Short Communications

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Prognosis of *TP53* and Its Concomitant *EGFR* Mutation in Lung Cancer Especially Non-Small Cell Lung Cancer

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Abstract

Background: Human Lung Carcinoma (LC) is among the most diagnosed cancers across the world among those non-small cell lung cancer (NSCLC) comprises about 85%. Next Generation Sequencing based detection of mutations are now well established in molecular oncology. With the advent of modern diagnostic methods, it is now well known that there are several mutations and gene rearrangements which are associated with the development of LC. Among those mutations, *TP53* is the most prevalent with the concomitant *EGFR* mutation. **Methods:** In this retrospective study, a total number of 414 patients have been incorporated who have attended RGCIRC in the period between November 2015 to March 2024. Clinical stage has been determined as per NCCN Guideline version 2.2024. Nucleic Acid (DNA and RNA) from FFPE samples were extracted and detection of mutation was performed by Next generation sequencing (NGS) method. **Results:** All 414 patients opted for the customised NGS panel for lung cancer among those 203 patients were *TP53* mutation and 87 patients were *EGFR* mutation positive. 62 patients were *TP53-EGFR* double mutation positive. The results of this study have shown that *TP53* mutated patients show poor prognosis with conventional therapy. However, *TP53-EGFR* co-mutated patient's recovery rates are comparatively promising due to the availability of the targeted therapy of *EGFR*. **Conclusion:** Studies have shown that *TP53* mutation is unlikely to derive clinical benefit in LC patients and shows poorer prognosis when compared to *TP53* wild type and *EGFR* mutated patients show improved recovery due to availability of the Kinase Inhibitor (KI) treatment. In this study we have observed and concluded that *TP53-EGFR* co-mutated group also shows promising prognosis for the application of KI treatment. A further large cohort study will establish this clinical observation and enlighten more therapeutically relevant information.

Keywords: Lung carcinoma- *TP53* mutation- *EGFR* co-mutation- prognosis

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Introduction

Lung Cancer (LC) is one of the deadliest diseases in the world consisting of 5.9 percent of all cancers diagnoses in India and Non-small cell lung cancer (NSCLC) comprises approximately 85%. *TP53* gene is supposed to function as tumor suppressor, but mutated *TP53* contributed to the tumorigenesis of the lung epithelial cells, playing a significant role in the development of lung cancer. It has a role in distant metastases, worsening the outcome of LC Prognosis. Mutant *TP53* is known to show resistance to standard chemotherapy medications, often making a condition untreatable. There are reports that 30 percent of *TP53* mutation occurs alongside concomitant *EGFR* mutation. Kinase Inhibitor (KI) therapy in *EGFR* mutated patients produces superior results in comparison to traditional therapy. Studies have shown that, when *TP53* mutation is concomitant with *EGFR* mutation, the standard 3rd generation *EGFR-TKI* therapy becomes less effective in producing results when it is compared with *TP53* wild type or *EGFR* single mutation in LC patients [1, 2].

In this study, we have included those who are affected by *TP53* mutation as well as associated other co-mutations with a special focus on *EGFR*. Our aim is to explore the comparative prognosis or percentage of patient survival of TP53 wild type and mutated group, and *EGFR* wild type and mutated group, *TP53-EGFR* double mutated group.

Materials and Methods

Patient selection

In this retrospective study, a total number of 414 patients have been incorporated who have attended RGCIRC in the period between November 2015 to March 2024. The study was approved by the ethical committee in the waiver of informed consent (letter number RGCIRC/IRB-BHR/63/2024). Medical records of all 414 patients were screened. All 414 patients opted for the customised

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NGS panel for lung cancer. Among those 203 patients were *TP53* mutation positive. Clinical stage has been determined as per NCCN Guideline version 2.2024. The pathogenicity of somatic variants is determined predominantly based on the clinical data reported in ClinVar, ACMG recommendation, AMP guidelines, International Agency for Research on Cancer (IARC). The Stratification has been defined based on their allele frequency, translational activity, conservation, amino acid physiochemical properties, in silico observations etc. Assessment and Comparison of Single Nucleotide variants SNVs have also been started for the identification of variants and their clinical association. The follow-up information was obtained by either reviewing the medical records or by telephonic interview [3, 4].

