RESEARCH ARTICLE

Clinico-pathological Profile of Lung Cancer at AIIMS: A Changing Paradigm in India

Prabhat Singh Malik[1], Mehar Chand Sharma[2], Bidhu Kalyan Mohanti[3], N K Shukla[4], SVS Deo[4], Anant Mohan[5], Guresh Kumar[6], Vinod Raina[1]*

Abstract

Background: Lung cancer is one of the commonest and most lethal cancers throughout the world. The epidemiological and pathological profile varies among different ethnicities and geographical regions. At present adenocarcinoma is the commonest histological subtype of non-small cell lung cancer (NSCLC) in most of the Western and Asian countries. However, in India squamous cell carcinoma has been reported as the commonest histological type in most of the series. The aim of the study was to analyze the current clinico-pathological profile and survival of lung cancer at our centre. Materials and Methods: We analyzed 434 pathologically confirmed lung cancer cases registered at our centre over a period of three years. They were evaluated for their clinical and pathological profiles, treatment received and outcome. The available histology slides were reviewed by an independent reviewer. Results: Median age was 55 years with a male:female ratio of 4.6:1. Some 68% of patients were smokers. There were 85.3% NSCLC and 14.7% SCLC cases. Among NSCLCs, adenocarcinoma was the commonest histological subtype after the pathology review. Among NSCLC, 56.8% cases were of stage IV while among SCLC 71.8% cases had extensive stage disease. Some 29% of patients did not receive any anticancer treatment. The median overall and progression free survivals of the patients who received treatment were 12.8 and 7.8 months for NSCLC and 9.1 and 6.8 months for SCLC. Conclusions: This analysis suggests that adenocarcinoma may now be the commonest histological subtype also in India, provided a careful pathological review is done. Most of the patients present at advanced stage and outcome remains poor.

Keywords: Lung cancer - clinicopathological profile - pathology review - NSCLC - survival - India

Asian Pacific J Cancer Prev, **14 (1)**, 489-494

Introduction

Lung cancer is one of the commonest cancers and cause of cancer related mortality worldwide. It accounts for 12.7% of all new cancer cases and 18.2% of all cancer related deaths, throughout the world (Parkin et al., 2008). In India, it is the commonest and most lethal cancer among males accounting for 10.9% of all cancer cases and 13% of cancer related mortality (Parkin et al., 2008). In general, the incidence of lung cancer throughout the world reflects the prevalence of smoking, and patterns of lung cancer appear attributable to the type of smoking (Valaitis et al., 1981).

In recent years, there has been a great interest in the histological characterization of lung cancer in view of newer histology guided therapeutic modalities and genomic classification of lung carcinoma (Standfield et al., 2011; Scagliotti et al., 2011). Broad classification of lung cancer into NSCLC and SCLC, is being challenged (Ettinger et al., 2012). In western countries and most of the Asian countries, adenocarcinoma has surpassed squamous cell carcinoma (Valaitis et al., 1981; Janssen-Heijnen et al., 2003). This shift seems to be attributable partly to the changed smoking pattern and increasing incidence of lung cancer in females and non smokers (Valaitis et al., 1981; Thun et al., 2006; Wakelee et al., 2007).

Most of the older and some recent Indian series have described squamous cell carcinoma as the commonest histology (Behera et al., 2004; Singh et al., 2010). Population based cancer registries in India give information of site wise distribution of cancer and histological subtypes are not taken into consideration. For such information we need large hospital based data. There is an immense need of information about the pattern of histological subtypes and clinical characteristics of the disease in the recent time because of paucity of such data in India. We have analyzed clinical and pathological profile and treatment outcome of lung cancer patients treated at our centre in last 3 years, which is a regional cancer centre registering approximately 8,000 new cancer cases every year.

