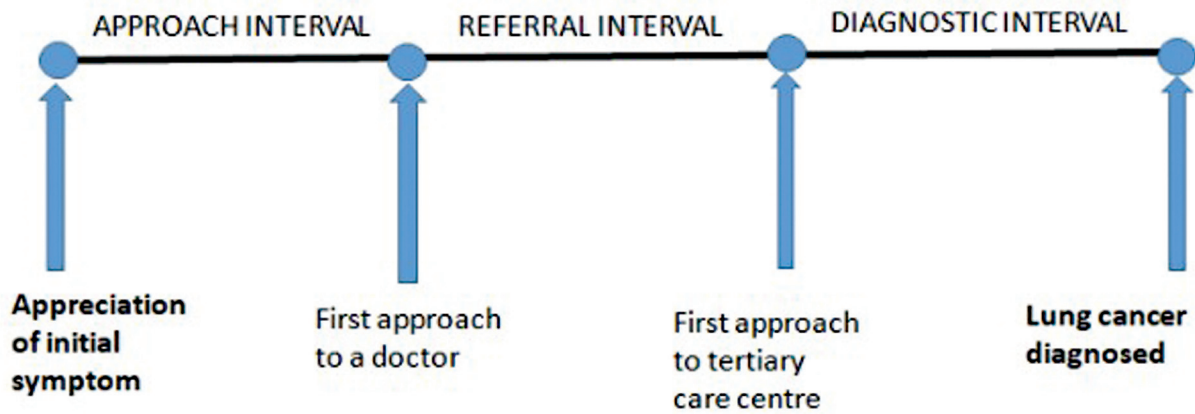


Fig. 1 Depicting a pictorial representation of different time intervals.

smoking status, concurrent COPD, history of tuberculosis, and a family history of lung cancer.

2. *Referral delay*—defined when referral interval was 3 weeks or more

The delay was chosen based on the NICE guidelines on the recognition and referral of suspected cancer patients. It is recommended to take a chest X-ray within 2 weeks of respiratory symptoms in high-risk patients and refer them accordingly.¹¹ Because we belong to one of the most populous countries, 2 weeks were considered as inadequate for assessment and hence we kept a 3-week interval. The factors considered were the specialization of the doctor and type of institution attended, initial diagnosis and treatment given, initial chest X-ray and CT (computed tomography) thorax—taken or not taken.

(Initial chest X-ray or CT was defined as the earliest radiology investigation done for the patient, before being referred to our institution).

3. *Diagnostic delay*—defined when diagnostic interval was 2 weeks and more.

The BTS (British Thoracic Society) guidelines were adapted for organizing the care of patients with lung cancer.¹² It suggests that the results of bronchoscopy or any other similar diagnostic test, including the histological or cytological result, should be available and communicated to the patient within two weeks of a decision to do it. Diagnostic delay was expected in lung lesions with an inaccessible location and greater number of diagnostic procedures used.

Based on the clinico-radiological examination, any of the following tests in isolation or combination were used to make a definite diagnosis.

- Ultrasound guided fine-needle aspiration cytology (FNAC) and/or biopsy of neck nodes.
- Ultrasonography(USG) or computed tomography(CT)-guided FNAC/transthoracic biopsy of lung masses.
- Flexible bronchoscopy with endobronchial biopsy with or without transbronchial needle aspiration (TBNA).
- Pleural fluid cytology and cell block
- Thoracoscopic pleural biopsy.

Patients diagnosed with lung cancer were staged based on the 8th edition of TNM staging of lung cancer (cTNM) with the available investigations at the time of tissue diagnosis.

Data Management and Analysis

Data were entered and sorted in Microsoft Excel. Analysis was done with the help of the SPSS software version 16.0. Frequencies were calculated for qualitative variables and mean with standard deviation for quantitative variables. We calculated correlation between interval delay and factors using Chi-square. The significance level was fixed at p -value of <0.05 . Multivariate logistic regression analysis was also done to assess association between the different delays and their corresponding factors.

Results

Out of 207 patients with a presumptive diagnosis of lung cancer, 150 patients were enrolled in the study. A total of 19 patients were excluded after getting an alternate histopathological diagnosis which included 5 with tuberculosis, 4 had metastases due to extrathoracic malignancy, 2 with actinomycosis, 3 with chronic aspergillosis, 2 had granulomatosis with polyangitis, 2 with lymphoma and 1 with alveolar sarcoidosis (→Fig. 2).