Flow chart describing enrollment of patients needs to show up

Assessment of Mutation by NGS Lung Panel

Detection of mutation was performed by Next generation sequencing (NGS) method (Iron torrent, Ion GeneStudio S5 plus System). Nucleic Acid (DNA and RNA) from FFPE samples were extracted by ReliaPrep FFPE Miniprep System from Promega, Library preparation was performed by Ion Ampliseq library kit plus. The assay utilizes a minimum of 20ng DNA and 20ng RNA at 500X coverage and provides an analytical sensitivity of more than equal to 5 percent for DNA based genetic alterations.

Customized Panel for Multi - Biomarker NGS Assay

Statistical Analyses

Statistical analysis has been performed using MS Excel, IBM SPSS version 29.0. Descriptive statistics have been applied for demographic information. Measures include summary statistics such as Median (Range) for continuous variable and frequency (percentage) for categorical variable. *TP53* subgroups and baseline characteristics including gender, age, stage, smoking status, comorbidity, family history, metastasis status, tumour size and vital status information have been screened. Kaplan Meier statistical approach has been performed to determine the overall survival (OS) graph over time and estimated per cent survival of the subjects at each point of time. Log rank test has been applied for comparing the significant differences between groups. Statistical significance has been determined by two tailed $p<0.05$.

Results

A total number of 414 patients have been incorporated in this study who has attended RGCIRC in the period between November 2015 to March 2024. Among those, there are 203 patients who exhibit *TP53* mutation. Total Number of *EGFR* mutated patients are 87, among those, EGFR-*TP53* double mutated patients are 62.

In *TP53* mutated group, mean age is 60.3 years. Male and female ratio is 145:58. In this cohort, most prevalent is stage IV (84%) and 37.4% of patients have smoking history. LC patients with *TP53* mutation, exhibit comorbidities like Diabetes mellitus (22.7%) and Hypertension (30%). About 15.8% patients have family history of cancer. In this cohort, LC patients with *TP53* mutation, exhibit brain metastases 35%, liver metastases 12.8% and bone metastases 24.1%. 54.2% *TP53* mutated LC patients exhibit tumour size >2 cm. In this tenure 88.2% patients are alive (Table 1).

To compare the prognosis and patient overall survival (OS) in *TP53* mutated and *EGFR* co-mutated patients, they have been subdivided into 4 groups. *TP53* wild type and *EGFR* wild type, *TP53* wild type and *EGFR* mutated, *TP53* mutated and *EGFR* wild type, *TP53* mutated, and *EGFR* mutated. All *TP53* and *EGFR* wild type and mutated groups are co-existent with other mutations viz. *KRAS, BRAF, EML4-ALK, STK11, KEAP1, KIF5B-RET, SMARCA4, PTEN, RB1*. Aside from these four groups, difference of OS has been determined between *TP53*-other gene mutated and *TP53-EGFR* mutated groups.

Overall survival of *TP53* wild type patient's group has been compared with *EGFR* wild type patient group (Figure 1A). The OS of the cohort is 78.5% in 102 months with median duration 19 months. Percentage of survival in *EGFR* wild type group is inferior (77.4%) to *TP53* wild type group (81%). In the *TP53* wild type group median survival is 20 months, 95% CI 9.5 – 30.4. In *EGFR* wild type group median survival is 19 months, 95% CI 13.5-24.4. Calculated survival probability (p value) between the groups is 0.739.