*[1]Departments of Medical Oncology, [2]Pathology, [3]Radiation Oncology, [4]Surgical Oncoloy, [5]Pulmonary Medicine, [6]Biostatistics, Dr. B.R.A. Institute Rotary Cancer Hospital, All India Institute of Medical Sciences, New Delhi, India *For correspondence: vinodraina@hotmail.com*

Materials and Methods

We analysed 434 consecutive, pathologically confirmed lung cancer patients, registered at our centre in Lung Cancer Chemotherapy Clinic between July 2008 and June 2011 (a period of 3 years). Clinical, demographic, treatment and outcome related informations were collected from the case record files and entered in a predesigned proforma. The available histopathology slides were retrieved from the archives and were reviewed by an independent pathologist. Slides were reviewed on the basis of morphology and available IHC (done at the time of initial reporting). Restaging was done according to AJCC staging system 7th edition based on the available clinical and radiological findings. For treatment outcome and survival analysis only those patients were included who had received at least one treatment modality i.e. surgery, radiotherapy (radical or palliative), chemotherapy (at least one course of chemotherapy) or tyrosine kinase inhibitors (TKIs). We excluded patients with incomplete clinical informations.

Patients were treated as per the departmental treatment policy with multidisciplinary team approach. Responses were ascertained clinically and radiologicaly and coded according to revised RECIST criteria (Eisenhauer et al., 2009). Patients, after completion of treatment or on oral TKI, were followed every 3 monthly or early if clinically indicated. Detailed physical examination and chest X ray were done on each visit. CECT or other imaging modality (PET-CT) was repeated every 3-6 monthly or early if indicated. Patients with disease progression were offered second line treatment or supportive care only as per patient's performance status and preference.

Patients were considered on continuous follow up if the last visit was within 3 months of data censoring. In cases where last visit was more than 3 months ago, attempts were made to contact the patient by telephone and/or a reply letter. Patients were followed from the date of registration to the date of death and were censored at the date they were last known to be alive i.e. date of last follow up (if lost to follow-up) or May 31, 2012, whichever came first.

Permission for viewing case records was obtained from the institute's committee and the medical record department. Confidentiality of the patient's identity was maintained.

Statistical analysis

The data was censored at 31st May 2012 or last follow up date (if lost to follow up). Descriptive statistics was used for describing demographic and clinical characteristics. Survival was estimated by the Kaplan–Meier method and the Cox Regression Model (univariate and multivariate) was used to identify significant prognostic factors. Factors which had p value <0.25 in univariate analysis were subjected to multivariate analysis. Analysis was done using the SPSS ver. 15(SPSS Inc, Illinois, Chicago).

Results

A total of 434 confirmed lung cancer cases were available for clinico-pathological analysis during the study period. The median age of the study population was 55 years (23-84years). Majority of the patients were between 50-70 years of age. Male to female ratio was 4.6:1. Out of the total population, 295 patients (67.97%) were smokers (active or former). Bidi (an indigenous form of tobacco) was the commonest mode of smoking (55.25%). There were 370 (85.25%) cases of NSCLC and 64 (14.75%) cases of SCLC. The diagnosis were predominantly based on biopsy (66.13%) followed by FNAC (25.12%). At presentation 71.4% patients had ECOG performance status ≤2. Among NSCLC, 56.75% patients were of stage IV. Early stage (I-IIIA) was present in only 24.99% of the patients. Remaining 54 (14.59%) patients had stage IIIB disease. Similarly among SCLC, 71.87% patients had extensive disease while only 23.4% patients presented with limited stage disease. 124 patients (29%) didn't receive any anticancer treatment due to various reasons,