The mean age was 64.63 years with a range of 43 to 81 years and most of the patients were in the age group of 61 to 70 years. The majority of the study population were males (88.7%, 133/150). Also, 137 patients (91.3%) were from rural background. All were literate and 60.7% (91/150) had completed upper primary education. Almost half of the patients were unskilled manual laborers. In all, 84% (126) of the patients were smokers. Smoking pack years ranged from 3 to 100 with a mean pack year of 32.65. Next, 33.3% (50/150) patients had COPD, 22.7% (34/150) had a history of prior pulmonary tuberculosis and 5.3% (8/150) had a family history of lung cancer. Cough was the most common initial symptom (39.3%, 59/150) in the study, closely followed by dyspnea (36%, 54/150). Other initial symptoms included chest pain, hemoptysis, fever, loss of appetite, and loss of weight.

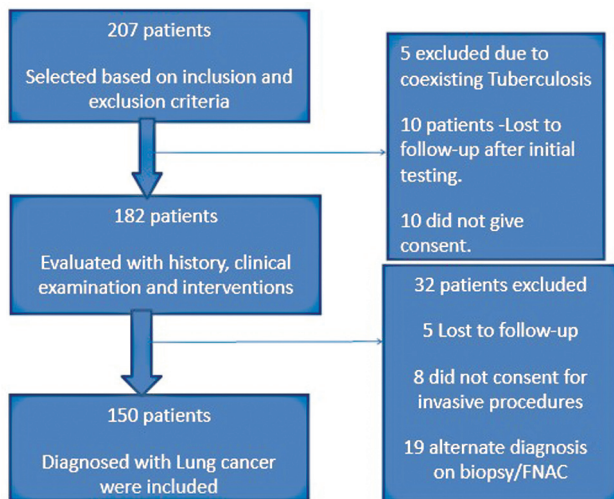


Fig. 2 Flow chart showing selection and exclusion of patients.

Approach Delay and Associated Factors

There was an approach delay in 78 cases (52%) and the mean approach interval was 62 days \pm SD 7.95, with a range of 0 to 336 days. Univariate analysis showed a statistically significant association of approach delay of 30 days or more being associated with an age less than 60 years ($p < 0.001$), belonging to the female gender ($p = 0.001$), coming from a rural area ($p = 0.001$), being unemployed ($p = 0.001$), and having cough ($p < 0.001$), and breathlessness ($p = 0.001$) as initial symptoms. Having chest pain ($p = 0.001$), the semi-skilled ($p = 0.011$) and those with a higher level of education ($p = 0.001$) presented early to a doctor, which was statistically significant. No statistical significance was found with smoking status or pack years, COPD as a comorbidity, prior history of tuberculosis, and family history of lung cancer. Multivariate analysis confirmed the significance of factors such as lower age group (less than 60 years), rural area of residence, cough and reduced appetite as initial symptoms (**Table 1**).

Referral Delay and Associated Factors

The mean referral interval was 4.98 weeks \pm SD 5.64, with a range of 1 to 26 weeks and a referral delay was seen in 71 (47.3%) cases. Being seen by a pulmonologist was significant in having no referral delay ($p = 0.027$). However, a statistically significant referral delay occurred when first seen by an alternate medical practitioner ($p = 0.001$) and first evaluation from a private hospital (0.034). Patients without an initial chest X-ray had significant referral delay ($p < 0.001$). A similar pattern was noted when CT thorax scans were not taken initially ($p = 0.001$). Multivariate analysis, however, did not show any significance in referral delay with any of the mentioned factors (**Table 2**). In the delay group, the majority had an initial diagnosis of lower respiratory tract infection (38%, 27/71) and pulmonary tuberculosis (28.16%, 20/71).

