RESEARCH COMMUNICATION

Delays during the Diagnostic Evaluation and Treatment of Lung Cancer

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Abstract

Objective: The majority of lung cancers are diagnosed and treated at an advanced stage. This may, in part, be due to a long lag period between the onset of symptoms, achieving a diagnosis and initiation of treatment. This lag period is highly variable in the limited studies conducted till date and dependent on several modifiable and non-modifiable factors. This study was conducted to determine the average time period required at various steps for diagnosing lung cancer from the onset of symptoms at a tertiary referral centre in Northern India. Methods: Newly diagnosed, histologically proven cases of lung cancer were studied during the period of 2002-08. The delay was calculated as: (a) symptom-to-diagnosis delay, between the onset of symptoms to confirmed diagnosis; (b) diagnosis-to-treatment delay, between diagnosis and treatment started; (c) symptom-to-treatment delay, between onset of symptoms and treatment. Results: Out of 165 patients studied (139 males, mean ± SD age, 57.6 ± 8.9 years; 26 females, 53.5 ± 11.1 years; 84.9% smokers with mean ± smoking pack-years of 37 ± 27.3, 86.7% non small cell lung cancers (NSCLCs) and 13.3% small cell lung cancers (SCLC)). At the time of diagnosis, 90.2% of NSCLC patients had stage IIIB or IV disease, while 81.8% of SCLC patients had extensive metastasis. A total of 28 (17%) patients had received antitubercular treatment (ATT) since onset of current symptoms. The median symptom-to-diagnosis delay, diagnosis-to-treatment delay, and symptom-to-treatment delay was 143 days (range, 4 to 721), 20 days (range, 1-380) and 185 days (18 to 870) respectively. Delay in diagnosis was significantly higher in patients who had received ATT initially (mean difference 65.5 days, 95% confidence interval of difference, 24.46 to 106.6; p= 0.002). Patients with higher KPS score had shorter symptom to diagnosis delay (p=0.075). Conclusion: In comparison with studies from European countries, there is an unacceptable longer lag period from symptom onset to initiation of treatment in Indian patients with lung cancer. Inappropriate treatment with ATT significantly prolongs this delay. These delays need to be shortened to the minimum possible in order to improve prognosis.

Key Words: Lung cancer - tuberculosis - treatment delay

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Introduction

The total number of new cases and death due to lung cancer in 2008 were estimated to be 215,020 and 161,840, respectively (accounts for approximately 15% of all cancers) (Cancer Facts & Figures 2008). The consolidated report of population based cancer registries of the National Cancer Registry Programme states that among males, lung cancer was the leading malignant disorder in several major Indian cities and the leading cause of tobacco related cancers, contributing to 20.2% - 28.6% of all. (Consolidated Report of the PBCRs: 2001-2004).

The majority of lung cancers (>80%) are diagnosed at an advanced stage, i.e. stage IIIB and IV, by when they are beyond the scope of curative resection (Mountain et al., 1997). This may, in part, be due to a long lag period between the onset of symptoms and establishment of a diagnosis and finally, initiation of treatment. The delay is variable and ranges from approximately 3 to 6 months in Western countries (Billing et al., 1996; Christensen et al., 1997; González et al., 2003; Myrdal et al., 2004; Yilmaz et al., 2008). The reasons for this lag period are yet uncertain and may be multifactorial, including patient awareness of the disease, accessibility to health care, and aggressiveness of the diagnostic approach. Since many of these factors are modifiable, it is important to quantify the lag period from symptom onset to treatment, as this has definite implications on patient survival. However, there are scarce data on this aspect, especially from the Asian subcontinent, where the presence of diseases such as pulmonary tuberculosis closely mimic lung cancer initially, thus hampering early diagnosis and treatment.

The present study was undertaken in order to determine the average lag period at various steps of patients' management for lung cancer from the onset of symptoms till initiation of treatment at a tertiary care hospital in New Delhi, India and compare them with similar data from other population groups.