Table 1. Demographic Features

Feature		NSCLC n=370 (%)	SCLC n=64 (%)
Age	Median (Range)	55 (23-84)	55.5 (25-76)
	<40	33 (8.92)	7 (10.94)
	41-50	89 (24.05)	12 (18.75)
	51-60	136 (36.76)	23 (35.94)
	61-70	86 (23.24)	18 (28.13)
	>70	26 (7.03)	4 (6.25)
Sex	Male	299 (80.81)	58 (90.63)
	Female	71 (19.19)	6 (9.38)
Smoking	Smoker	239 (64.59)	56 (87.50)
	Non Smoker	119 (32.16)	8 (12.50)
	NA	12 (3.24)	
Type of smoking		(239.00)	56
	Bidi	121(50.64)	42 (75.00)
	Cigarette	50 (20.92)	4 (7.15)
	Others/NA	68 (28.45)	10 (17.85)
Pathological Subtype			
	Squamous cell carcinoma	109 (29.46)	
	Adenocarcinoma	168 (45.41)	
	Large cell carcinoma	7 (1.89)	
	BAC	10 (2.70)	
	NOS	76 (20.54)	
Small Cell Carcinoma			64 (100)
Method of diagnosis			
	Biopsy	239 (64.59)	48 (75.00)
	FNAC	94 (25.41)	15 (23.44)
	Fluid cytology	22 (5.95)	0
	Sputum	2 (0.54)	0
	BAL	13 (3.51)	1 (1.56)
Performance Status (ECOG)			
	≤2	266 (71.89)	44 (68.75)
	>2	69 (17.83)	17 (26.56)
	NA	35 (9.45)	3 (1.45)
Stage	IA	1 (0.27)	
	IB	9 (2.40)	
	IIA	6 (1.60)	
	IIB	24 (6.40)	
	IIIA	53 (14.32)	
	IIIB	54 (14.59)	
	IV	210 (56.75)	
	Limited		15 (23.40)
	Extensive		46 (71.87)
	NA	13 (3.50)	3 (4.60)
Treatment	Yes	261 (70.54)	49 (76.56)
	No	109 (29.46)	15 (23.44)

like poor PS, significant co morbidities, logistics and patient's preferences. Baseline demographic details according to main pathological subtypes are summarized in Table 1.

Pathology review

We retrieved 174 slides for review from our archives. On review there was discordance from the initial report in 42 patients (24.13%). On review 24 patients of unclassified group could be reclassified into squamous cell carcinoma (10), adenocarcinoma (12) and large cell carcinoma (2). One patient with adenocarcinoma and one patient with squamous cell carcinoma were found to be poorly differentiated and regrouped with NSCLC NOS. Nine patients who were initially reported to have squamous cell carcinoma but found to be adenocarcinoma after review. Among the biopsy slides which were subjected to independent review, squamous cell carcinoma was the commonest histological subtype (33.33%) as per the initial report, but after review adenocarcinoma was found to be the commonest histology (37.3%). Two patients were found to have metastatic lung lesions (one squamous and one adenocarcinoma) and excluded from further analysis. Similarly one patient was found to have atypical carcinoid (initially reported as small cell carcinoma) and excluded from analysis. Table 2 summarizes the pathological profile before and after review.

Table 2. Pathological Profile, before and after Review

	Before	After
NSCLC		
Squmaous cell carcinoma	58 (33.33%)	56 (32.1%)
Adenocarcinoma	43 (24.7%)	65 (37.3%)
Large cell carcinoma	5 (2.8%)	5 (2.8%)
BAC	3 (1.7%)	3 (1.7%)
NOS	36 (20.68%)	14 (8.04%)
SCLC	29 (16.67%)	28 (16.1%)
Atypical Carcinoid	-	1 (0.57%)
Metastasis	-	2 (1.14%)

Clinical presentation

Most common presenting symptom in both NSCLC and SCLC was cough (57.03% and 57.8% respectively) followed by chest pain (51.89% and 48.44%). Fever was present in 20.54% patients of NSCLC and 15.63% of SCLC. Clinical features of SVC obstruction were present in 5.42% of NSCLC patients and 25% of SCLC patients respectively. Pleural effusion was present in 26.76%