Overall survival comparison between *TP53* wild type and *EGFR* mutated patient groups has been calculated (Figure 1B). *TP53* wild type group has shown decreased survival than *EGFR* mutated patient group. The OS of the

Table 1. Demographic and Clinical Covariates of *TP53* Gene Mutated Patients

		TP53 mutated Group N=203
Mean Age (SD) in years		60.3 (±10.9)
Gender	Male	145 (71.4%)
	Female	58 (28.6%)
Stage, n (%)	Stage 4	170 (83.7%)
	Other	33 (16.3%)
Smoking Status, n (%)	Smoker	76 (37.4%)
Comorbidities, n (%)	Type 2 Diabetes Mellitus	46 (22.7%)
	Hypertension	61 (30%)
	Other (COPD, Bronchial Asthma, Autoimmune Disorders)	20 (9.9%)
Family History of Cancer, n (%)		32 (15.8%)
Metastases Status, n (%)	Brain	71 (35%)
	Liver	26 (12.8%)
	Bone	49 (24.1%)
Tumour Size, n (%)	<2.0 cm	17 (8.4%)
	>2.0 cm	110 (54.2%)
Vital Status, n (%)	Alive	179 (88.2%)
	Dead	24 (11.8%)

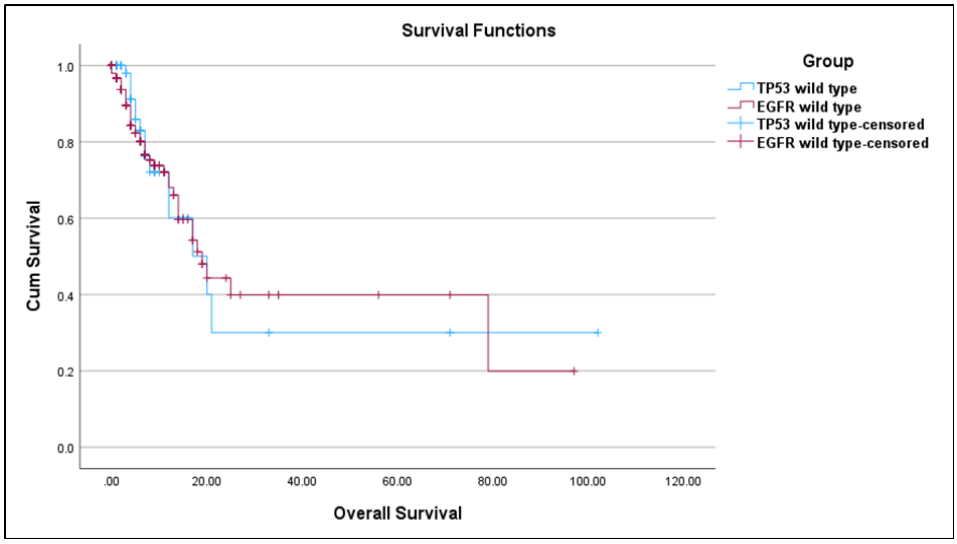

Figure 1 (A). Comparison of OS (in months) between *TP53* Wild Type and *EGFR* Wild Type Groups: Kaplan-Meier survival curve showing the difference in OS of 102 months between *TP53* wild type and EGFR wild type group (p=0.739).

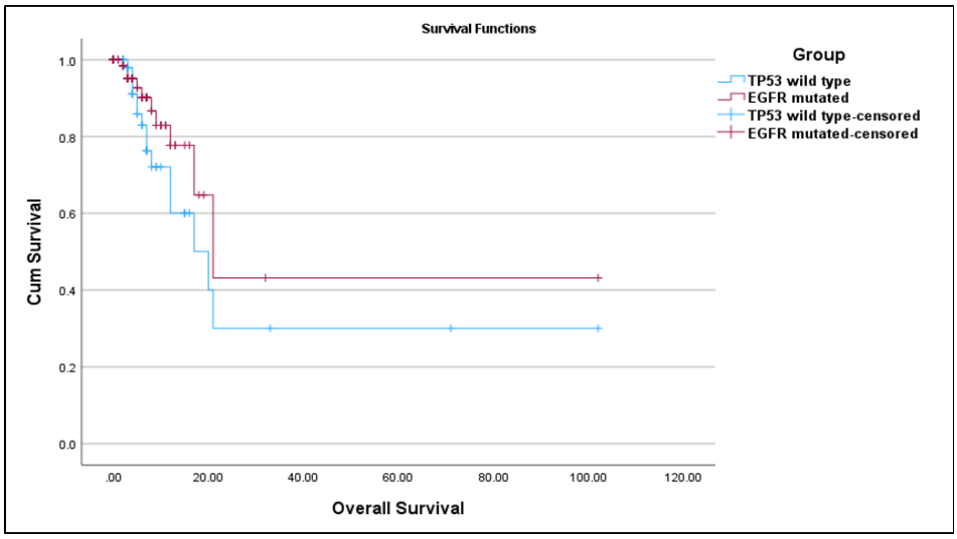

Figure 1 (B). Comparison of OS (in months) between *TP53* Wild Type and *EGFR* Mutated Groups: Kaplan-Meier survival curve showing the difference in OS of 102 months between *TP53* wild type and EGFR mutated groups (p=0.167).

