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Effect of various prognostic factors on response pattern in patients of non-small cell lung carcinoma treated with definitive concurrent chemo radiation: A mono institutional study

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Abstract
Introduction: Lung cancer in India is the second most commonly diagnosed cancer in men. For NSCLC, even with discovery of modern techniques to deliver high dose radiotherapy and various targeted agents for advanced disease, the overall prognosis is dismal. Various prognostic factors have been reported in literature, however, due to their heterogeneity, these may not be directly applied in clinical practice. We undertook this study to understand the impact of various prognostic factors on survival in our study population.
Materials and Methods: 60 patients with locally advanced non-small cell lung carcinoma underwent concurrent chemo radiation to a total dose of 60 Gy. Prognostic factors like age, tumor volume, KPS, Pulmonary function, TNM stage, pre-treatment haemoglobin were assessed for their impact on PFS using univariate analysis, Kaplan meier and log rank test. The toxicity data was collected weekly during treatment, 6 weeks after treatment and then 3 monthly during follow up.
Results: At the end of treatment, 10 patients had complete response, 25 had partial response and 25 had stable disease. KPS>70, T_1-T_2 primary, N0-N1 nodal status and tumor volume of <=120 cc were good prognostic factors with median PFS benefit of 8, 4, 2 and 3 months respectively. Patients with decrease in FEV1/FVC ratio of >4% had significantly higher grade 3-4 radiation pneumonitis compared to patients who had <=4% change in FEV1/FVC ratio (42.86% vs. 8.82%, p 0.006). Overall, 20% patients had grade 3-4 radiation pneumonitis.
Conclusion: In the locally advanced non-small cell lung cancer the prognostic criteria affecting progression free survival were gross tumor volume, Karnofsky performance status, tumor size and stage of the disease. These results underline once again that importance of careful staging and necessity of concurrent chemotherapy in eligible patients.

Keywords: Non-small cell lung cancer, prognostic factor, lung cancer, chemo radiation

Introduction
Lung carcinoma is the 4th most common cancer in incidence in the Indian subcontinent accounting for 67795 new cases and 63475 deaths according to GLOBOCAN 2018 [1]. It is the 2nd most commonly diagnosed cancer in men accounting for 48698 cases, with the highest reported incidences from Mizoram in both males and females (Age adjusted rate 28.3 and 28.7 per 100,000 population in males and females, respectively) [2]. Non-small cell lung cancer is a heterogenous group of disease and comprises 80% of all lung cancer cases. Historically, thoracic radiotherapy have played a major role in the management of locally advanced lung cancer and many prospective trials have established the role of incorporating chemotherapy with radiotherapy over radiotherapy alone [3]. In recent years the improvement in survival rates have been attributed to development of modern chemotherapeutic agents and advances in radiation therapy techniques, however overall survival and prognosis is still poor in locally advanced NSCLC [4]. Definitive chemo radiation is the standard for locally advanced inoperable NSCLC [5, 6]. Prediction of prognosis is inherently complex. There are many factors that contribute to the prognosis, these can be roughly divided into environmental factors, tumor related factors and patient related factors.

The staging of cancer is one of the most reproducible prognostic factors. An increasing tumour size worsens prognosis and the lymph node involvement is *per se* a major prognostic characteristic which has also an impact on the possibility of surgical treatment (N3 involvement being generally a contraindication to surgery) [7]. The second most reproducible prognostic factor, also very useful to guide therapy is performance status measured on the Karnofsky scale or on the Eastern Cooperative Oncology Group (ECOG) scale although its value has mostly been demonstrated for non-resected patients [8, 9]. Female sex, histology, haemoglobin level (<12gm/dl) have been reported as prognostic factors in some studies [15, 16, 17]. Blood vessel invasion is associated to an increased risk of relapse and death as shown by a meta-analysis (multivariate combined hazard ratio for relapse free survival 3.98 (95% CI 2.24-7.06) and for survival 1.90 (95% CI 1.65-2.19) [13]. However, due to the design and often retrospective nature of prognostic factors studies, few of these factors can really be used in routine care to guide management and to determine prognosis.

In view of the recent studies, the present study entitled was taken to evaluate the various patient and tumor related prognostic factors on response to concurrent chemo radiation in non-small cell lung cancer, so that it improves patient selection and identify strategies to improve prognosis as each prognostic criteria has independent effect on loco regional response.

