

Trends of Molecular Testing for Lung Cancer at the King Faisal Hospital, Kigali: Therapeutic and Survival Implications



Achille Van Christ Manirakiza, MD,^{a,*} Fidel Rubagumya, MD,^{b,c,d,e}
Eulade Rugengamanzi, MD,^f Alphonsine Mukandekazi, MD,^g Jessica Beneyo, BMLS,^a
Maurice Musoni, MD,^a Thierry Zawadi Muvunyi, MD^a

^aKing Faisal Hospital, Kigali, Rwanda

^bDivision of Cancer Care and Epidemiology, Queen's University Cancer Research Institute, Kingston, Ontario, Canada

^cDepartment of Oncology, Queen's University, Kingston, Ontario, Canada

^dDepartment of Public Health Sciences, Queen's University, Kingston, Ontario, Canada

^eRwanda Military Hospital, Kigali, Rwanda

^fMuhimbili University of Health and Allied Sciences, Dar es Salaam, Tanzania

^gAnatomical Pathology Department, School of Medicine, University of Rwanda, Kigali, Rwanda

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ABSTRACT

Introduction: Lung cancer is the leading cause of cancer mortality worldwide, both in high and low resource settings. Knowledge has been generated elsewhere regarding molecular subtyping and subsequent targeted therapy development, contributing substantially to patient survival. Little is known on the data around lung cancer and its treatment outcomes in Sub-Saharan Africa. This study describes the experience in lung cancer diagnosis, molecular and biomarker testing, and treatment for advanced cases in a single institution in East Africa, between the years 2019 and 2021.

Methods: This was a retrospective observational study evaluating patients with metastatic (stage IV) lung cancer. Data on patient demographics, histologic diagnosis, molecular and biomarker testing, and treatment details and outcomes were collected. Molecular test results were reported as positive if there were biomarkers identified (e.g., *EGFR*, *ALK*, programmed death-ligand 1), and patients who had negative test results were reported as negative for biomarkers.

Results: A total of 14 patients were diagnosed with having stage IV disease, and all were proposed to undergo molecular testing. For 12 (86%) patients who were able to have molecular testing done, *EGFR* and programmed death-ligand 1 were the most common with 66.7% ($N = 8$) of tissues with either finding. For all 14 patients, treatment changes were made for eight patients (57.1%) after being primarily placed on a combination of paclitaxel and carboplatin for an average of six cycles. Changing treatment

significantly improved the 2-year overall survival (85% versus 25%, $p = 0.0006$).

Conclusions: Despite being the number one cause of mortality, gains are being made in poor-resource settings to improve the survival of patients with advanced lung cancers. Limitations to this quest remain misdiagnosis and delayed diagnosis and resource constraints for both molecular testing and subsequent treatments.

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*Corresponding author.

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Address for correspondence: Achille Van Christ Manirakiza, MD, King Faisal Hospital, KG 544 Street, Kigali 3344, Rwanda. E-mail: achille.manirakiza@gmail.com

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Introduction

Regardless of resource settings, lung cancer remains the most fatal malignancy in the world.¹ Despite multiple prevention and control efforts, such as first- and secondhand smoking exposure reduction, there are an increasing number of cases of lung cancers in young, never-smoker patients worldwide.²

In resource-constrained settings, given the scarcity of proper investigation tools and similarities in presentations between lung cancer and other diseases, lung cancer numbers hide behind many diagnoses, such as pulmonary tuberculosis.³

A large portion of patients with lung cancer in resource-constrained settings has advanced disease at presentation.^{1,4} Although surgery with either chemotherapy or radiation therapy constitutes the standard of care for patients with early stage diseases, the use of systemic therapy (cytotoxic chemotherapy, targeted and immunotherapies) is the mainstay treatment for patients with advanced stages of lung cancer.⁵ Multiple challenges exist with chemotherapy agents used in this disease setting, as they represent a source of multiple generalized side effects for patients with already advanced disease.⁶ Diagnostic and therapeutic solutions have since evolved, and with an example from multiple other malignancies with germ-line or with somatic mutations, deleterious genetic mutations have been found to drive lung cancers, with differing rates depending on the studied populations.^{7,8} Finding mutation drivers provides room for targeted therapy with a direct impact on the first and second lines of treatment and offers a subsequent improved overall survival.⁹

