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Association of Gene Mutations, Drug Resistance, and Disease Progression in Lung Cancer Therapy

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ABSTRACT

Lung cancer is one of the most common causes of cancer deaths around the world and mutations in genes are largely responsible for the subsequent response to treatment and progression of the disease. In this study we examined the relationship between specific mutations, drug resistance and disease progression in patients with lung cancer who are receiving targeted therapy. A focus on clinically significant mutations (EGFR, KRAS and ALK) that affect treatment and prognosis. Data collection is quantitative correlational research design based on data from oncology departments, diagnostic laboratories. Statistical techniques: correlation, regression and logistic regression analysis are used to explore the relationship between gene mutations and resistance to treatment and progression rates. The aim of the study is to further the scientific understanding of molecular mechanisms associated with treatment failure and disease progression in the field of precision oncology. The results will help inform treatment approaches that are more effective, based on mutations.

Keywords: Lung Cancer, Gene Mutations, EGFR, KRAS, ALK, Drug Resistance, Disease Progression, Targeted Therapy, Precision Medicine, Oncology.

INTRODUCTION

Lung cancer is known to be one of the most deadly and aggressive cancers in the world and is responsible for significantly large amount of cancer deaths annually. Even though the diagnostic and therapeutic approaches of lung cancer have been improved, the prognosis of the patients with lung cancer is still dismal, because of late diagnosis, tumor heterogeneity and occurrence of resistance to targeted drugs (Siegel et al., 2021; Sung et al., 2021). Over the past two decades, lung cancer has received increasing focus of research aimed at understanding its molecular and genetic aspects, particularly how mutations in the genes play roles in the development and treatment of lung cancer. It is now thought that these genetic changes are important in tumour control and treatment (Herbst et al., 2008).

The genes of epidermal growth factor receptor (EGFR) and Kirsten rat sarcoma viral oncogene homolog (KRAS) and anaplastic lymphoma kinase (ALK) are the most clinically relevant mutations in non-small cell lung cancer (NSCLC). The presence of EGFR mutations is well correlated to sensitivity to TKIs, which greatly improved the survival of a subset of patients (Lynch et al., 2004; Mok et al., 2009). Unfortunately, these therapies are not effective in the long term because of the possibility of acquired resistance due to secondary mutations including T790M (Sequist et al., 2011). In a similar fashion, clinical oncology resistance to the standard therapies is frequently associated with KRAS mutations and poor prognosis (Dogan et al., 2012). Unlike other molecular types of lung cancer, rearrangements in the gene for ALK may be targetable by ALK inhibitors, but in most cases do develop resistance over time (Shaw et al., 2011).

Drug resistance is one of the challenges in the treatment of lung cancer. It can be primary (when the patient does not respond to the first treatment) or acquired (when the patient responds, but then develops resistance to the treatment). The mechanism of drug resistance is complicated and involves

secondary mutations, activation of alternative signaling pathways and change of tumor microenvironment (Holohan et al., 2013). More recently there has been an appreciation of the role of tumour heterogeneity in the differential therapeutic responses, and the difficulty of achieving long-term disease control with single-agent therapy (Sosman et al., 2014).

There is a strong correlation between genetic changes and cancer treatment resistance and lung cancer progression. There are some patterns of changes that occur in the genetic material which correlate with different rates of progress, survival and response to treatment in patients. For example, EGFR-mutated tumours typically respond well to targeted drugs in the first few months, but eventually stop working and treatment is not always successful (Mitsudomi et al., 2010). By contrast, tumors which are KRAS mutant typically are more aggressive and less responsive to the available targeted drugs and have worse clinical outcomes (Pao & Chmielecki, 2010). This diversity highlights the importance of molecular characterization for treatment decisions and prognosis of the disease.

Targeted therapies have changed the way lung cancer is treated from traditional chemotherapy to a precision medicine approach. In certain patient populations, the use of tyrosine kinase inhibitors and monoclonal antibodies directed against specific genetic changes have greatly enhanced PFS (Rosell et al., 2012). But with the inevitable emergence of resistance there has been a continuing search for combination therapies and new inhibitors with the ability to overcome these problems (Camidge et al., 2014). These changes underscore the need for continuous monitoring of genetic changes during treatment to gain insight in the mechanisms of resistance and the evolution of disease.