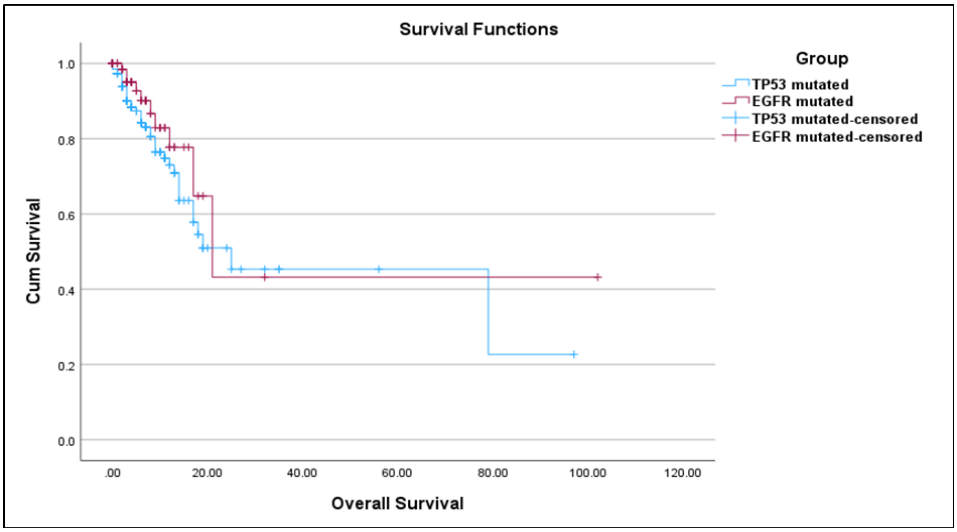

Figure 1 (C). Comparison of OS (in months) between *TP53* Mutated, and *EGFR* Mutated Groups: Kaplan-Meier survival curve showing the difference in OS of 102 months between *TP53* mutated, and EGFR mutated groups (p=0.205).

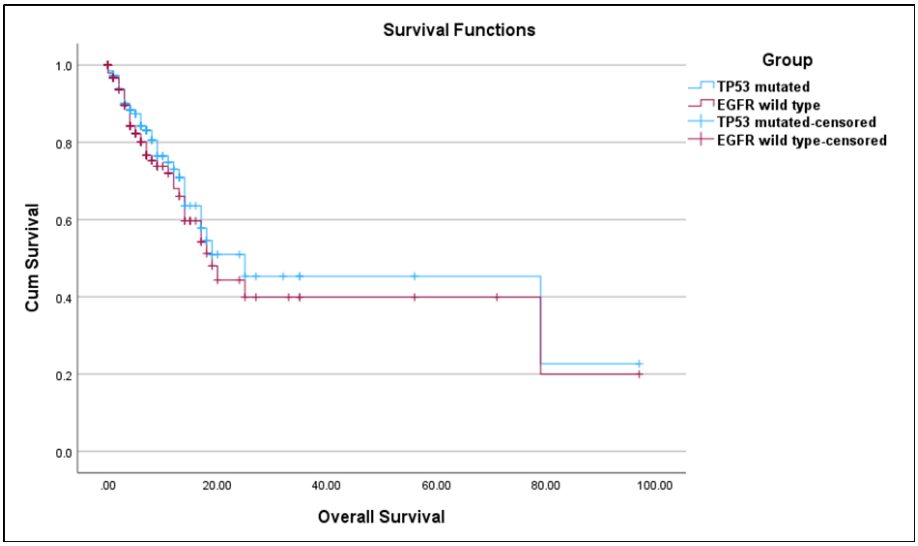

Figure 1 (D). Comparison of OS (in months) between *TP53* Mutated and *EGFR* Wild Type Groups: Kaplan-Meier survival curve showing the difference in OS of 102 months between *TP53* mutated and EGFR wild type groups (p=0.426).

