Clinicopathological profile and treatment outcome in non-small cell lung carcinoma patients and six month survival analysis at a tertiary care center in south India

Shivalinga Swamy Salimath[1], MD Majeed Pasha[2,*], Mohan Rao K N[3], Mahendra M[4], Sujith Halappa[5]

[1,2]Assistant Professor, [3]Professor and HOD, Dept. of Respiratory Medicine, Rajarajeshwari Medical College and Hospital, Bangalore, Karnataka, [4]Assistant Professor, Dept. of Respiratory Medicine, Shimoga Institute of Medical Science, Bangalore, Karnataka, [5]Senior Resident, Dept. of Respiratory Medicine, Subbiah Institute of Medical Sciences, Karnataka, India

***Corresponding Author:**
Email: mdmajeedr@gmail.com

Abstract:

Background: Lung cancer is the most common cancer and a leading cause of cancer related deaths worldwide. Non-small cell lung cancer (NSCLC) is the most common histological type. The aim of our study was to analyze clinico-pathological profile, treatment outcome and survival of NSCLC patients at a tertiary care centre.

Methodology: A total of 50 patients diagnosed histopathologically to have NSCLC were included in the study. This study was done at J.S.S Medical College and Hospital, Mysore. All patients were prospectively followed up for 6 months. Clinico-pathological profile, treatment outcome, overall survival and performance status were analyzed using Cox Proportional hazard model.

Results: Our study included a total of 50 cases with 44 male (88%) and 6 (12%) female patients with a median age of 65 years (range 42-90 years). 27 cases were adenocarcinomas (54%), 14 Squamous cell carcinomas (28%), 7 poorly differentiated carcinomas (14%) and 2 large cell carcinomas (4%).

Overall survival (OS) among patients receiving treatment was significantly better [HR=2.44(95% CI 1.14-5.22) p=0.02]. Patients treated with Chemotherapy (Carboplatin-Paclitaxel ± Gefitinib) showed significant better survival compared to patients who did not receive chemotherapy [HR=2.73(95% CI 1.03-7.25) p=0.004].

Performance status as measured by both Karnofsky score [HR=5.02(95% CI 1.51-16.67) p=0.008] and ECOG scores [HR=0.26(95% CI 0.09-0.69) p=0.006] were significantly associated with better survival in patients who took treatment.

Conclusions: NSCLC patients who took chemotherapy have a significant better survival and good quality of life.

Keywords: Chemotherapy; NSCLC; Survival.

Introduction:

Lung cancer has been the most common cancer in the world for several decades. There are estimated to be 1.8 million new cases in 2012 (12.9% of the total), 58% of which occurred in the less developed regions. It is the most common cause of death from cancer worldwide, estimated to be responsible for nearly one in five (1.59 million deaths, 19.4% of the total). Because of its high fatality (the overall ratio of mortality to incidence is 0.87) [1]. In India, Lung cancer is the second most common cause of cancer related deaths [2,3].

Smoking remains the most common risk factor for lung cancer followed by environmental tobacco smoke (ETS) exposure, air pollution and occupational exposures like radon, asbestos, arsenic metals. Tobacco use is responsible for the death of approximately 7 million people every year globally; more than 6 million deaths result from direct tobacco use and more than 890,000 deaths result from exposure to second-hand smoke [4]. Globally, cigarette smoking by itself is responsible for over 80 percent of all lung cancer cases [5]. In India, tobacco smoking is mainly in the form of beedi, followed by cigarette, hookah, chillum and chutta [6].

The overall global statistics estimate that 15% of lung cancers in men and up to 53% in women are not attributable to smoking, with never smokers accounting for 25% of all lung cancer cases worldwide [7]. The incidence of Lung cancer is increasing in never smokers, especially in Asian population and more in females. Increased frequency of EGFR mutations is seen in lung adenocarcinomas of never smokers, younger patients, especially in Asian cohorts [8,9].

Non-small cell lung carcinoma is the most common histopathological type of Lung cancer accounting for 85% of Lung cancers with a very dismal prognosis [10,11]. The overall 5‑year survival rate of advanced lung cancer is very poor and remains in the range of 5%–15% only [12]. The stage at diagnosis along with the presence of local, regional, or distant metastasis plays a key role in determining the overall 5‑year survival rates [13].