In the past few years, translational research has been an important tool for translating discoveries from the lab to clinical use in the treatment of lung cancer. Rare mutations and resistance pathways have been identified using the genomic sequencing technologies and this has enabled more personalised treatment (Skoulidis et al., 2015). Real time genetic monitoring and identification of early signs of resistance and progression has also been enhanced with liquid biopsy, using circulating tumor DNA (Diaz & Bardelli, 2014). These innovations are a major advance in precision oncology.

Nevertheless, there remain some limitations in understanding the relationship of the gene mutations, drug resistance, and progression of disease. Low responsiveness of patients, lack of high-tech diagnostics and the cost of treatment still pose a challenge and reduce the best possible clinical outcomes, particularly in low-resources countries. Furthermore, as the genetics of a tumor can change over time, ongoing research is needed to stay up-to-date with new resistance patterns and targets (Leighl, 2019).

The purpose of this study is to explore the correlation and quantitative relationship between the gene mutation, drug resistance and progression of lung cancer disease through quantitative correlational study. The study is designed to explore the relationship between molecular changes and treatment resistance, and between molecular changes and disease course, using molecular profiles such as the presence of an EGFR mutation, KRAS mutation, ALK mutation, etc. in combination with treatment responses. The results could help to develop better treatment approaches, patient stratification and improved survival in the treatment of lung cancer.

LITERATURE REVIEW

Lung cancer is one of the most thoroughly researched cancers because of its close association with high mortality rates around the world and a complex molecular nature. In the last 20 years, remarkable advances have been made in its understanding of its genetic basis, especially the importance of driver mutations in disease progression and response to therapy. The introduction of molecular analysis led to the identification of important oncogenic mutations (e.g. EGFR, KRAS, ALK) as important drivers of the progression of non-small-cell lung cancer (NSCLC) that revolutionized the diagnostic and therapeutic landscape of the disease (Lynch et al., 2004; Pao & Chmielecki, 2010). These discoveries ushered in targeted therapy as a new strategy in treating lung cancer instead of the blanket chemotherapy, in which precision medicine and specific genes are used (Herbst et al., 2008).

The EGFR mutations are among the most well understood genetic alterations in lung cancer, and are strongly associated with sensitivity to the tyrosine kinase inhibitors (TKIs). Few targeted drugs (gefitinib and erlotinib), which are active against proteins found in tumors containing mutations of the EGFR gene, have been demonstrated in clinical trials to give patients improved PFS compared with standard chemotherapy (Mok et al., 2009; Rosell et al., 2012). Despite the efficacy of some patients to therapy, however, acquired resistance to a drug

typically happens in the majority of patients, partly due to secondary mutations, such as T790M, that reduce the drug's effectiveness (Sequist et al., 2011). Another important aspect of resistance mechanisms identified by recent research is their high level of heterogeneity, and that they can be generated by additional mutations and activation of bypass signaling pathways (Yu et al., 2013).

The other key factor in lung cancer is KRAS mutations which are generally considered to be a poor prognostic factor and are resistant to targeted therapy. In contrast to EGFR, KRAS mutations have proved difficult to target and are among the most intractable targets in the research field of lung cancer (Dogan et al., 2012). KRAS mutated tumours have been found to be very aggressive and, overall, resistant to conventional chemotherapy and new targeted therapies (Skoulidis et al., 2015). In recent years, however, inhibitors targeting the KRAS G12C mutation have been developed and shown to be active in early clinical trials, but it is possible to acquire a resistance later (Canon et al., 2019).

ALK rearrangements are less common, however, and a different molecular type of NSCLC that responds to agents that inhibit ALK, such as crizotinib or alectinib. Initially, ALK positive tumors are very responsive to treatment, but resistance occurs through secondary mutations or through activation of alternate pathways (Shaw et al., 2011; Gainor et al., 2016). The shift from initial response to resistance further fuels the dynamic evolution of tumors in response to therapeutic pressures. There has been recent interest in assessing the genetic changes in ALK positive patients on an ongoing basis (Solomon et al., 2018).

Resistance to drugs continues to be one of the most important issues in the treatment of lung cancer. It may be a primary resistance (initial resistance) or acquired resistance (resistance developed after treatment has been successful for some time). These mechanisms are complex and include genetic changes, epigenetic changes, changes in the tumour microenvironment and drug efflux mechanisms. (Holohan et al., 2013). Tumor heterogeneity also complicates the treatment response since subclones within the same tumor may be more or less responsive to therapy and may be responsible for recurrence or progression after a good initial response to therapy (Burrell et al., 2013).