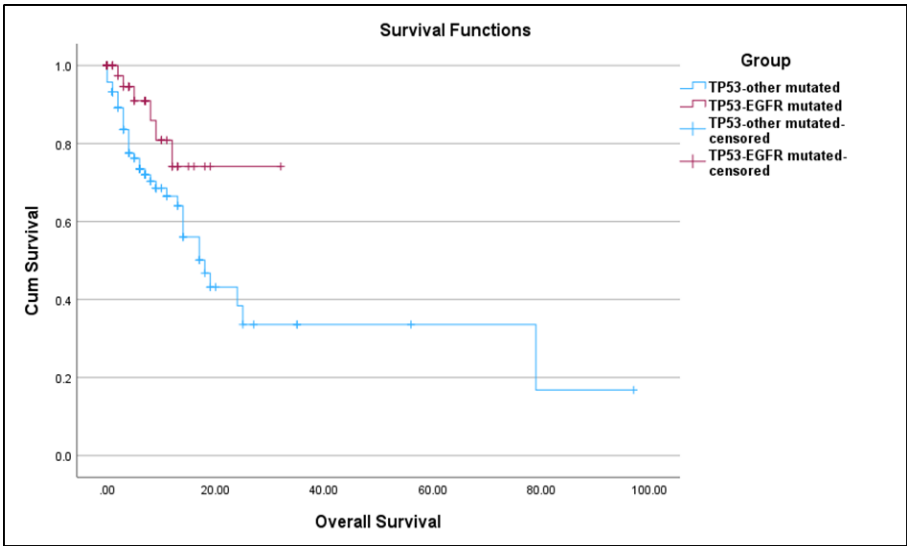

Figure 1 (E) Comparison of OS (in months) between *TP53*-other Gene Mutated, and *TP53-EGFR* Mutated Groups: Kaplan-Meier survival curve showing the difference in OS of 102 months between TP53-other gene mutated, and TP53-EGFR mutated groups (p=0.031).

cohort is 84.8% in 102 months with median duration 21 months. Percentage of survival in *TP53* wild type group is lesser (81%) than *EGFR* mutated group (88.4%). In the *TP53* wild type group median survival is 20 months, 95% CI 9.5 – 30.4. In *EGFR* mutated group median survival is 21 months, 95% CI 13.8 – 28.1. Calculated survival probability (p value) between the groups is 0.167.

OS comparison between *TP53* mutated and *EGFR* mutated patient groups has been calculated (Figure 1C). *TP53* mutated group has shown inferior survival to *EGFR* mutated patient group. The OS of the cohort is 83% in 102 months with median duration 21 months. Percentage of survival in *TP53* mutated group is lesser (80.7%) than *EGFR* mutated group (88.4%). In the *TP53* mutated group median survival is 25 months, 95% CI 0.0 – 54.4. In *EGFR* mutated group median survival is 21 months, 95% CI 13.8 – 28.1. Calculated survival probability (p value) between the groups is 0.205.

Overall survival comparison calculated between *TP53* mutated and *EGFR* wild type patient groups (Figure 1D). *EGFR* wild type group has shown decreased survival compared to *TP53* mutated patient group. The OS of the cohort is 79.1% in 102 months with median duration 19 months. Percentage of survival in *TP53* mutated group is higher (80.7%) than *EGFR* wild type group (77.4%). In the *TP53* mutated group median survival is 25 months, 95% CI 0.0 – 54.4. In *EGFR* wild type group median survival is 19 months, 95% CI 13.5 – 24.4. Calculated survival probability (p value) between the groups is 0.426.