Delay in Diagnostic Interval and Associated Factors

There were 25 (16.7%) cases of diagnostic delay with 9.21 days \pm SD 7.18 being the mean diagnostic interval (range: 3–41 days). Central location of the lesion (defined as lesions within 2 cm of proximal bronchial tree, heart, great vessels, trachea) were significantly associated with a diagnostic delay ($p = 0.008$) (**Table 3**). Most of the cases were diagnosed with lymph node FNAC/biopsy (36%, 54/150) and flexible bronchoscopy-guided endobronchial biopsy (31.3%, 47/150). There were 64/150 (42.7%) cases of adenocarcinoma, 46/150 (30.7%) cases of squamous cell carcinoma, 10/150 (6.7%) cases of small cell carcinoma, and 30/150 (20%) miscellaneous cases namely Poorly differentiated carcinoma, Large cell, Adenosquamous, Adenoid cystic and Sarcomas. The majority of patients (57.3%, 86/150) were diagnosed when in Stage IIIb, 26% patients in Stage IV (39/150), 10.7% (16/150) in Stage 3c, 3.3% (5/150) in Stage 3a, 2.7% (4/150) in stage II, and none in stage I.

Discussion

Lung cancer diagnosis is a challenge to doctors all over the world. India, with a current population of 1.67 billion, is no exception in this regard. With the rising costs of medical treatment, inflation, limited health insurance penetration, unemployment, and pay loss during leaves, many patients delay seeking general medical treatment and advice. This study attempted to find out specific reasons for a delayed diagnosis in lung cancer patients. Sociodemographic characters of the subjects showed that the majority were males (88.7%) with a mean age of 64.63 years (\pm SD 8.42). Most patients were from a rural background, had upper primary education and were un-skilled laborers. Cough and breathlessness were the major initial symptoms.

The mean approach interval was 62 days \pm SD 7.95, with a range of 0 to 336 days. This is in contrast to studies from India, conducted by Chatterjee et al and Chandra et al, where the mean approach interval was 92 days and 143 days, respectively.^{10,13} Jindal et al studied that 32.6% of lung cancer patients presented within 3 months, 46.4% of patients within 3 to 6 months, and 21% beyond 6 months of development of symptoms.¹⁴ Though our approach interval (a mean of 62 days) is less compared to other Indian studies, we still lag behind when compared to an approach interval of 14-21 days in international studies.^{15,16} There was an approach delay in 78 cases (52%) in our study. In the delayed group, 63 were males and 15 were females which accounts for 47.36% of total 133 males and 88.2% of the total 17 females. There was a significant approach delay in females, all being homemakers or housewives ($p = 0.001$). When queried on the possible reasons for not approaching a doctor, majority of the females said they were not able to come early due to their work and family pressures, social issues of stigmatization as tuberculosis, fear of being out-cast and cough being self-attributed to allergies, environmental pollution, and aging.

Table 1 Association between approach delay and related factors

Factors assessed for approach delay	No approach delay (<1 month)	Approach delay (≥1 month)	Significance level (p-Value) univariate analysis	Significance level (p-Value) multivariate analysis
Age			<.001	<.001
< 60 years	12	36		
≥ 60 years	60	42		
Sex			0.001	
Female (17)	2	15		
Male(133)	70	63		
Education				
Lower primary	15	21	0.383	
Upper primary	42	49	0.574	
High school	6	8	0.686	
Graduate	9	0	0.001	
Residence			0.001	<0.001
Rural area	60	77		
Urban area	12	1		
Occupation				
Unskilled	35	39	0.87	
Semi-skilled	25	13	0.011	
Skilled	10	11	0.970	
Not working	2	15	0.001	
Pack years				
1–19	16	19	0.757	
≥20	47	44	0.267	
Concurrent COPD	22	28	0.488	
Past history of Tuberculosis	16	18	0.901	
Family history of lung cancer	4	4	0.907	
Initial symptoms				
Dyspnea	37	17	0.001	
Cough	8	51	<0.001	<0.001
Chest pain	15	1	0.001	
Hemoptysis	3	0	.069	
Fever	4	1	.145	
LOA	4	8	.289	0.019
LOW	1	0	.296	

Abbreviations: LOA, loss of appetite and LOW- significant Loss of weight.