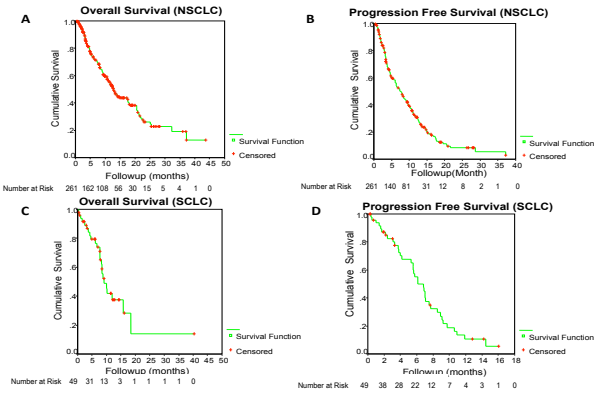

Figure 1. Kaplan Meir Survival Curves. A) Overall Survival, NSCLC, B) Progression Free Survival, NSCLC, C) Overall Survival, SCLC and D) Progression Free Survival, SCLC

Table 3. Cox Proportion Hazard Model (Univariate and Multivariate) for Overall and Progression Free Survival among Patients with NSCLC

Variable		Overall Survival				Progression Free Survivval			
		HR (95%CI) (Univariate analysis)		P	HR (95%CI) (Multivariate analysis)	HR (95%CI) (Univariate analysis)		P	HR (95%CI) (Multivariate analysis)
Age	<60	1			1				
	>60	1.15	(0.80-1.65)	0.43	-	1.21	(0.75-1.38)	0.89	-
Sex	Male	1			1				
	Female	1.14	(0.76-1.72)	0.51	-	0.98	(0.69-1.39)	0.91	-
Smoking	No	1			1				
	Yes	1.11	(0.78-1.58)	0.55	-	1.03	(0.77-1.38)	0.81	-
PS	≤2	1		1	1	1			
	>2	2.40	(1.53-3.79)	<0.001	3.06 (1.69-5.35)	1.96	(1.33-2.88)	<0.001	2.98 (1.86-4.76)
Stage	1-3A	1			1				
	3B	1.01	(0.58-2.06)	0.76		1.46	(0.9-2.38)	0.12	
	4	1.68	(1.09-2.59)	0.018	-	1.67	(1.17-2.38)	0.004	-
Histology	Squamous	1		1	1	1			
	Adenocarcinoma	1.09	(0.72-1.66)	0.66	0.84 (0.5-1.44)	1.05	(0.75-1.47)	0.74	0.89 (0.59-1.36)
	Large cell	0.71	(0.17-2.92)	0.64	0.31 (0.04-2.41)	0.58	(0.14-2.39)	0.45	0.27 (0.03-2.06)
	BAC	1.11	(0.43-2.84)	0.82	0.73 (0.27-2.0)	0.84	(0.38-1.85)	0.67	0.56 (0.32-1.38)
	NOS	1.81	(1.10-2.98)	0.018	2.13 (1.16-3.92)	1.37	(0.91-2.06)	0.12	1.61 (0.97-2.65)
SVCO	Absent	1			1				
	Present	1.66	(0.84-3.2)	0.14	-	1.65	(0.94-2.92)	0.08	-
Pleural Effusion	Absent	1			1				
	Present	1.37	(0.95-1.98)	0.086	-	1.12	(0.82-1.53)	0.44	-
Hemoglobin	≥12	1			1				
	<12	1.41	(0.96-2.06)	0.07	-	1.22	(0.89-1.66)	0.2	-
Albumin	≥3.5	1		1	1				
	<3.5	2.089	(1.28-3.4)	0.003	1.96 (1.11-3.45)	1.43	(0.94-2.18)	0.089	-

Table 4. Cox Proportion Hazard Model (Univariate and Multivariate) for Overall and Progression Free Survival among Patients with SCLC