The most common subtype of lung cancer is NSCLC (85%) followed by the small cell and neuroendocrine types.⁹ Most of the molecular testing work has focused on NSCLC and has found at least 10 clinically relevant genes driving lung cancer.^{10,11} Programmed death-ligand 1 (PD-L1), an immune protein counted by its expression, has been added on the number of tests done for both predictive and prognostic purposes, for patients with squamous and nonsquamous lung cancer diagnoses.

Despite black race being associated with poor prognosis, there is a dearth of data on molecular testing for lung cancer in Sub-Saharan Africa, which could be explained by the cost of both these tests and the subsequent targeted therapies.^{12,13}

Since 2019, King Faisal Hospital, Kigali (KFH, K) improved its medical oncology unit with capacity to provide both targeted and immunotherapies. Patients with lung cancer and eligible for further testing are

informed of the potential survival benefits and cost implications of the testing and referred to the Lancet Laboratories (Kigali, Rwanda) for further testing, with a turnaround time spanning 2 to 3 weeks from the time of request. This study aimed at highlighting the existing proportions of patients with known mutations and the therapeutic and survival implications of lung cancer molecular profiling at KFH, K.

Materials and Methods

This was a retrospective observational study that also reported on the characteristics of patients with metastatic lung cancer seen in the KFH, K cancer unit between 2019 and 2021. These years were specifically chosen, as there was an active change that started in 2019 in availing the molecular tests and targeted therapy medications for lung cancer.

Data collection focused on patient demographics, histology type (and subtypes), stage at presentation, and potential risk factors. For eligible patients with advanced disease, and for whom a request for molecular testing was made, results were retrieved from the Lancet Laboratories reports. Biomarker testing requested was *EGFR*, *ALK*, *ROS-1*, and PD-L1 and was performed on tissue biopsies taken either on bronchoscopy or lymph node samples. Results were reported from those with positive test results (e.g., *EGFR*, *ALK*, PD-L1), and patients who had negative test results were reported as intact.

EGFR was detected using a real-time polymerase chain reaction that quantitatively detected 42 genes (T790M included). *ALK* and *ROS-1* were detected using the fluorescence in situ hybridization technique. PD-L1 was detected with immunohistochemistry, using two clones viz. 22C3 (Dako) and SP142 (Roche) run on the Ventana platform.

Data analysis was done using Stata 14. Continuous variables were summarized by means, medians, SD, and range. Categorical data were summarized using frequencies and percentages, whereas tables, figures, and texts were used to present the summarized data. Pearson's chi-square test and Fisher's exact test were used to compare the proportions of two nominal variables. Kaplan-Meier curve was used to identify and compare overall survival rate. As one of the assumptions of using the log-rank test, outcomes consisted of two states, "censored" and "events." "Events" was the outcome of interest, in this case death. "Censored" included outcomes such as being alive and/or lost to follow-up. Cox regression analysis was used to identify predictors of survival with a *p* value less than 0.05 considered statistically significant.

Ethical approval was obtained from the Institutional Review Board at the King Faisal Hospital. Because the study was retrospective in nature, a waiver was obtained

Table 1. Characteristics of Patients With Molecular Testing

Characteristics	Frequency	(%)
Sex		
Female	3	21
Male	11	79
Age group		
<50	5	36
>50	9	64
Histology		
SCC	1	7
Adenocarcinoma	13	93
Stage		
Stage IV	14	100
Smoking history	2	14%

SCC, small cell cancer.

from the Ethics Board to not use informed consent to patients whose data were retrieved.