Material and Method

Patient selection: Patients visiting the Outpatient department (OPD) with biopsy proven locally advanced non-small cell lung carcinoma (NSCLC) was taken for study. Patients within age 40-70 years, non-small cell histology of adenocarcinoma, squamous cell, adenosquamous or large cell, Eastern Cooperative Performance Status (ECOG) 0-2, baseline haemoglobin more than 11gm/dl, baseline FEV1(forced expiratory volume at 1 sec) >2l and who provided informed consent were taken for the study. Patients with distant metastasis at presentation, other NSCLC histology, who have received prior surgery, chemotherapy and/or radiotherapy for the present illness, any history of chest wall irradiation were excluded.

Radiation planning and treatment

All patients underwent a CT simulation in supine position with 3 mm slices from base of skull above to lower extent of liver below. Treatment planning was done on Varian Eclipse treatment planning system (Varian Medical Systems, Palo Alto, California) for Cobalt 60 teletherapy. The prescription dose was 60 Gy delivered in 30 fractions, 2Gy per fraction, delivered 5 days a week. Plan was optimized to cover the PTV (Planning Target Volume) with 95% isodose. Treatment was delivered with Theratron 780c cobalt 60 teletherapy machine (Best Theratronics, Canada). Chemotherapy was given concurrently with radiotherapy with cisplatin 50mg/m2 on days 1, 8, 9, 36 and etoposide 50 mg/m2 on days 1-5, 29-33.

Data collection and statistical analysis

Patient and tumour related factors affecting treatment outcome are assessed by taking detailed history of present illness, clinical examination, histology, contrast enhanced CT scan of thorax and abdomen, complete haemogram, biochemistry (Urea, Creatinine, LFT) and pulmonary function test. During treatment weekly toxicity assessment done using clinical status, laboratory tests and graded according to WHO Common Criteria for Adverse Events (CTCAE) version 4.0. Acute toxicity assessment continued for an additional 8 Weeks from the last date of radiation. Patients are followed up for one & half year 3 monthly for late toxicity. Response assessed by using the Response assessment Criteria in Solid Tumors (RECIST) version 1.1.

The basic characteristics, diagnostic and tumour data was analysed using univariate analysis and descriptive statistics. The progression free survival for different factors were assessed using Kaplan meier and log rank. All data was tabulated and analysed using SPSS (Statistical Package for Social Sciences) version 23.

Results

60 patients were taken for our study. The baseline patient and tumour characteristics are described in Table 1.