In India, most of the NSCLC cases are detected late in their 3rd or 4th stages. In early stages, surgery remains the most important treatment strategy, followed by Chemo-radiation. In patients with advanced-stage disease, chemotherapy or epidermal growth factor receptor (EGFR) kinase inhibitors offer modest improvements in median survival, though overall survival is poor [14,15]. With the advent of EGFR tyrosine kinase inhibitors (TKIs), pemetrexed- and taxane- based platinum doublet, survivals in NSCLC were significantly improved along with marked improvement in quality of life [16-18]. It has repeatedly been demonstrated that performance status as measured

by Karnofsky and European Cooperative Oncology Group (ECOG) scales is an important prognostic factor for non-small cell lung cancer [19,20]. These scales determine the quality of life in cancer patients.

The present prospective study was carried out to estimate the clinico-pathological profile, treatment outcome, quality of life and six months survival among NSCLC patients along with the evaluation of their clinical characteristics at a tertiary care hospital in Southern India.

Materials and Methods:

This study was done at J.S.S Medical College and Hospital, Mysore. A total of 50 histopathologically confirmed NSCLC patients were included in the study. After obtaining Institutional Ethical Committee clearance, the subjects were included prospectively after taking written informed consent, for a period of one year. All patients were diagnosed by FNAC/Biopsy from the primary lung mass and histopathologically proved to have NSCLC. Clinical and radiological staging was done and all the patients included were of stage 3B and 4.

All the patients were followed up for a total period of six months. Demographic data was taken at the time of diagnosis. Using a validated Proforma, the details of clinical history, physical examination, relevant Investigations (Complete Hemogram, Renal and Liver function tests, CECT Thorax, PET-CT, MRI), overall survival, performance status as measured by Karnofsky and ECOG scales, treatment taken including chemotherapy (Pemetrexed‑ and taxane‑based platinum doublet), EGFR-TKI therapy (Oral Gefitinib 250mg) were taken at the time of diagnosis and then on a monthly follow-up for a total period of six months.

Statistical Analysis: For continuous variables, the P-value was calculated using the unpaired t‑test to compare the means. For categorical data such as stage, smoking, sex, performance status, and RRs, the two‑tailed P value was calculated using Fisher's exact test and 2 × 2 contingency table.

ROC curves were used to get the cut off value for continuous variables at the point of maximum sensitivity and specificity and continuous variables were converted to binomial variables using the cut off for further analysis.

Univariate analysis to assess effect of various parameters on survival was done using Cox Proportional hazard model. Hazard ratio was calculated and p-value was obtained. P value ≤ 0.05 was considered significant.

Softwares used foe analysis were Epi Info™ 7.1.0.6 (Centers for Disease Control and Prevention (CDC), SigmaPlot for Windows verion 11.0 and Microsoft Office.

Results:

In this prospective study, a total of 50 NSCLC patients with male to female ratio of 5.5:1 were included. Median age is 65 years (range 42–90 years). Most of the cases were Adenocarcinoma (27 patients, 54%) followed by Squamous cell Carcinoma (7 patients, 14%). Demographic data is presented in table 1. 21 patients (42%) survived and 29 patients (58%) died during the follow up period of six months. Most of the patients had cachexia, Cough and breathlessness (70%), Chest pain (58%), hemoptysis (18%) and Hoarseness of voice (24%).

A total of 20 patients (40%) were under Chemotherapy with Paclitaxel and Cisplatin/Carboplatin combination along with EGFR tyrosine Kinase Inhibitor - Gefitinib. Among them, 14 patients survived through the follow up period.

Univariate analysis was done to assess the effect of various parameters on survival using Cox proportional hazards model. The hazard ratio was calculated and p value was obtained. (Table 2) We found that patients who were treated with Chemotherapy (Platinum- and taxane – based doublet with gefitinib 250mg once daily orally) had a significant better survival. The performance status was assessed using Karnofsky performance scale and ECOG scale. The patients who took treatment with a better performance status had a significant better survival. (Fig. 1,2,3)

On multivariate analysis we found patients who took treatment, chemotherapy and with good performance status (Karnofsky score >65 and ECOG >2.5) had better survival at 6 months (Table 3).