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Materials and Methods

Health care settings and patients

A retrospective review was carried out of patients with newly diagnosed lung cancer between January 2002 to December-2008 the in the department of Medicine at All India institute of Medical Sciences (AIIMS), New Delhi. Patients with suspected lung malignancies are referred from this primary care to regional physicians from all across the Northern part of India for further assessment. All the patients were diagnosed on the basis of cytological/ histological examination of malignant tissue. Staging was done after complete workup for metastasis using CT-chest and abdomen, bone scan, and PET scan. MRI brain was done in patients with clinical features of brain metastasis.

Data collection and follow up

The patient records were searched for details regarding onset and type of symptoms, smoking and occupational exposure, past illness and treatment history, especially history of antitubercular therapy. Karnofsky Performance Status (KPS) was used to assess functional impairment. The date of establishment of a definitive diagnosis and initiation of treatment was recorded and used to calculate the delay periods. Note was also made of the procedure which provided the confirmatory diagnosis.

Statistical analysis

SPSS version 11.5 was used for data analysis. A descriptive statistical analysis was used for demographic and clinical characterization of the patients. For central tendency of variables, mean ±SD has been used for variable with normal distribution and median with range for variables with skewed distribution of observations. Median and range also been used for KPS as it's a discrete variable. Correlation between continuous variables was defined using Pearsons' correlation. For categorical variables, we performed the chi square test to compare groups. Independent-t test was used to compare mean between two groups.

Definitions

Three delays were studied; (a) Symptom-to-diagnosis delay (SDD) - delay between the onset of symptoms to confirmed diagnosis, (b) diagnosis-to-treatment delay (DTD) - delay between diagnosis and treatment started, and (c) symptom-to-treatment delay (STD) - delay between onset of symptoms and treatment (see Figure 1). SDD was available for all the patients, but DDT and STD were calculated only for patients receiving chemotherapy.

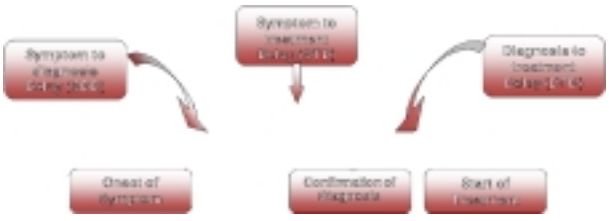

Figure 1. Schematic Diagram to Depict the Time Scales of Calculating Delay during Management of Lung Cancer

Table 1. Major Clinical Features at the Time of Diagnosis of Lung Cancer

Clinical Features	Percentage Occurrence
Coughing	75.2
Shortness of breath	66.9
Weight loss	63.7
Chest pain	63.1
Hemoptysis	33.1
Hoarseness of voice	29.3
Excessive weakness/ fatigue	26.8
Clubbing	22.9
Dysphagia	9.3
SVC	8.0

Results

A total of 165 newly diagnosed patients with lung cancer were included in the study (139 male, mean age±SD, 57.6±8.9) years; 26 females, 53.5±11.1years). Of the patients,78.2% were smokers with median (range) smoking pack-years of 25 (0.5-125). A higher percentage of men smoked compared to women (84.9% and 42.3%, respectively) and had higher mean smoking pack-years (35.2 and 15.3. respectively). 86.7 % of our cohort had non small cell lung cancer (NSCLC) and 13.3% had small cell lung cancer (SCLC). At the time of diagnosis, 90.2% of the NSCLC patients had stage IIIB or IV disease, while 81.8% of SCLC patients had extensive disease. The percent prevalences of major clinical features at the time of diagnosis of lung cancer are shown in Table 1. Median (range) KPS score was 70 (20-90) at the time of diagnosis. In the entire cohort, 28 patients (17%) were initially labeled with a diagnosis of tuberculosis and received antitubercular treatment (ATT) since onset of current symptoms. Sputum or bronchoalveolar lavage (BAL) for acid-fast bacilli (AFB) was found positive in only 3 of these patients. The remainder were diagnosed and treated presumptively on the basis of symptoms and radiographic findings. 123 patients (74.5%) needed only 1 diagnostic investigation while the remainder required more than one procedure for diagnosis.