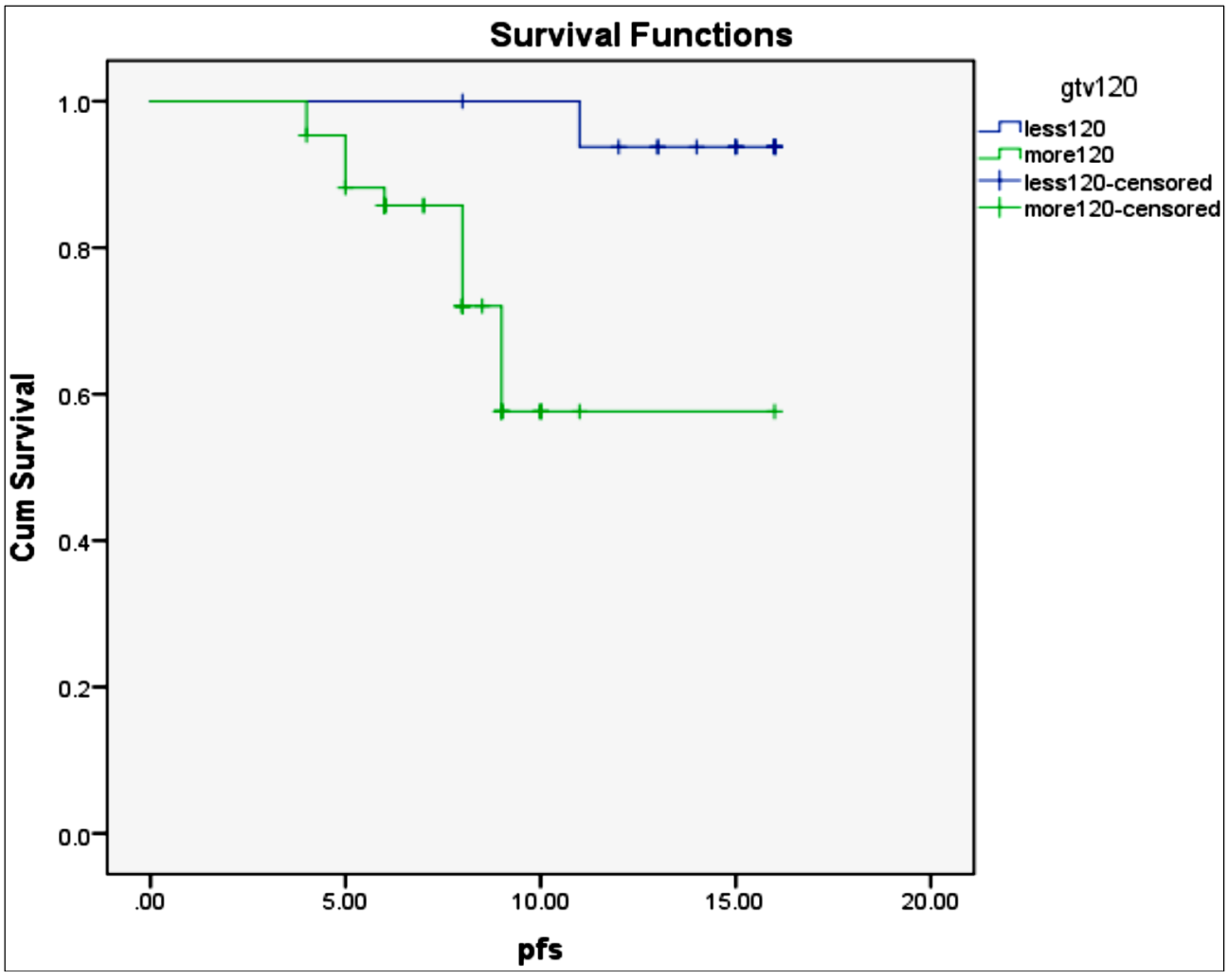
Table 1: Baseline patient and tumor characteristics

Characteristics	Percentage of patients(n=60)	
Age (Mean 60.6years)	>50 years	71.6(43)
	<=50 years	28.4(17)
Sex	Male	71.6(43)
	Female	28.4(17)
Smoking History	Present	70.2
	Absent	29.8
Presenting Symptoms	Chest pain	28.8
	Haemoptysis	11.3
	Cough	27.9
	Dyspnoea	12.2
	Asymptomatic	2.1
KPS	>70	55(31)
	<=70	45(29)
Histology	Adenocarcinoma	43.8
	Squamous cell carcinoma	26.8
	Large cell carcinoma	2.1
	Others	8.9
T stage	T1-T2	28.33(17)
	T3-T4	71.66(43)
N stage	N0	13.6
	N1	8.9
	N2	48.2
	N3	29.3
Stage	Stage II	36.66(22)
	Stage III	63.33(38)
GTV volume (mean 157.5cc)	>120cc	71.66(43)
	<=120cc	28.33(17)

At the end of treatment, 10 patients had complete response, 25 had partial response and 25 had stable disease. Median follow-up was 12 months. Various patient and tumor related factors were assessed for their impact on the progression free survival (Table 2, Figure 1). Tumor size, baseline KPS, T and N stage significantly affected the progression free survival. KPS>70, T_1-T2 primary, N0-N1 nodal status and tumor volume of <=120 cc were good prognostic factors with median PFS benefit of 8, 4, 2 and 3 months respectively. Age <=50 years, Stage II disease, adenocarcinoma histology, good pulmonary function although conferred PFS benefit, these factors did not attain statistical significance.

Table 2: Univariate analysis of various patient and tumour related factors in terms of progression free survival

Characteristics		Median PFS	p-value (log rank)
Age	<=50 years >50 years	8.2 5.9	0.49
Tumor volume	>120cc <=120cc	12.3 15.6	0.005
KPS	>70 <=70	15.1 7.8	<0.001
T stage	T1-T2 T3-T4	15.2 11.3	0.024
N stage	N0-N1 N2-N3	10.2 7.9	0.023
Overall stage (AJCC 8th)	Stage 2 Stage 3	14.9 10.6	0.38
Histology	Adenocarcinoma Squamous	9.2 8.9	0.092
Pre-Treatment Hb	>11 gm/dl <=11 gm/dl	13.16 14.01	0.583
Pulmonary Function (FEV1/FVC)	>75 <75	14.19 12.27	0.117