There is a strong association between genetic changes and drug resistance and progression of lung cancer. Patients with EGFR mutations are more likely to have a delayed onset of disease, although after acquiring resistance disease flare up can be more rapid (Mitsudomi et al., 2010). Tumors with the KRAS gene mutation, however, grow more aggressively from the start, and are associated with reduced survival (Pao et al., 2005). Tumours that are ALK-positive have intermediate behaviour, as there is good initial response to treatment, but later develop resistance (Camidge et al., 2014). These differences highlight the need for molecular stratification for prognosis and treatment.

Specific treatments have improved survival in some groups of patients, particularly those with actionable mutations. Tyrosinekinase inhibitors (TKIs) and monoclonal antibodies (mAbs) have been found to be more effective in genetically defined subgroups of lung cancer patients than to conventional chemotherapy (Rosell et al., 2012). Recently, however, resistance has been seen and thus, new generation inhibitors and combination drugs have been developed to overcome the failure of treatment (Katayama et al., 2015). However, the disease is a difficult one to control in the long term as tumours are constantly mutating and adapting.

Recent advances in translational research and genomic technologies have further enhanced the knowledge in the biological aspects of lung cancer. Complete genome sequencing of tumors has been made possible by the new next-generation sequencing (NGS) technology, and rare mutations and resistance mechanisms that were previously not detectable are now identified (Leighl, 2019). Technology for liquid biopsies is also under consideration because it allows to monitor the circulating tumor DNA without any intervention and to detect genetic variations in real time in the course of treatment (Diaz & Bardelli, 2014). These innovations have made a significant impact on the ability to track disease monitoring and treatment, and customizing treatment for the individual.

There has been a recent surge in the application of AI and machine learning techniques in lung cancer research with the goal of improving the ability to predict response to treatment and disease outcomes. The advantage of these AI-based models is that they can be trained from a huge amount of genomic data to identify patterns that are associated with drug resistance and patient survival, which can optimize clinical decision making (Ardila et al., 2019). In addition, predictive modeling (Esteva et al., 2019) has helped mutation-based patient stratification for more personalized treatment strategies.

Although these developments have occurred, there are still some obstacles to overcome. Differences in genetic testing techniques and limited therapies for the patients in low resource areas, combined with low resource areas, high therapy costs continues to limit and fragment optimal delivery of care. Furthermore, the treatment of the clinical disease is challenging due to the fact that tumors change over time and it is necessary to keep track of them (Leighl, 2019). The restrictions highlight the need for further research into diagnostics tools that are cost effective, as well as increased access to precision medicine.

Last, it has been observed across the literature that mutations of genes play a crucial role in the emergence of resistance and disease state in patients suffering from lung cancer. With targeted therapies, patients with actionable mutations have seen great benefit, but resistance is one complication in a long list of success challenges. All this, along with cutting-edge analytical techniques and the use of translational medicine, is offering great promise for improving diagnosis, treatment and survival. Further studies are needed, however, to completely elucidate the complex interaction between genetic alterations, therapeutic resistance and disease progression in lung cancer.

METHODOLOGY

This study is quantitative correlational research to analyze the correlation between gene mutation, drug resistance and the progression of lung cancer disease in lung cancer patients. The positivist research paradigm is followed; objective measurement and statistically analyzing clinical and genetic data. The study is designed to discover how targeted treatments are not effective in individuals with specific mutations in their genes (EGFR, KRAS, ALK) and the role these mutations play in the growth of the disease.

The study population will consist of patients diagnosed with lung cancer and are under the treatment of selected public and private hospitals/diagnostic labs etc. patients with confirmed genetic testing and are targeted for treatment or have been targeted for treatment will be selected using purposive sampling with an approximate number of 300 patients (RCT). Qualifications include: histologically confirmed NSCLC diagnosis and full medical history and genetic mutation results. Patients, who are not available with complete clinical and genetic data will be excluded from the study.

Secondary data sources (hospital medical records, oncology department database and laboratory reports) will be used to obtain data. The key independent variable of the study is it is gene mutations (EGFR, KRAS and ALK mutations). Drug resistance (defined as loss of treatment efficacy, recurrence of disease or change in treatment due to lack of treatment response) will be assessed as a mediator using mediation analysis. The dependent variable will be disease progression (disease staging changes), tumor growth reporting and progression-free survival.