Variable		Overall Survival HR (95%CI) (Univariate analysis)	P	Progression Free Survivval HR (95%CI) (Univariate analysis)	P
Age	≤60	1		1	
	>60	2.53 (1.09-5.89)	0.03	1.35 (0.67-2.71)	0.39
Sex	Male	1	1		
	Female	0.77 (0.1-5.96)	0.8	0.32 (0.04-2.53)	0.28
Smoking					
	No	1		1	
	Yes	2.26 (0.52-9.77)	0.27	1.97 (0.68-5.68)	0.2
PS	≤2	1		1	
	>2	1.76 (0.68-4.53)	0.23	1.55 (0.71-3.35)	0.24
Stage	Limited	1		1	
	Extensive	2.85 (0.94-8.62)	0.069	2.91 (1.24-6.83)	0.014
SVCO	Absent	1		1	
	Present	1.07 (0.46-2.48)	0.87	0.64 (0.30-1.34)	0.24
Pleural Effusion					
	Absent	1		1	
	Present	1.46 (0.53-3.97)	0.459	1.15 (0.5-2.63)	0.74
Hb	>12	1		1	
	≤12	0.84 (0.34-2.05)	0.7	0.92 (0.46-1.85)	0.82
Albumin					
	>3.5	1		1	
	≤3.5	2.43 (0.77-7.6)	0.12	2.05 (0.82-5.16)	0.12

of NSCLC and 18.75% of SCLC patients out of which 51.52% in NSCLC and 16.6% in SCLC had positive fluid cytology. Most common site of metastasis was bones (20.33%) in NSCLC and liver (25%) in SCLC. Adrenal metastases were present in 5.69% cases of NSCLC and 12.5% cases of SCLC. At the time of presentation, some 4.6% of NSCLC and 6.25% of SCLC patients had brain metastasis.

Treatment

All patients were treated by multidisciplinary approach. Out of total patients who received anticancer treatment, only 5.36% of NSCLC underwent curative surgery. But the proportion of patients with NSCLC undergoing surgery out of operable stage patients was 15.05%. Among patients with NSCLC, 39.08% while 36.7% of SCLC patients received radiotherapy to primary site. Majority of the patients (64.7% of NSCLC and 72.2% of SCLC) could receive palliative doses of radiation. Chemotherapy was given to 75.47% of NSCLC patients and 100% of SCLC patients. Only 37.56% of NSCLC and 42.86% of SCLC patients could complete 4-6 courses. The most common regimen used was combinations of Paclitaxel and Carboplatin for NSCLC and Cisplatin and Etoposide for SCLC. A total of 100 patients with NSCLC received TKIs, 50% of which were given as first line treatment. The decisions of TKI were mostly based on clinical predictors and not on mutation results.

Survival analysis and prognostic factors

All patients were treated with multidisciplinary approach according to patient's characteristics. Median follow up time for patients with NSCLC and SCLC were 14.9 months and 11.5 months. The median overall survival of patients with NSCLC was 12.8 months (95%CI 11.0-14.7) and the median progression free survival was 7.8 months (95%CI 6.1-8.8). On the other hand, the median overall survival of patients with SCLC was 9.1 months (95%CI 6.8-11.4) and the median progression free survival was 6.8 months (95%CI 5.3-8.3). The Kaplan Meir survival curves are shown in Figure 1.

We analyzed patient's characteristics for their impact on survival in NSCLC and SCLC separately by univariate and multivariate cox regression analysis. Multivariate analysis identified PS>2, poorly differentiated/unclassified histology and serum albumin <3.5 mg/dl as significant adverse risk factors for overall survival while for progression free survival only PS>2 was significant among patients with NSCLC (Table 3). For SCLC none of these factors was found to be significant on multivariate analysis (Table 4).

Discussion

The aim of this analysis was to study the current clinico-pathological profile of lung cancer patients at our centre and to assess their outcome. A total of 434 confirmed lung cancer patients who were diagnosed and treated over a period of 3 years were analyzed. As compared to Western population, median age of our patients was a decade younger (Blanchon et al., 2006; Cetin et al., 2011; Albain et al., 1991). Most of the previous studies Indian have reported the similar median age (Behera et al., 2004; Singh et al.,2010; Prasad et al 2004; Khan et al.,2006). Smoking is associated with most of the lung cancer cases (Vineis et al., 2004; Giovino et al.,2002). In our study, we found that up to 70% patients were smokers (current or former). Majority were bidi smokers which is an indigenously prepared, unfiltered and crude form of tobacco smoking prevalent mainly in the rural population. Previous Indian series have shown that majority of patients with lung cancer were bidi smokers (Behera et al.,2004; Prasad et al 2004).