Table 1: Demographic data of patients with non-small cell carcinoma patients

Variables	Number=50 (%)
Age, mean (SD) in years	65±12.25
Gender, male n (%)	44(88)
Gender, Female	6 (12)
Shortness of breath	35(70)
Fever	14(28)
Chest pain	29(56)
Loss of appetite	45(90)
Weight loss	43(86)
Hemoptysis	9(18)
Hoarseness of voice	12(24)
Adenocarcinoma	27(54)
Squamous cell carcinoma	14(28)
Poorly differentiated carcinoma	7(14)
Large cell carcinoma	2(4)
Treatment taken	26(52)
Chemotherapy	20(40)
Survived at 6 months	21(42)

Table 2: Univariate Cox regression analysis for factors influencing survival in all patients with Non-small cell carcinoma

Variables, n (%)	Total (50)	Survivors (21)	Non-survivors (29)	Hazard ratio (95% CI)	p value
Age (>67 years)	12	3 (25%)	9 (75%)	2.7 (0.63-11.55)	0.20
BMI (<23.8)	43	16 (37.2 %)	27(62.7%)	2.99 (0.71-12.6)	0.13
Symptom duration (>1.5 months)	31	16 (51.61%)	15(48.38%)	1.72 (0.83-3.58)	0.14
Comorbidities	22	8 (36.36%)	14 (63.6%)	0.8 (0.38-1.66)	0.55
Smoking Index (>632)	36	13(36.1%)	23(63.9%)	0.59 (0.24-1.47)	0.26
Size of tumor (>67.5mm)	30	9(30%)	21(70%)	0.54 (0.23-1.22)	0.14
Peripheral lymph node involvement	16	4 (25%)	12 (75%)	0.53 (0.25-1.12)	0.10
Mediastinal lymph node involvement	41	15 (35.7%)	27 (64.3%)	0.30 (0.07-1.26)	0.10
Chemotherapy	20	14 (70%)	6 (30%)	3.69 (1.48-9.14)	**0.004**
Karnofsky performance score (>65)	14	11 (78.6)	3 (21.4)	5.02 (1.51-16.6)	**0.008**
ECOG score (>2.5)	33	9 (27.3)	24 (72.7)	0.26 (0.09-0.69)	**0.006**

ECOG- Eastern Cooperative Oncology Group

Table 3: Multivariate Cox regression analysis for factors influencing survival in NSCLC

S.No.	Variables	Hazard ratio (95%CI)	p value	Multinomial Hazard ratio (95%CI)	p value
1	Chemotherapy	3.69(1.48-9.14)	0.004	2.25(1.75-5.25)	0.032
2	Karnofsky performance score(>65)	5.02(1.51-16.6)	0.008	3.04(1.75-8.92)	0.02
3	ECOG score (>2.5)	0.26(0.09-0.69)	0.006	0.12(0.04-0.19)	0.01

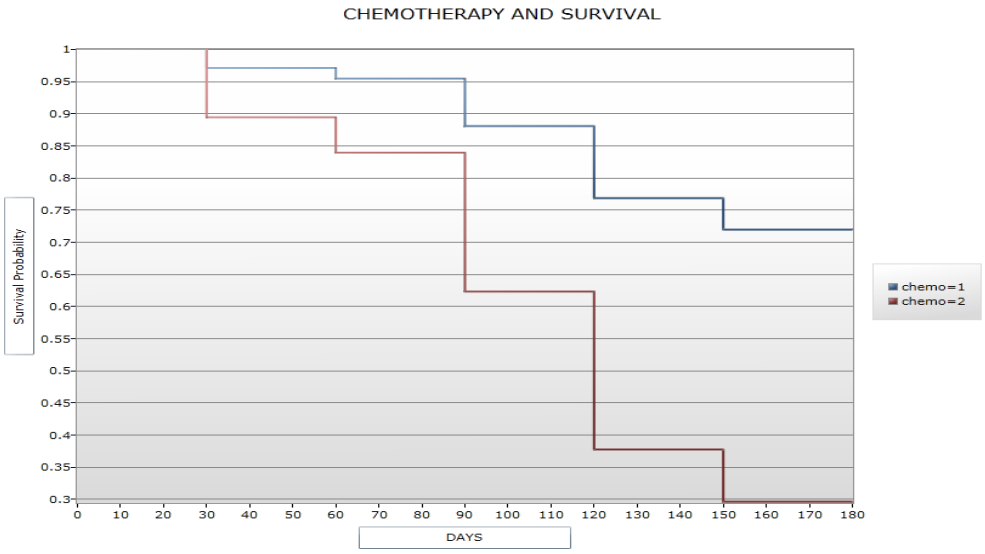

Fig. 1: Survival among NSCLC patients who have received chemotherapy vs patients who have not received chemotherapy