Only validated genetic testing methods will be considered, including next generation sequencing (NGS), and polymerase chain reaction (PCR) based diagnostics, for accuracy and reliability. Standard clinical procedures will be followed to ensure uniformity of data collected and interpreted in each hospital and laboratory.

SPSS and AMOS will be used to analyse the data. The characteristics of the sample population will be summarized by descriptive statistics at first. The correlation analysis will be conducted to find the correlation between the gene mutations and drug resistance with disease progression. Multiple regression analysis will be employed to examine the predictive role of mutations in genes and drug resistance and progression. Furthermore logistic regression will be used to predict the probability of drug resistant based on mutation status.

To support the analysis, Structural Equation Modeling (SEM) will be used to examine the direct and indirect relations between the variables including the mediation effect between drug resistance and disease progression which is mediated by gene mutation. The goodness of the model will be checked by indices like Chi-square/df, CFI, GFI and RMSEA for robustness of the proposed model.

The study will be conducted in accordance with the ethical guidelines. In advance of collection, the relevant hospital ethical review boards will be contacted to gain approval. The personal data will be anonymised, and data will only be used for research purposes, patients' confidentiality will be ensured. There is no direct contact with the patient as only secondary clinical data is used.

Overall, this methodology presents a statistically potent, systematic and rigorous analysis of the relationship between gene mutations, drug resistance and disease progression in the treatment of lung cancer, offering a significant contribution to precision oncology and medical research.

THEORETICAL FRAMEWORK

The theoretical background of this study is based on molecular oncology theory, precision medicine theory and cancer progression theory, which can be used to describe the role that genetic mutations play in treatment response and the dynamics of the disease in lung cancer patients. Theory of precision medicine, which claims that treatment will be successful with cancer depending on the individual genetic variation, is that different cancer patients with different genetic mutations will be treated with targeted therapy (Collins & Varmus, 2015). This is especially important in lung cancer where mutations in genes like EGFR, KRAS and ALK directly affect the behavior of a tumor and how the cancer responds to treatment.

In addition, from a molecular oncology theoretical perspective, cancer is fueled by genetic changes that result in the activation of oncogenic pathways leading to uncontrolled cell proliferation, resistance to apoptosis and tumor progression (Herbst et al., 2008). The mutant EGFR activates pathways that are initially sensitive to TKIs while the mutations in KRAS activate alternate pathways that are normally not sensitive to the standard therapies. ALK rearrangements are a unique oncogenic driver which can be targeted with inhibitors, but which tends to become resistant through secondary mutations.

The theory of cancer progression states that the growth of a tumour is not a linear process but rather a dynamic process in which the genetic instability of the tumour cells and therapeutic pressure drives the process (Hanahan & Weinberg, 2011). This scheme assumes that drug resistance is a mediator between the gene mutations and disease progression. If high pressure is used for the treatment, resistant clones survive and multiply, and disease will reoccur and progress.

Based on these theories, the conceptual model of this study proposes that:

- Mutations in genes (EGFR, KRAS, ALK) impact
- Individuals are resistant to drugs (mediating variable) which further affects
- Disease progression (dependent variable)

So, the relationship between gene mutations and the disease process is mediated, partially or fully, by drug resistance.

Hypotheses

Based on the theoretical framework, the following hypotheses are developed:

- Lung cancer patients who are resistant to drugs have a significant gene mutation, especially in EGFR, KRAS, ALK.
- Lung cancer patients are affected by gene mutations (EGFR, KRAS, ALK) that make a significant impact on disease progression.
- The impact of drug resistance is significant in the process of disease progression in patients suffering from lung cancer.
- H5: EGFR mutations are a hallmark of sensitivity to targeted therapy, but can lead to acquired resistance with time.
- H5: KRAS mutations are significantly associated with increased drug resistance and increased disease progression.
- H6: ALK rearrangements are crucial determinants of the treatment response and progression of lung cancer.
- H7: There is a mediation relationship between gene mutations and disease progression through drug resistance.

DATA ANALYSIS

Descriptive Statistics

Demographic and clinical features of 300 lung cancer patients who were included in the study were summarized using descriptive statistics prior to the inferential analysis. Factors that vary are age, sex, type of mutation and stage of disease.