In our study, we found adenocarcinoma to be the commonest histological subtype, accounting for 39% of all lung cancer cases. Over last few years there has been a shift of histological profile towards adenocarcinoma worldwide (Valaitis et al., 1981). However, most of the Indian series still report squamous cell carcinoma to be the commonest subtype (Behera et al., 2004; Singh et al.,2010; Prasad et al 2004; Khan et al.,2006). As a result of recent evolution in newer histology based treatment approaches, there is a need of proper histological sub typing of lung cancer (Scagliotti et al., 2011; Cooper et al.,2011). In our study we observed that up to 21% of lung cancer cases were still labelled with the generic term of NSCLC. However, on independent review, this proportion was reduced to 8% and we could reclassify many cases from the unclassified group. This signifies the critical role of pathology review in lung cancer in the present era of personalised treatment. Field et al (2004) have previously shown the relevance of independent pathology review from SEER database. Interestingly, most common histological subtype among the slides which were reviewed was squamous cell carcinoma according to the initial report, but on review adenocarcinoma turned out to be the commonest subtype. This under diagnosis may be one reason of reporting

lower frequency of adenocarcinoma by most of the Indian studies. An independent central review can reveal the actual pathological profile of lung cancer in countries like India where squamous cell carcinoma is still reported to be higher in frequency in contrast to the developed world.

Most of the patients in our study had advanced disease (stage IIIB-IV) at the time of presentation (70% in NSCLC and 71% in SCLC). In the series from west as well as from India, it is reported that 50-70% cases of NSCLC and up to 2/3rd of SCLC usually present in advanced stage (Behera et al., 2004; Blanchon et al., 2006; Govindan et al 2006; Grivaux et al 2011).

It is a well known fact that not all patients with lung cancer are able to receive anti cancer treatment. In our study 28.57% patients (29.46% of NSCLC and 23.44% of SCLC) didn't receive any anticancer treatment. These figures varies from 19% in USA, 33% in Australia, 37% in Scotland, and 50% in Ireland and New Zealand (Fry et al., 1999; Vinod et al., 2008; Erridge et al., 2008; Mahmud et al., 2003; Stevens et al., 2007). Vinod et al (2010) have addressed this issue in their study and found that in actual practice 20% patients didn't receive any treatment; however guideline recommendations for no treatment were there in only 4% patients. On multivariate analysis, it was observed that main factors responsible for this discrepancy were older age, poor PS, NSCLC histology and social reasons.

Among NSCLC, only 5.36% patients underwent surgery. This proportion appears to be quite low considering the fact that we had about 25% cases of NSCLC with stage I-IIIA. If we look at the proportion of patient undergoing surgery out of early stage (operable) disease, then it would be 15% (14/93). Even studies from United States demonstrate that 30-60% of cases of early stage lung cancer don't undergo surgery. They found racial differences in proportion of patients undergoing surgery, apart from disease related factors and co morbidities (Esnaola et al., 2008; Cykert et al., 2010). In our study, 39.08% of NSCLC and 36.7% of SCLC patients received radiotherapy to the primary site, out of which only 29.4% (of patients receiving radiotherapy) of NSCLC and 27.7% of SCLC, received radiotherapy in radical doses. There was marked underutilization of this treatment modality. Generally guidelines recommend that up to 76% of lung cancer patients should receive radiotherapy at some time point during their treatment. However in actual practice, 36-70% cases actually receive radiotherapy, worldwide (Delaney et al., 2005).