Results

Patient Characteristics

A total of 14 patients were seen with metastatic disease (stage IV) in our clinic and are the focus of this study. These patients were eligible for molecular testing and were further counseled and tested for this purpose. Most of the patients in the group were of male sex (79%, $n = 11$), and the mean age was 53.7 years ($SD = \pm 10.62$). The most common subtype of lung cancer found was adenocarcinoma (93%, $n = 13$) (Table 1).

A total of 13 patients were started on systemic chemotherapy with most receiving at least six cycles of the carboplatin and paclitaxel regimen (79%, $n = 11$), for an average of 5.5 months. Only 1 patient received a pembrolizumab-based regimen (combined with pemetrexed and cisplatin) from diagnosis (Table 2).

Molecular Profiling

Most of the patients were able to have molecular profiling done on their tissue samples, whereas two (14%) were not able to. *EGFR* and PD-L1 were the most common with 66% of tissue sampled having either of the two biomarker findings. Of the two patients who had a smoking history, one was found with PD-L1 and the other with intact findings on molecular testing (Fig. 1).

On the basis of these findings, from the 14 patients, eight (57%) had their treatment regimens modified to suit their molecular findings, whereas five (36%) were kept on the same regimen from lack of funds (either for testing or for medications) or as their findings did not yield any targetable mutation. One had his targeted therapy started from the beginning of his treatment*, but died after 20 months on treatment. All patients found with the *EGFR* mutation were placed on erlotinib (150 mg once a day orally), those with *ALK* on alectinib (400 mg twice a day orally), and those with PD-L1 positivity were placed on pembrolizumab (at a dose of 200 mg every 3 wk), with additions made for the rest of the agents according to the percentage of expression (one had 80% expression and had pembrolizumab, pemetrexed, and cisplatin, two had <50% expression and had an addition of pembrolizumab on their carboplatin and paclitaxel base) (Fig. 2). All four patients placed on erlotinib are still alive (mean survival = 15.7 mo), one of two placed on alectinib is alive (mean survival = 7 mo), whereas two of the three patients placed on pembrolizumab are alive (mean survival = 15.6 mo) (Table 3).

As treatment is still ongoing for some patients, survival analysis was limited to only 2 years. The 1- and 2-year overall survival rate was 70% and 46%, respectively.

Keeping the previous treatment regimens, whether from intact molecular findings or lack of funds resulted in significantly decreased 2-year survival rates (25%), when compared with patients whose regimens were changed (85%, $p = 0.0006$) (Fig. 3).

Discussion

Lung cancer remains a less encountered yet highly fatal malignancy in resource-constrained settings. Leading factors behind this have been largely documented in these settings and consist of inadequate health care practitioner knowledge, little public health awareness of lung cancer, and limited diagnostic facilities.^{3,4,14}

The mean age of patients with advanced lung cancer disease in our study was 53.7 years, correlating with findings in similar African settings and contrasting with the usually older mean age in different races.^{12,15,16} Adenocarcinoma was also the most often found in studied African populations.¹²

Table 2. Treatment Information of the Study Participants (N = 14)

Variables	Categories	Frequency	Percent
Chemotherapy	Carboplatin + paclitaxel	13	93
	Pembrolizumab	1	7
Chemotherapy cycles	<6	3	21
	>6	11	79