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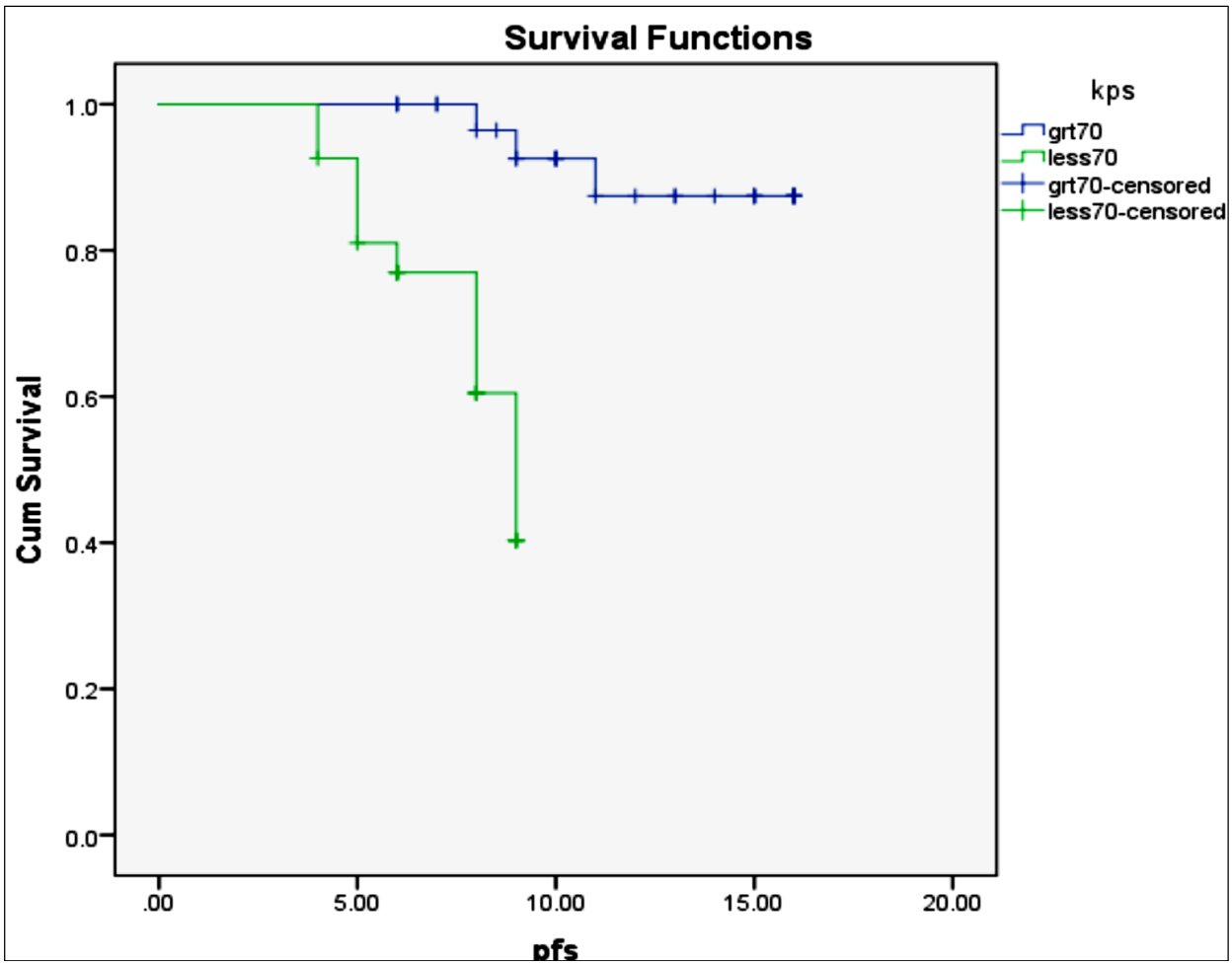
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