A productive younger age group (< 60 years) presenting late for medical care is a cause for concern. Patients in this age group did not consider malignancy as a cause for their symptoms and hence kept avoiding doctor or hospital visits. This association was statistically significant. Dwelling into the education level of the study population, being a graduate had statistical significance in presenting early to a specialist. However, the numbers are too low ($n = 9$) and further studies on the level of education as a cause of delay in lung cancer diagnosis are needed. Semi-skilled persons such as carpenters,

electricians, and plumbers also presented early to a specialist with an approach delay of less than a month. This maybe assumed due to their symptoms affecting their livelihood. In contrast, unemployed people approached after at least a month due to their lack of concern for their health and financial constraints. Because most of our patients (91.3%) were from rural areas, residence showed a statistical significance with approach delay ($p = 0.001$), which is likely a referral bias. A study by Sulu et al in Turkey attributed pre-hospital delays to level of patient education and complex

Table 2 Association between referral delay and related factors (COPD-Chronic Obstructive Pulmonary disease, LRTI-Lower Respiratory tract infection, PTB-Pulmonary Tuberculosis; Others included Asthma, Acute bronchitis, Interstitial Lung disease)

Factors	Referral done (within 3 weeks)	Referral delay present (>3 weeks)	Significance univariate analysis
Doctor first visited			
General practitioner	44	30	0.100
Physician	25	29	0.241
Pulmonologist	10	2	0.027
Alternate medicine practitioner	0	10	<0.001
Institution first visited			
Government	46	29	0.034
Private	33	42	
Initial diagnosis			
COPD	0	14	<0.001
LRTI	17	27	0.027
PTB	1	20	<0.001
Lung malignancy	61	5	<0.001
Others	0	5	0.016
Chest X-ray			
Taken	79	55	
Not taken	0	16	<0.001
CT thorax			
Taken	70	43	<0.001
Not taken	9	29	

socioeconomic factors.¹⁷ In contrast, Smith et al showed that neither deprivation nor a rural location was significantly associated with time to consultation in Scotland.¹⁸

Cough, as the initial symptom, is a significant factor for causing delay in approach to a doctor ($p = 0.01$). These patients assumed that their cough was because of smoking, acute respiratory illness, environmental pollution, and lack of rest. This is in concordance with a study by Chatterjee et al

and Sachdev et al.¹⁹ In the latter study, the most important cause for a patient-related delay in approaching a doctor was procrastination. Buccheri et al concluded that seeking medical advice for an unexplained cough or for a respiratory infection was a sign of a better ultimate outcome, independent of all other prognostic factors.²⁰ In the delay group of 78 patients, 80.76% (63/78) were smokers and 35.8% (28/78) had COPD. There was no statistical significance with smoking

Table 3 Association between diagnostic delay and related factors

Factors	No diagnostic delay	Diagnostic delay present	Significance
Lesion location			
Central	55	20	0.008
Peripheral	70	5	
Procedure yielding diagnosis			
Lymph node FNAC/biopsy	49	5	
USG-guided FNAC/biopsy	28	2	
CT-guided FNAC/biopsy	6	0	
FOB-biopsy	31	16	
Medical thoracoscopy biopsy	10	1	
Pleural fluid cytology	1	1	

status, COPD as a comorbidity, prior history of tuberculosis and family history of lung cancer.

Referral delay was seen in 71 (47.3%) cases. A visit to a pulmonologist was significant in causing no referral delay ($p=0.027$), while visit to alternate medicine physicians was significantly associated with delay ($p=0.001$). This is probably because pulmonologists have a higher suspicion of lung malignancy. The number of patients approaching a specialist are less in our study (12/150). This may be true around the globe because of an initial visit to a family practitioner or a general physician. However, visiting a pulmonologist first and subsequent referral delay was not significant in the multivariate analysis.

As supported by different studies, low index of suspicion for lung cancer was concluded as the most common cause for referral delay in a study by Sulu et al.¹⁷ Similarly, Buccheri et al have suggested in his study that prompt referral to a pulmonologist is the most important pre-requisite for an early diagnosis.²¹ In addition, Koyi et al, in a prospective study, concluded that a high index of suspicion among the general physicians and a low threshold for referral is important, and a defeatist attitude toward lung cancer may cause a subconscious tendency to avoid diagnosing lung cancer.¹⁶

In the referral delay group, 38% (27/71) were diagnosed as lower respiratory tract infections and 28.16% (20/71) as PTB. These patients were treated with antibiotics and empirical anti-tuberculous chemotherapy (ATT). This corresponds to data from Chandra et al and Ramachandran et al that referral delay in countries such as India were due to misinterpretation of chest radiograph findings and starting empirical ATT for suspicious opacities on chest X-ray without resorting to further investigations.²² A study conducted in AIIMS Delhi by Singh et al proposed a review of diagnosis after 5 weeks of treatment with anti-tuberculous chemotherapy in smear-negative PTB, if no improvement or a worsening occurred.²³

There was a statistically significant delay in being referred when chest X-rays were not taken, as seen in 16 of our patients. NICE clinical guidelines recommend taking a chest X-ray in patients who present with persistent or recurrent chest infection, finger clubbing, supraclavicular lymphadenopathy, thrombocytosis, and signs consistent with lung cancer.¹¹

In our study, not taking a CT scan of the thorax was also associated with referral delay ($p=0.001$). At the time of doing this study, universal health insurance was not freely available and accessible, and patients had to pay out of their pockets for diagnostic tests. This probably explains why physicians avoided such investigations in spite of suspicious chest X-ray abnormalities.