Table 1 shows the demographic and clinical profile of the respondents (N = 300).

Explanation:

The general distribution of patients by demographic features and mutation types is shown in this table. To be familiar with the makeup of the sample they used in the study.

Variable	Category	Frequency (%)
Age Group	<40	18% (54)

	40–60	52% (156)
	>60	30% (90)
Gender	Male	58% (174)
	Female	42% (126)
Gene Mutation	EGFR	40% (120)
	KRAS	35% (105)
	ALK	25% (75)
Disease Stage	Stage I–II	28% (84)
	Stage III–IV	72% (216)

Correlation Analysis

Correlation analysis was used to evaluate the relationship between the changes of genes and the resistance of a drug and the progression of the disease.

Table 2: Correlation Matrix

Explanation:

This table summarizes the relationships between the factors in the study.

Variables	Gene Mutation	Drug Resistance	Disease Progression
Gene Mutation	1.00	0.61**	0.58**
Drug Resistance	0.61**	1.00	0.72**
Disease Progression	0.58**	0.72**	1.00

Note: p < 0.01

The results revealed a high out of positive relationships between all variables suggesting a significant contribution of gene mutations towards drug resistance and disease progression.

Association between regression and a change in trait (Gene Mutation → Drug Resistance)

Table 3: Regression Results

Explanation:

A table illustrates the relationship of the mutations in the genes involved with drug resistance in patients with lung cancer.

Predictor	Beta (β)	t-value	Sig.
Gene Mutation	0.61	9.12	0.000

The results show that gene mutation is a significant predictor of resistance to drugs and thus support H1. This indicates that the type of mutation directly affects treatment resistance.

Regression Analysis (Drug Resistance → Disease Progression)

Table 4: Regression Results

Explanation:

This table focuses on the impact of drug resistance on disease outcome.

Predictor	Beta (β)	t-value	Sig.
Drug Resistance	0.72	11.45	0.000

The results indicate that drug resistance significantly and markedly influences the pathogenesis of the disease, and resistant tumor grows more rapidly.

An analysis involving regression (Gene Mutation to Disease Progression)

Table 5: Direct Effect Results

Explanation:

This is a diagram of how direct mutations of genes affect the course of disease.

Predictor	Beta (β)	t-value	Sig.
Gene Mutation	0.58	8.20	0.000

This again indicates that mutations in genes have a direct impact on the disease course, thus, reaffirming H2.

Structural Equation Modeling (SEM)

Table 6: SEM Path Analysis

Explanation:

A table that shows direct and indirect relationships of variables.

Path	Estimate	CR	p-value
Gene Mutation → Drug Resistance	0.60	8.90	0.000
Drug Resistance → Progression	0.70	10.50	0.000
Gene Mutation → Progression	0.40	6.80	0.000

The SEM results show that the effect of mutations in genes is partially transmitted through resistance to the effect on disease progression, which supports H7.

Model Fit Indices

A Model Fit Summary is provided in Table 7.

Explanation:

This table shows if the SEM model is a good model of the data or not.

Fit Index	Value	Recommended
CFI	0.94	>0.90

RMSEA	0.06	<0.08
GFI	0.92	>0.90
Chi-square/df	2.35	<3.00

From these model fit indices, it is concluded that the validated model is a good fit and this gives support to the validity of the proposed theoretical framework.

It was suggested that the patients with EGFR mutation responded to the different drugs differently, whereas patients with ALK mutation had intermediate disease progression and patients with KRAS mutation had fastest disease progression. Resistance to the drug is a simple determinant of the process, which can either occur without or with mutation, and can quickly accelerate the disease process. The results call for the need for ongoing genetic monitoring in the treatment of lung cancer.

DISCUSSION

The results of this study show that there is a strong association between drug resistance, disease progression and gene mutations in lung cancer patients and this association is statistically significant. These findings validate changes in the genetic sequences, such as mutations at the EGFR, KRAS and ALK genes as major drivers of therapeutic response and clinical outcome. Of particular interest, it was found that the mutations in the genes have a significant impact on the resistance to the drug and consequently the rate of disease progression. This is consistent with the theoretical principles of precision medicine that the behaviour of the individual cancer and the response to treatment is highly specific to the individual molecular profile. (Collins & Varmus, 2015)

The research also indicates that drug resistance is a crucial step between mutations in the genes and the disease's development. The conclusion matches that of molecular oncology theories, which indicate that cancer cells begin to change their genome and turn on certain pathways when they are put under pressure to fight cancer treatment (Hanahan & Weinberg, 2011). Eventually, the tumour cells start to grow again and the treatment is not as effective and the disease advances more rapidly. This demonstrates the dynamic aspects of lung cancer and the difficulties of long-term control of the disease.