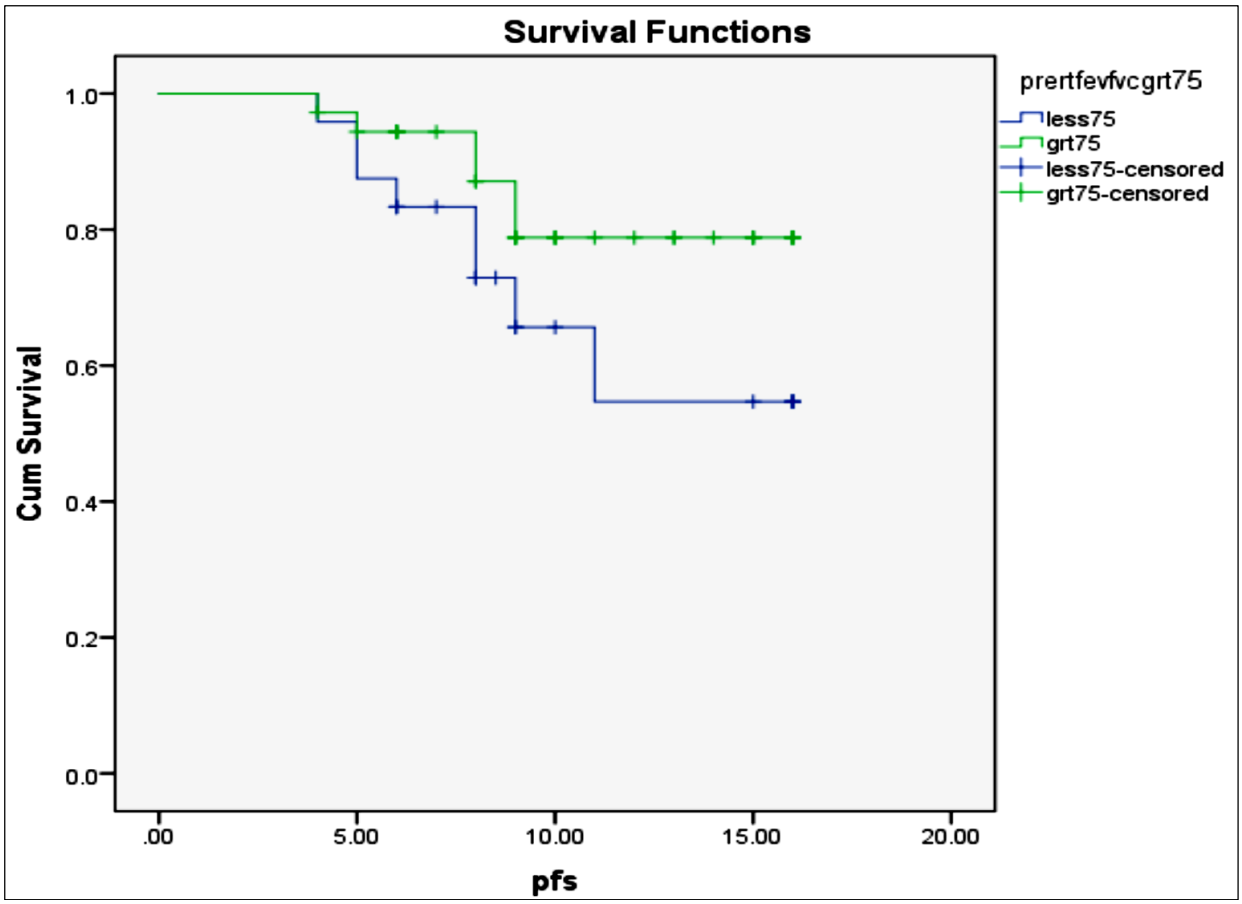
(B)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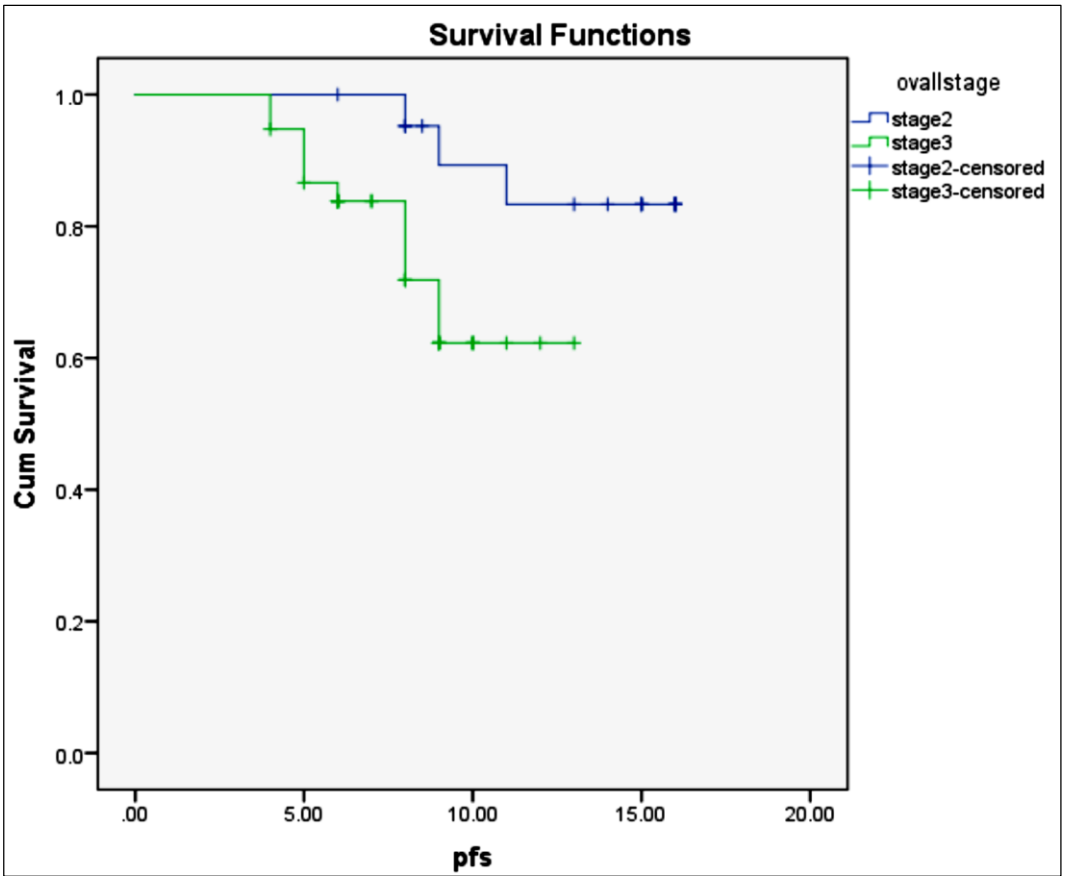