As per the BTS guidelines, the results of bronchoscopy or any other similar diagnostic test should be communicated to the patient within 2 weeks of a decision to do it.¹² Also, $9.21 \text{ days} \pm \text{SD of } 7.18$ was our mean diagnostic interval (range of 3–41 days). In all, 25 people (16.7%) had diagnostic delay. In the delay group of 25 cases, a delay in doing the procedure occurred in 13 cases, while there was delay in tissue diagnosis in 19 cases. The procedure delay group required over one attempt to reach a final diagnosis.

Central location of the lesion was significantly associated with diagnostic delay ($p=0.008$). Central lesions usually need to be approached with specific procedures such as cTBNA or repeat flexible bronchoscopy with delays occurring in procuring dates.

Among the cases with a histological diagnosis, majority of the patients (86 cases; 57.3%) were diagnosed as stage IIIB of malignancy (TNM 8th edition).

In various international studies, 7 to 10 days is the recommended time for diagnosis of NSCLC.²⁴ The mean diagnostic interval in our study almost corresponds to the stipulated time. However, even in cases with no delay in the diagnosis of lung malignancy, such as those detected with FNAC or biopsy-imprint smears, specific treatment could be started only after confirmation of the biopsy report. In such a scenario, more rapid diagnostic methods and fast-track portal for specimens of suspected malignant cases need to be considered.

Strengths and Limitations of the Study

Our study is one of the largest source of data available on the probable delays in the diagnosis of lung cancer from this part of the country, which maybe representative of regions with similar literacy and accessibility to health care institutions. Because we based the approach interval on the subjective nature of the symptoms perceived by patients, it may have led to a recall bias with varying approach interval. Ours is a tertiary care government hospital which caters to all tiers of society, especially the economically deprived. This might be an inadequate representation of the general population and has an amount of referral bias. Most of the patients are referred to our center due to persistent symptoms or after being explained about the possibility of lung cancer, but we were not able to capture the exact delay in reaching our institution after referral by the physician. In addition, many patients with metastatic symptoms and paraneoplastic manifestation may have been admitted to other departments and not been adequately represented. However, we have tried to include all possible patients with lung cancer, being the primary referral center in the central part of the state. Lack of facility for doing an EBUS-guided TBNA may have increased the diagnostic delay. A follow-up of the delay group would have shown whether a delayed diagnosis corroborates with a poor outcome, which was not done in our study.

Conclusion

There is a significant delay in diagnosis of lung cancer in our population. Not approaching a doctor despite symptoms is a major cause for delay in diagnosis, closely followed by a delay in proper referral to specialists.

Encouraging females to disclose their respiratory symptoms, needs addressing through information education sessions and social media, as incidence of lung cancer in females are on the rise. Chronic cough, as a symptom is ignored, and as anticipated, is a major cause for delay in approaching a doctor. The need for getting medical help for persistent cough should be highlighted, especially among chronic smokers.

Respiratory symptoms should always be carefully evaluated, especially in patients with risk factors for lung malignancy and accordingly referred for specific tests when needed. A simple well positioned digital chest X-ray, if interpreted systematically, is helpful in detecting cases. All clinically diagnosed TB patients have to be under strict follow-up with serial weight assessment, and monitoring for clinical resolution and radiological improvement to pick up a missed or coexisting diagnosis of lung malignancy.

Though intuitively, patients with central tumors may present earlier, diagnosis requires more invasive procedures such as flexible bronchoscopy or EBUS-guided biopsies and more than one attempt for tissue diagnosis. More rapid diagnostic methods such as liquid biopsy and fast-track portal for specimens of suspected malignant cases is required to reduce diagnostic delay and improve the overall dismal survival of lung malignancy patients.

Funding

None.

Conflict of Interest

None declared.

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