Median overall survival and median progression free survival of patients with NSCLC were 12.8 months and 7.5 months respectively. This reflects the large proportion of advanced stage disease in the study population. Furthermore, many of early stage patients could not complete the intended treatment and hence had inferior survival than expected. On multivariate analysis we found that PS>2, poorly differentiated histology and serum albumin levels <3.5mg/dl were associated with inferior survival however for progression free survival only PS>2 was found to be significant adverse risk factor. In a larger study of 4669 patients, Blanchon et al (2006) have developed a prognostic score for NSCLC and demonstrated that age, stage, PS, histology and treatment modalities used had a significant impact on survival. In SWOG (South-West Oncology Group) experience of advanced NSCLC, PS, female sex, age, haemoglobin and serum LDH were found to be independent prognostic factors (Albain et al., 1991).

The outcome of SCLC in our study was poorer than that of NSCLC. The median survival of SCLC patients was 9.1 months and median progression free survival was 6.8 months. These figures are consistent with the literature (Albain et al., 1990). On multivariate analysis none of the factors was found to be significant. This may be due to small number of patients among SCLC group. Mohan et al (2006) have previously demonstrated in their study that, PS, stage, Hb and symptom burden were independent prognostic factors for survival. Analysis of SWOG database also shows that age, PS, LDH, female sex were independent factors for survival for limited disease while only LDH was significant for extensive stage disease (Albain et al., 1990).

In conclusion, there is a paradigm shift in the clinico-pathological profile of lung cancer in India. Adenocarcinoma may be the commonest histological subtype in this part of the world also, provided a careful independent pathology review is done. Analysis of a larger cohort from multiple institutions would reflect the true pattern. Outcome of these patients still remain poor because of presentation in advanced stage and poor PS and many of them are not able to receive adequate treatment.

Acknowledgements

We are thankful to all our patients and their relatives for their cooperation.

References

Albain KS, Crowley JJ, LeBlanc M, et al (1990). Determinants of improved outcome in small-cell lung cancer: an analysis of the 2,580-patient southwest oncology group data base. *J Clin Oncol*, **8**, 1563-74.

Albain KS, Crowley JJ, LeBlanc M, et al (1991). Survival determinants in extensive-stage non-small-cell lung cancer: the southwest oncology group experience. *J Clin Oncol*, **9**, 1618-26.

Behera D, Balamugesh T (2004). Lung cancer in India. *Indian J Chest Dis Allied Sci*, **46**, 269-81.

Blanchon F, Grivaux M, Asselain B, et al (2006). 4-year mortality in patients with non-small-cell lung cancer: development and validation of a prognostic index. *Lancet Oncol*, **7**, 829-36.

Cetin K, Ettinger DS, Hei Y-J, et al (2011). Survival by histologic subtype in stage IV nonsmall cell lung cancer based on data from the Surveillance, Epidemiology and End Results Program. *Clin Epidemiol*, **3**, 139-48.

Cooper WA, O'toole S, Boyer M, et al (2011). What's new in non-small cell lung cancer for pathologists: the importance of accurate subtyping, EGFR mutations and ALK rearrangements. *Pathology*, **43**, 103-15.

Cykert S, Dilworth-Anderson P, Monroe MH, et al (2010). Factors associated with decisions to undergo surgery among patients with newly diagnosed early-stage lung cancer. *JAMA*, **303**, 2368-76.

Delaney G, Jacob S, Featherstone C, et al (2005). The role

of radiotherapy in cancer treatment: estimating optimal utilization from a review of evidence-based clinical guidelines. *Cancer*, **104**, 1129-37.

Eisenhauer EA, Therasse P, Bogaerts J, et al (2009). New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*, **45**, 228-47.

Erridge SC, Murray B, Price A, et al (2008). Improved treatment and survival for lung cancer patients in South-East Scotland. *J Thorac Oncol*, **3**, 491-8.

Esnaola NF, Gebregziabher M, Knott K, et al (2008). Underuse of surgical resection for localized, non-small cell lung cancer among whites and African Americans in South Carolina. *Ann Thorac Surg*, **86**, 220-6.