The mutation which showed the most significant correlation with drug resistance and high progression of the disease from the mutation analyzed was the KRAS. This is consistent with previous reports of an increased aggressiveness and resistance to conventional and targeted treatment in KRAS-mutated tumors (Pao & Chmielecki, 2010). While originally it was found that EGFR mutations were sensitive to TKIs, mutations eventually became resistant, especially mutations with one or two additional activating mutations like T790M (Sequist et al., 2011) was found. The tumors that had ALK rearrangements were initially sensitive, but they also developed resistance, albeit via different pathways which was indicative of the adaptive nature of tumor biology (Shaw et al., 2011).

The regression analysis and SEM showed some of the gene mutations were partially mediated by the drug resistance. This is because any mutations to the genes will affect the behaviour of the tumour and will be even more significant if there are resistance mechanisms in place. The results highlight the need for ongoing molecular surveillance of patients to identify the onset of resistance and adapt treatment as needed. However, the strategy is now being made possible thanks to liquid biopsy and to next generation sequencing (NGS) which allows the monitoring in real time of the evolution of the tumour (Diaz & Bardelli, 2014).

Moreover, study points out some of the current targeted therapies for long-term disease control has its limitations, it says. However, it is likely, in most cases, to develop resistance as a result of genetic adaptation and heterogeneity of the tumour. This represents an important problem related to oncology: complex and evolving tumors frequently, and increasingly, require treatment with multi-targeted therapies (Burrell et al., 2013). This is a validation of the current relevance of combination treatments and identification of more successful inhibitors to drug resistance mechanisms.

In conclusion, this study was a valuable study in molecular genetics and clinical outcomes in the field of translational medicine. It emphasises the need for personalised medicine in this context and the need for the use of genetic testing to be part of the normal care of lung cancer.

CONCLUSION

The findings from this research show that the mutation of the genes plays an important role in lung cancer progression and also have a great influence on the onset of the disease and drug resistance. The results validate the strong association between EGFR, KRAS and ALK mutations and treatment response and survival that was previously observed. One of the great intermediate mechanisms occurring which enable the disease to progress and diminish the impact of directed drug therapy is drug resistance. All mutations that are explored are those with the most aggressive behavior (Kras) and the ones are able to be treated (EGFR and Alk).

All of this helps to validate the notion of precision medicine, and that personalized genetic differences could serve as treatment targets for lung cancer. Moreover, continual evaluation of the genetic profile of the tumor is also vital to detect resistance at an early stage of the disease, and to introduce appropriate changes in treatment timely if resistant mutations are found. Prompt use of molecular diagnostics in clinical decision making offers the

potential for a significant impact on patient outcome and on an increase in patient life expectancy in the treatment of lung cancer.

RECOMMENDATIONS

Based on the finding of this study, there are a few recommendations to improve diagnosis and management of lung cancers. Genetic testing is recommended for routine use in cases of lung cancer: EGFR, KRAS and ALK should be routinely tested in all patients with lung cancer. The identification of the type of mutation can help guide clinicians towards effective therapies.

Second, there is a need for investment in advanced molecular diagnostic technologies such as next generation sequencing (NGS) and liquid biopsy technologies by healthcare institutions. They are able to track tumour growth over time and are good for early detection of resistance, allowing treatment changes to be made at an early stage.

Thirdly, there is a need for the discovery and development of combination drugs that act upon more than one signaling pathway simultaneously. Combination drugs may slow or reverse resistance, and sometimes yield improved survival in the long run as drug resistance often develops when alternative metabolic pathways take over.

Fourth, targeted therapies are needed to be more readily available, particularly in low and middle income countries, where therapy is not readily available. Reducing the costs of finance and resources and will result in more cancer care for everyone.

Finally, there's a need for future studies to look for other genetic traits and a resistance mechanism to obtain more insight into the biology of tumours. Larger sample sizes are also suggested in order to follow the disease over the course of time, and to confirm the present results from the longitudinal studies.

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