OS comparison calculated between *TP53*-other mutated, and *TP53-EGFR* mutated patient groups (Figure 1E). *TP53*-other gene co-mutated group has shown inferior survival compared to *TP53-EGFR* double mutated patient group. Percentage of survival in *TP53*-other gene

mutated group is lesser (70.9%) than *TP53-EGFR* mutated group (90.2%). In the *TP53*-other gene mutated group median survival is 18 months and in *TP53-EGFR* wild type group median survival is 19 months, Overall, 95% CI is 10.6 – 27.3. Calculated survival probability (p value) between the groups is 0.031. Figure 1(E), suggests that when *TP53-EGFR* double mutated group OS is compared with *TP53*-other gene mutated group (for e.g. *KRAS*, *MET, ROS, EML4-ALK* etc.), *TP53-EGFR* mutated group with KI treatment have shown better prognosis and survival (p=0.031).

Discussion

The p53 directly influences transcription of genes which are involved in metastasis by binding promoters of a variety of genes known to be involved in regulating cell motility and adhesion processes that are important for metastasis. In this study the percentage of metastases in the vital organs like brain, liver, bone is quite high in *TP53* mutated group. Apart from these, thyroid, oral cavity, buccal mucosa, thorax, colon, uterine metastases have also been observed. Most prevalent clinical stage found is stage IV. It has been observed that patient's age (>60 years), male gender and smoking status are the other parameters which are associated with poor prognosis in *TP53* mutated group [5, 6, 7].

The complete loss of *TP53* functions can accelerate the transformation potential for driver oncogenes in lung cancers. The p53 loss not only prevents incipient tumor cells from undergoing oncogene-induced senescence and apoptosis but also perturbs cell cycle checkpoints. This enables p53-deficient tumor cells with DNA damage to continue cycling, creating a permissive environment for the acquisition of additional mutations. In this study we found >50% *TP53* mutations are associated with other Co-Mutations viz. *EGFR, KRAS, EML4-ALK* etc. [7, 8].

In this study, *TP53* with concomitant *EGFR* mutation are treated with *EGFR-KI*, whereas *TP53* with other mutations have been treated by chemotherapy and or anti-angiogenic medications. In the 4 subgroups of *TP53* wild type and mutated, *EGFR* wild type and mutated, Kaplan–Meier (KM) survival curve analysis shows that overall survival (OS) is better in patients with concomitant *EGFR* mutations who received treatment of Kinase Inhibitors (KI) preferentially [9].

Superior prognosis was observed in a group which received KI therapy due to presence of *EGFR* mutation. The prognosis and overall survival of *TP53* mutated group is inferior to *EGFR* mutated group suggesting presence of *TP53* mutation leads to poor treatment efficacy in LC patients. *EGFR* wild type group which received traditional therapy, showed worse prognosis due to the presence of other co-mutations. The prognosis is worse in the group afflicted by *TP53* mutation compared to *TP53* wild type. Kaplan-Meier survival curve demonstrates that the possibility of survival is much higher in the group with *TP53-EGFR* co-mutation because of the KI treatment, compared to group with *TP53*-other gene mutations where *EGFR* is absent. *TP53* wild type group also fails to show good prognosis if there are presence of other mutations [10, 11, 12].

In conclusion, this can be mentioned that the presence of *TP53* mutation leads to increased risk of fatality, which is amplified due to the presence of other co-mutations despite the traditional chemotherapeutic treatments. On the contrary, *TP53-EGFR* co-mutated patients recovery rates are much more promising due to the availability of the targeted therapy. Further prospective study would help to understand the pathways through which *EGFR-KI* therapy acts effectively even in the presence of *TP53* mutation to strengthen and establish our observation.

Author Contribution Statement

AM conceptualised the study, AGM analysed the data and written the manuscript, SM reviewed the manuscript and made necessary changes, SM and SD performed the laboratory testing and report authorisation, UB provided the patient samples.

Acknowledgements

Scientific Body Approval

This study has been reviewed and approved to conduct by the Institutional Scientific Committee (letter number RES/SCM/63/2024/19).

Ethical Committee Approval

This study has been approved by the Institutional Review Board and considered as a waiver from consenting (letter number RGCIRC/IRB-BHR/63/2024).

Conflict of Interest

The authors have no conflicts of interest to declare.

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