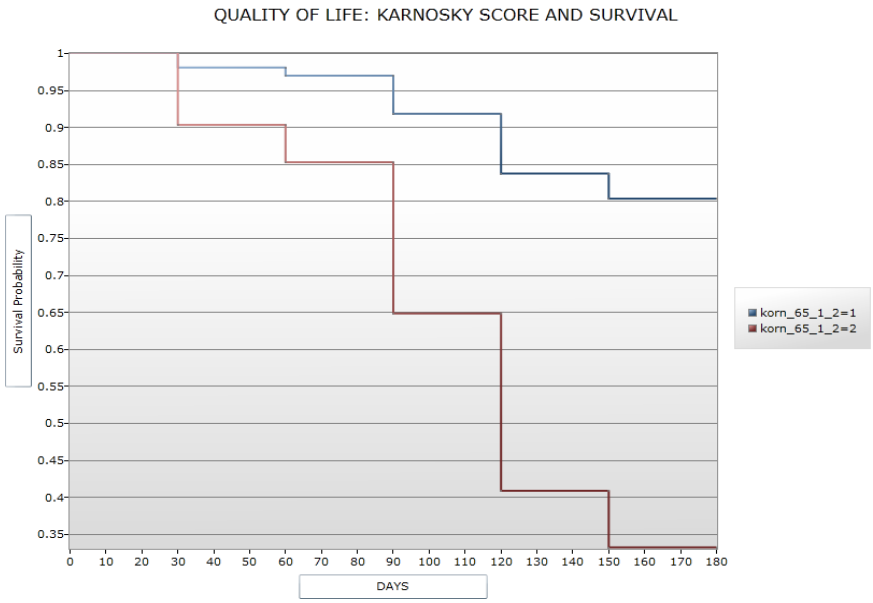

Fig. 2: Cox Proportional hazard univariate analysis of karnofsky performance Score in NSCLC patients receiving chemotherapy vs patients who have not received chemotherapy

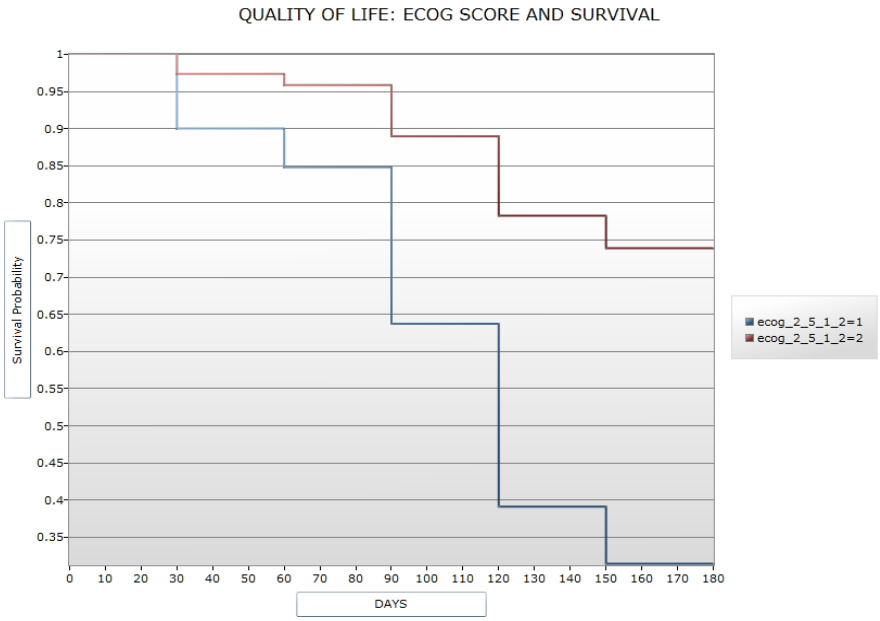

Fig. 3: Cox Proportional Hazard Univariate analysis of European Cooperative Oncology Group (ECOG) Score in NSCLC patients receiving chemotherapy vs patients who have not received chemotherapy

Discussion

Lung cancer is one of the leading causes of cancer related deaths worldwide. Non-small cell lung carcinoma comprises of 85% of cases followed by small cell lung carcinoma around 15%. In India, most of the cases are presented in advanced stages of the disease, where only chemotherapy, radiotherapy, targeted therapy and palliation remain the treatment options. The overall survival of the NSCLC patients is poor around 15%. With the advent of chemotherapy and EGF TKIs, the survival has significantly improved and quality of life of NSCLC patients has been better.