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Cum Survival
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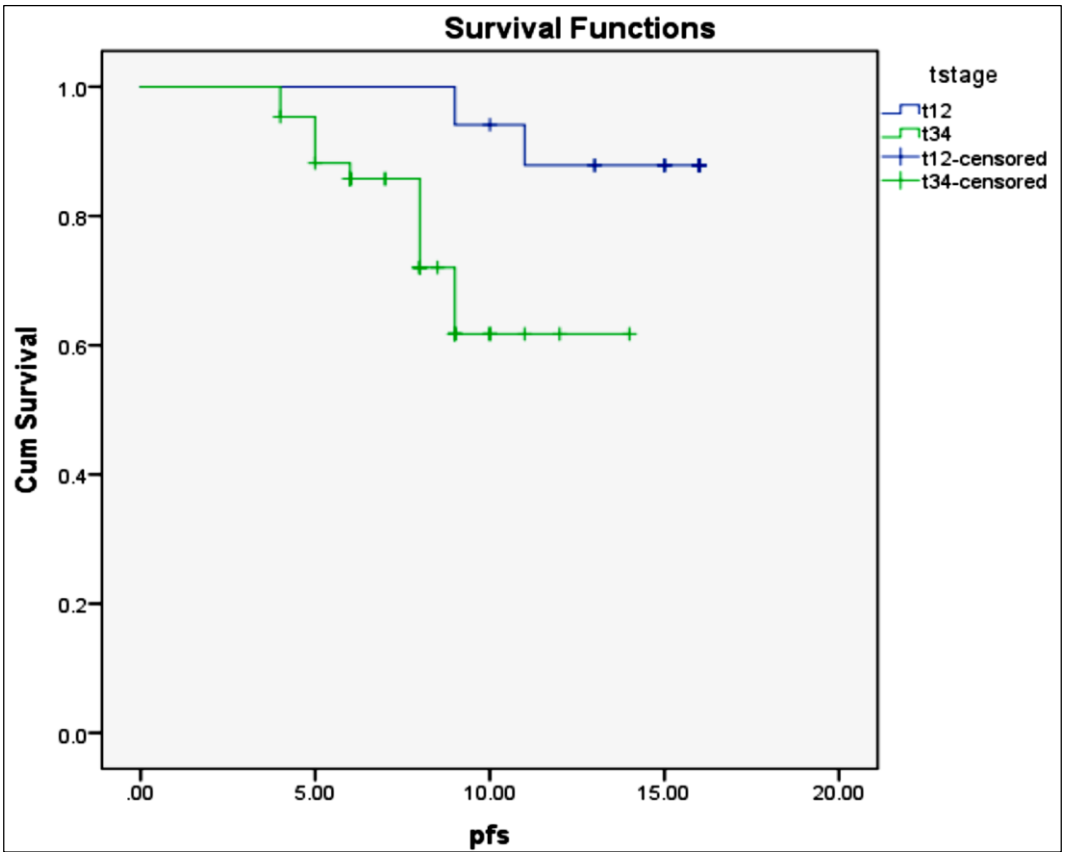
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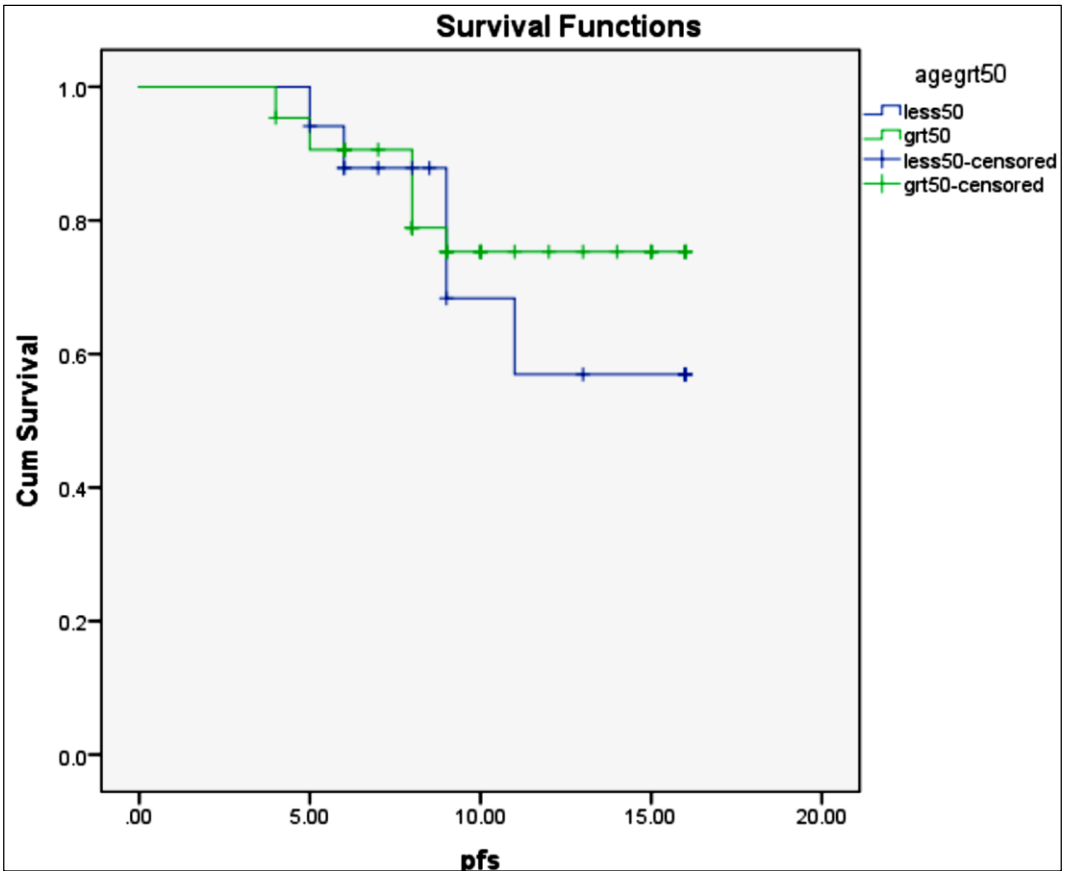
(E)