The median SDD, DTD and STD were 143, 20 and 185 days, respectively, with ranges of 4 to 721, 1 to 380 and 18 to 870, days. No correlation has been found between age of the patient at the time of diagnosis and delay during diagnosis or treatment. SDD had no correlation with presence of cough, shortness of breath, chest pain, hemoptysis or hoarseness of voice. Delay in diagnosis was significantly higher in patients who had received ATT initially (mean difference 65.5 days, 95% confidence interval of difference, 24.5 to 106.6; p= 0.002). The difference in SDD between NSCLC and SCLC was not statistical significant (p=0.457). Patients with higher KPS score had shorter SDD (p=0.075) compared to patients with poorer KPS.

Table 2 shows SDD in patients according to the definitive procedure leading to the diagnosis of lung cancer to the patient. This was highest in patients who were diagnosed by performing CT-guided fine needle

Table 2. Symptom-Diagnosis Delay According to the Definitive Diagnostic Procedure

Diagnostic Procedure	n	Mean	Std. Deviation	Std. Error	95% CI	Minimum	Maximum
Bronchoscopic Biopsy	80	147.3	122.1	13.65	120.2 - 174.5	7	709
CT-guided-FNAC	54	184.8	132.0	17.96	148.8 - 220.9	21	705
CT-guided-Biopsy	15	142.1	111.2	28.71	80.5 - 203.6	4	391
Pleural Fluid Cytology/Biopsy	3	156.3	59.1	34.12	9.5 - 303.1	93	210
Lymph Node FNAC/Biopsy	6	137.0	107.3	43.80	24.9 - 250.1	10	328
Sputum Cytology	1	157.0	--	--	-- --	--	--
Bronchial Aspirate Cytology	6	181.3	100.7	41.12	75.6 - 287.0	56	347
Total	165	162.9	126.8	9.87	143.4 - 182.4	4	709

CI, Confidence Interval

aspiration (FNAC) and least in cases which have been diagnosed by lymph node biopsy/FNAC, the difference reaching statistical significance (p=0.015).

Discussion

In our study, we did not find any correlation between delay and age of patient or clinical presentation at the time of diagnosis. Patients with a higher KPS (>60) had shorter SDD, implying perhaps that patients with better performance status are investigated more aggressively in anticipation of better response to therapy. SDD was highest in patients who were diagnosed by CT-guided FNAC/ biopsy and least in patients diagnosed by lymph node biopsy/FNAC. These may reflect local diagnostic strategies and length of waiting list rather than any proof of superiority of one diagnostic technique over another. Delay in diagnosis was significantly high in patients who had received ATT for current symptoms and the mean difference was 65.6 days compared with those who did not receive ATT. An additional disturbing fact was that only a small proportion of these patients had a conclusive microbiological diagnosis of tuberculosis. This indicates that lung cancer is often misdiagnosed as pulmonary Kochs and these patients are presumptively given ATT, hence causing significant delay in diagnosing cancer. Although majority of our patients were diagnosed after one investigation itself, the requirement of multiple investigations did not increase the delay time in the remainder.

Table 3 lists the major studies where median delay in diagnosis and treatment of lung cancer has been calculated at various steps. There is substantial variation in the magnitude of delay periods from different patient groups. Median SDD, DTT and STD in our study were higher than most of the previously published studies. Most studies have shown that there was no higher survival in patients with shorter delay in diagnosis (Annakkaya et al.2007, Saloma et al. 2005, Yilmaz et al. 2008). This could be attributed to slow growing tumor presenting later where as fast growing tumor present sooner and have poorer survival. The late presentation to a physician was most