The present prospective study aims at evaluating the clinicopathological profile, treatment outcome, overall survival and performance status of Non-small cell lung carcinoma patients over a period of six months.

In our study, the median age at the presentation was 65 years (42–90 years) and gender ratio (M:F) of 5.5:1, which is similar to other Indian studies like Bala et al., [21] (58 years), Krishnamurthy et al., [22] (56 years) and western studies like George Deeb et al., [23] (65 years) and Ludovini et al., [24] (66 years). Most common histopathological subtype was

adenocarcinoma in our study (27 cases, 54%) similar to other studies like Bala et al., [21] (71%), Krishnamurthy et al., [22] (50%) and Norohna et al., [25] (44%). Squamous cell carcinoma comprised of 28% of cases in our study, which was similar to Bala et al., [21] (18.7%), and Dey et al., [26] (35%).

In our study, only 21 patients survived through the follow-up period of six months. The overall six months survival of the patients in our study was 42% which is poor, similar to other studies like Bala et al., [21] (1 year survival – 51%) and Rajappa et al., [27] (1 year survival–29%).

In our study, 20 out of 50 patients (40%) took chemotherapy. On univariate analysis, we found that there was a significant improvement in the survival. [HR 3.69 (1.48-9.14) p=0.004]. Further, on multivariate analysis, we found that Chemotherapy was significantly and independently associated with better survival. [HR 2.25(1.75-5.25) p=0.032]. This is because of use of newer platinum doublets and EGFR-TKI in most of the patients.

Similar to our study, IRESSA trial done by Tony Mok et al., [17] studied the efficacy of Gefitinib with Paclitaxel as compared to Carboplatin-Paclitaxel combination in Pulmonary Adenocarcinoma and concluded that Gefitinib-Paclitaxel chemotherapy treated patients had a significant progression free survival as compared to the patients treated with Carboplatin-Paclitaxel group [HR=0.74 (95% CI 0.65-0.85), P<0.001)]. Similarly, IPASS (IRESSA Pan-Asia Study)(28) done by Fukuoka et al., was an open label, randomized, parallel-group study that assessed the efficacy, safety and tolerability of IRESSA versus doublet chemotherapy (carboplatin/paclitaxel) as 1st line treatment in a clinically selected population of patients from Asia (n=1217). Results demonstrated superior Progression free survival (PFS) compared with doublet chemotherapy in the overall population of clinically selected patients with advanced NSCLC in Asia [HR=0.74 (95% CI 0.65-0.85), p<0.0001]. Further, sub-group analyses showed that PFS was significantly longer for IRESSA than doublet chemotherapy in patients with EGFR mutation positive tumors [HR=0.48 (95% CI 0.36-0.64), p<0.0001].

Performance status is an important prognostic factor for survival in various malignancies, including NSCLC. A population based study done by Radzikowska et al., [29] evaluated Lung carcinoma in women (n=15657) showed that good performance status of the patients is significantly associated with better survival among lung cancer patients on multivariate analysis. A study done by Mohamed et al., [30] evaluated performance status in patients with advanced NSCLC who were treated with Gefitinib and found that good performance status in advanced NSCLC cases have a significant association with survival (p=0.0002).Strength of our study is it is a prospective study with a six months follow up data on survival. Limitations of the study were a small sample size and most subjects had advanced disease, hence our findings cannot be generalized to all subjects with lung cancers.

Conclusions:

Our study has significant clinical implications. Our study signifies that, even in advanced stage Non-small cell lung carcinoma, chemotherapy and targeted therapy significantly improves the survival and quality of life. Better Performance status at the time of presentation and during the follow up is a strong and independent predictor of better survival in advanced stage of NSCLC cases.

Conflicts of Interest: None declared

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