(F)

Fig 1: Kaplan Meier curve for progression free survival in terms of various patient and tumor related factors. (a) PFS for patients with GTV volume <=120cc had significantly better median PFS, (b) KPS>70 patinets had a PFS benefit of 8 months. (c) Patients with FEV1/FVC of >75% had a non-significant PFS benefit of 2 months. (d) Stage 2 patients had median 4.3 months median PFS benefit, although not significant. (e) T_1-T_2 primary had significantly better median PFS than T_3 T_4. (f) Age <=50 years had non-significant 2 months median PFS benefit

Pre and post treatment pulmonary function tests had a significant impact on severity of radiation pneumonitis. Patients with decrease in FEV1/FVC ratio of >4% had significantly higher grade 3-4 radiation pneumonitis compared to patients who had <=4% change in FEV1/FVC ratio (42.86% vs 8.82%, p 0.006).

Overall, 20% patients had grade 3-4 radiation pneumonitis, 18.33% patients had grade 2 or more skin toxicity, 45% patients had grade 2 esophagitis and 50% patients had grade 2 or more haematological toxicity.

Discussion

It is important to understand the progression of non-small cell lung carcinoma which has low survival despite the advancing treatment modalities. For this purpose, prognostic factors have been investigated in a number of studies. The most well-known prognostic factors include stage, performance status, female gender [14] and absence of significant weight loss. Several factors such as histopathological type of tumor, age, smoking status, presence of co-morbidity and treatment modality (chemo radiotherapy, radiotherapy or chemotherapy alone) may be other prognostic factors influencing treatment and survival [6, 15, 16]. With the introduction of novel molecular markers and use of specific drugs targeted towards these markers have also added a new dimension to prognostication of non-small cell lung carcinoma [17, 18].

The problem with information available in the literature regarding prognostic factors is the heterogeneity of data thus making it difficult to implement the information in clinical practice. These factors may change with change in patient population and treatment protocol. Thus, we undertook this study to have a brief idea of the prognostic factors which positively impact our patient population.

Maximum number of the patients with NSCLC are 70 years or older at the time of diagnosis [19, 20]. In our study, the average age of the patients were 60. Prognosis was better in young patients. Literature has also reported similar findings with respect to age [19]. Poor prognosis was seen in elderly patients might be due lack of directing these patients to standard curative treatment [21], as most elderly patients would present with additional comorbidity which would not be fit to receive concurrent chemotherapy. Our study although implemented concurrent chemo radiotherapy for the whole study sample, showed poor median PFS for >50 years old which was not significant.

Performance status have has been an important prognostic factor in almost all cancer sites, which holds true for non-small cell lung carcinoma [22, 23]. In our study patients with good performance status had a longer PFS than those with poor performance status, a significant survival benefit of 4 months in those with KPS >70. Also advanced stage was more negatively found to influence survival. Stage II patients had mean survival benefit of 4 months.

Histology has heterogenous impact on survival as both adenocarcinoma and squamous cell carcinoma patients have shown different survival patterns based on specific subtypes of each histology [24]. With the advent of new molecular

markers and targeted therapy survival have improved specifically in the adenocarcinoma histology [25]. However, in our study a significant difference in survival was noted between adenocarcinoma and squamous cell carcinoma histology. This could be due to the limited availability of newer therapy to the study population thus similar treatment protocol was employed irrespective of histology. In our study, patients with GTV of > 120cc and FEV1/FVC of < 75% had worse prognosis, GTV volume being highly significant. Similar events have been reported in studies in literature which states that larger GTV and poor pulmonary function gives poor outcome [26, 27]. It is possible that patients with higher pulmonary function test may possess a higher radiation tolerance for larger tumors and more aggressive radiation therapy schedule. Additionally, increased disease burden has long been hypothesized to lead to unavoidable increase in lung exposure (i.e. lung V20), which in turn can have negative impact on survival and toxicity. This further suggests that limiting lung toxicity and lung dose as a measure post- treatment residual pulmonary function may help to maximize the prognosis.

Our study have shown no significant difference in PFS between patients with Hb level <=11 and >11 gm/dl. However, literature have consistently reported poor clinical outcome with low pre-treatment haemoglobin which is related to tumor hypoxia and radio resistance [28]. Similar poor outcome have been reported with low pre-treatment haemoglobin in non-small cell lung carcinoma.

Conclusion

Prognostic factors are very useful to get information about disease evolution and to construct homogenous group of patients. They can sometimes guide therapy and identify subgroups of patients where more aggressive therapy is needed. However they are not powerful to be used at individual level.

In conclusion, in the locally advanced non-small cell lung cancer the prognostic criteria affecting progression free survival were gross tumor volume, Karnofsky performance status, tumor size and stage of the disease. These results underline once again that importance of careful staging and necessity of concurrent chemotherapy in eligible patients.

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