Table 2. Comparison of Previously Published Studies Evaluating Delay Periods

Study characteristics			Median delay (in days)								Remarks
Author	Period	Design (subjects)	S-1st GP	R De	Sp D	1st GP-D	1st GP-T	SDD	DTT	STD	
Yilmaz et al 2008	Jan 05-June 06	Prosp (138)	18	21	-	56	-	-	19	98	Presence of delay or length of delay does not correlate with tumour stage in patients who underwent thoracotomy.
Annakkaya et al 2007	Jan 02-June 05	Retro (103)	42	-	-	-	-	-	10	90	No significant difference in survival was detected between lung cancer patients with an STD shorter or longer than 45 days. Patients with an STD longer than 60 days had significantly increased survival.
Saloma et al 2005	Jan 01-Dec 01	Retro (132)	14	8	15	52	73	98	15	112	Long specialist treatment delays were not associated with worse prognosis in patients with advanced disease. Rapid diagnostic investigations without long delays might increase the number of resectable tumors and thereby improve the prognosis of lung cancer patients
Ozlu et al 2004	Jan 92-Dec 99	Retro (226)	30	-	-	8	30	22	18	72	The late presentation to a physician was most probably related to patient behaviour and the nature of the illness. The DTT was mostly associated with large patient numbers.
Koyi et al 2002	Feb 97-Feb 98	Prosp (134)	21	33	9	-	-	110	-	189	A high index of suspicion among the GPs and a low threshold for referral is important. Defeatist attitude toward lung cancer may cause GP to avoid diagnosing lung cancer subconsciously.
Radzikowska et al 2001	1995 - 1998	Retro (20,561)	46	38	46	65	84	-	30	-	-

S, symptom; Sp, Specialist; Prosp, Prospective; Retro, Retrospective, RDe, Referral delay; D, Diagnosis; T, Treatment

probably related to patient behaviour and the nature of the illness (Ozlu et al. 2004). Achieving a rapid diagnosis might increase the proportion of early-stage resectable tumors and thereby improve the prognosis of lung cancer patients (Saloma et al. 2005). A high index of suspicion among the General Physicians (GP) 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 (Koyi et al. 2002).

The British Thoracic Society (BTS) recommends that all patients should be seen for an initial evaluation by a pulmonary physician within 1 week of referral from their primary care physician and, diagnostic testing should be performed within 2 weeks of the decision (BTS Recommendations 1998). In cancer units where chemotherapy is given for lung cancer, patients should begin treatment within seven working days of the decision to employ a particular protocol. In the Canadian recommendations, a maximum of 4 weeks lapse between the first visit to a general practitioner and diagnosis is considered acceptable, and the waiting time for surgery should not exceed 2 weeks (Simunovic et al. 2001). Although this delay is not been calculated accurately in our study, considering the long SDD, it is reasonable to assume that doctor-diagnosis delay would far exceed the above mentioned recommendations. In our study group, only 6 patients could be initiated on treatment within a week of confirming the diagnosis. In the UK and other healthcare systems such as in Scandinavia, national recommendations exist for these pathways which are conceived on the assumption that reducing these intervals will reduce patient distress and improve survival (NHS Executive 2000).

In developing countries like India, the main delay is accounted by patients' ignorance in reporting to general practitioners, misinterpretation of chest radiograph findings and starting ATT for suspicious opacities on chest radiograph without proper evaluation using appropriate investigative modalities like CT scan, sputum cytology, and bronchoscopy.

Clinicians associate lung cancer with high case-fatality and start ATT without detailed investigation. This defeatist attitude toward lung cancer may avoid diagnosing lung cancer subconsciously.

The high cost and inaccessibility of diagnostic investigations such as CT scan, and bronchoscopy may contribute to their inadequate utilization early enough. In tertiary centers, waiting period for these investigations is often unacceptably long, further adding to the delay. The financial burden of chemotherapy, compounded by the relative poor response rates, may result in delayed initiation of treatment even after the diagnosis has been established.

Contrasting with previously published studies, we calculated the median delay instead of the mean, which allowed a more accurate measurement of central tendency in skewed distribution. However, this study has some limitations as well. Being a retrospective analysis, details of all dates were not available, notably the date of first contact with a physician. As a result, first symptom to first consultation delay and first consultation to diagnosis delay could not be calculated. In spite of these shortcomings, we feel that this data adds important information to the existing scarce knowledge regarding delays occurring at various stages during the management of lung cancer and may encourage further work to try and minimize these.

To conclude, there appears to be an unacceptable delay during the diagnosis and treatment of lung cancer. These may be due to both pre-hospital and hospital related factors and may contribute, at least partly, to the poor prognosis of this disease even after treatment. Attempts need to be made to minimize this lag period by maintaining a high index of suspicion, early referral and aggressive as well as appropriate investigative workup and prompt initiation of treatment.

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