Ettinger DS. NCCN Clinical Practice Guidelines in Oncology for Non Small Cell Lung Cancer, Ver 2.2012 [Internet]. Natinal Comprehensive Cancer Network; 2012. Available from: www.nccn.com

Field RW, Smith BJ, Platz CE, et al (2004). Lung cancer histologic type in the surveillance, epidemiology, and end results registry versus independent review. *J Natl Cancer Inst*, **96**, 1105-7.

Fry WA, Phillips JL, Menck HR.(1999). Ten-year survey of lung cancer treatment and survival in hospitals in the United States: a national cancer data base report. *Cancer*, **86**, 1867-76.

Giovino GA (2002). Epidemiology of tobacco use in the United States. *Oncogene*, **21**, 7326-40.

Govindan R, Page N, Morgensztern D, et al (2006). Changing epidemiology of small-cell lung cancer in the United States over the last 30 years: analysis of the surveillance, epidemiologic, and end results database. *J Clin Oncol*, **24**, 4539-44.

Grivaux M, Zureik M, Marsal L, et al.(2011). Five-year survival for lung cancer patients managed in general hospitals. *Rev Mal Respir*, **28**, 31-8.

Janssen-Heijnen MLG, Coebergh J-WW (2003). The changing epidemiology of lung cancer in Europe. *Lung Cancer*, **41**, 245-58.

Khan NA, Afroz F, Lone MM, et al (2006). Profile of lung cancer in Kashmir, India: a five-year study. *Indian J Chest Dis Allied Sci*, **48**, 187-90.

Mahmud SM, Reilly M, Comber H (2003). Patterns of initial management of lung cancer in the Republic of Ireland: a population-based observational study. *Lung Cancer*, **41**, 57-64.

Mohan A, Goyal A, Singh P, et al (2006). Survival in small cell lung cancer in India: prognostic utility of clinical features, laboratory parameters and response to treatment. *Indian J Cancer*, **43**, 67-74.

Parkin DM FJ. GLOBOCAN 2008 V1.2, Cancer Incidence and Mortality Worldwide [Internet]. IARC Cancer Base No.10; Available from: http://globocan.iarc.fr

Prasad R, James P, Kesarwani V, et al (20004). Clinicopathological study of bronchogenic carcinoma. *Respirology*, **9**, 557-60.

Scagliotti G, Brodowicz T, Shepherd FA, et al (2011). Treatment-by-histology interaction analyses in three phase III trials show superiority of pemetrexed in nonsquamous non-small cell lung cancer. *J Thorac Oncol*, **6**, 64-70

Singh N, Aggarwal AN, Gupta D, et al (2010). Unchanging clinico-epidemiological profile of lung cancer in north India over three decades. *Cancer Epidemiol*, **34**, 101-4.

Standfield L, Weston AR, Barraclough H, et al (2011). Histology as a treatment effect modifier in advanced non-small cell lung cancer: a systematic review of the evidence. *Respirology*, **16**, 1210-20.

Stevens W, Stevens G, Kolbe J, et al (2007). Lung cancer in New Zealand: patterns of secondary care and implications for survival. *J Thorac Oncol*, **2**, 481-93.

Thun MJ, Henley SJ, Burns D, et al. (2006). Lung cancer death rates in lifelong nonsmokers. *J Natl Cancer Inst*, **98**, 691-9.

Valaitis J, Warren S, Gamble D (1981). Increasing incidence of adenocarcinoma of the lung. *Cancer*, **47**, 1042-6.

Vineis P, Alavanja M, Buffler P, et al (2004). Tobacco and cancer: recent epidemiological evidence. *J Natl Cancer Inst*, **96**, 99-106.

Vinod SK, O'Connell DL, Simonella L, et al (2008). Gaps in optimal care for lung cancer. *J Thorac Oncol*, **3**, 871-9.

Vinod SK, Sidhom MA, Gabriel GS, et al (2010). Why do some lung cancer patients receive no anticancer treatment? *J Thorac Oncol*, **5**, 1025-32.

Wakelee HA, Chang ET, Gomez SL, et al (2007). Lung cancer incidence in never smokers. *J Clin Oncol*, **25**, 472-8.