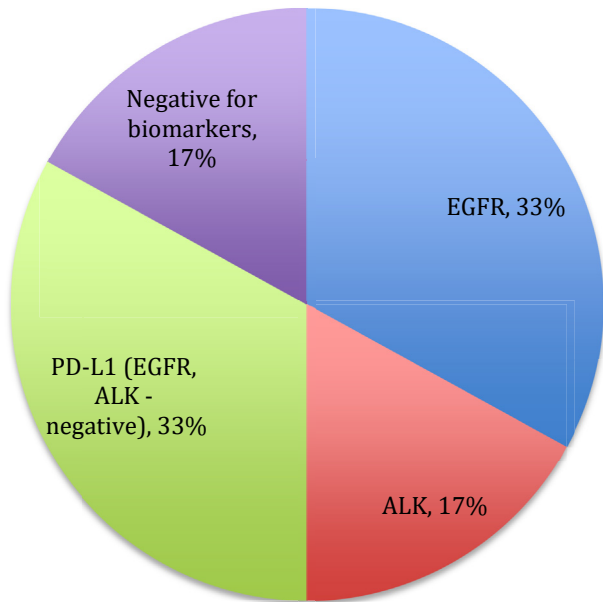


Figure 1. Distribution of biomarker findings on the sampled tissues. There were one patient who had PD-L1 high expression (70%) and three who had low PD-L1 expression (>1%, <50%). PD-L1, programmed death-ligand 1.

Owing to the delay of requested molecular testing results, nearly all patients were placed first on systemic chemotherapy with the carboplatin and paclitaxel regimen. Although this protocol has contributed to patient survival until treatment was later modified for the few patients who afforded, side effects remain the precluding factor in continuing the regimen. Where feasible, molecular testing guided treatment from diagnosis.

Available international guidelines provide clarity on the type of molecular testing to be performed for patients with metastatic lung cancers.^{10,11} We limited our testing recommendations to clinically relevant molecular testing, and for which medications could be readily available. *EGFR*, *ALK*, *ROS-1*, and PD-L1 were the most often requested for the adenocarcinoma subtype, whereas PD-L1 alone was requested for the only patient with the squamous cell carcinoma subtype. As found elsewhere, in similar settings,^{12,17} *EGFR* and *ALK* were the most often encountered driver oncogenes.

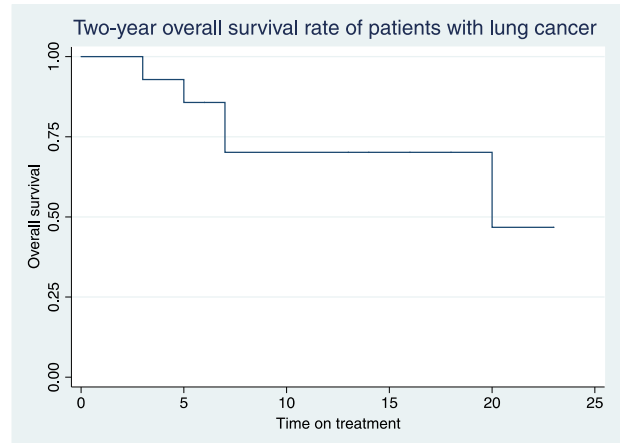


Figure 2. Lung cancer 2-year overall survival curves.

Our study results corroborate with findings elsewhere, giving survival benefit for patients placed on *EGFR* targeted therapy.¹⁸ Alectinib was chosen for its survival benefit when compared with crizotinib as the first line for *ALK*-positive patients in a different population.¹⁹ Pembrolizumab is an established agent for PD-L1-positive patients (from >1% of expression upward).²⁰

Generally, availability and expertise in lung cancer molecular testing are lacking in resource-constrained settings.²¹ Most of the molecular testing in the East African region is done at one center, which outsources further expertise for analysis purposes, and consequently increases the cost of access to this diagnosis and predictive modality. Beyond here, the costs of targeted therapy end being a burden to patients, uniformly making this modality far-fetched to most patients with lung cancer in low-income countries. It is noteworthy to mention that all patients who had their molecular testing done and targeted therapy started have private health insurance or other schemes reimbursing both the testing and treatment, leaving a large group of patients with lung cancer uncovered.

Our study has a number of limitations, one of which was a small sample size analyzed, as our hospital is a quaternary national referral facility serving mostly patients with private insurances or other funding schemes

Table 3. Cross-Tabulation Table of Treatment Impact Versus Status

Variables	Categories	Status		p Value
		Alive n (%)	Deceased n (%)	
Treatment impact	Treatment modified	7 (87.5)	1 (12.50)	0.063
	Treatment kept	5 (36)	3 (66.67)	

Note: Patient who had pembrolizumab started from diagnosis was considered as part of the treatment unchanged group.

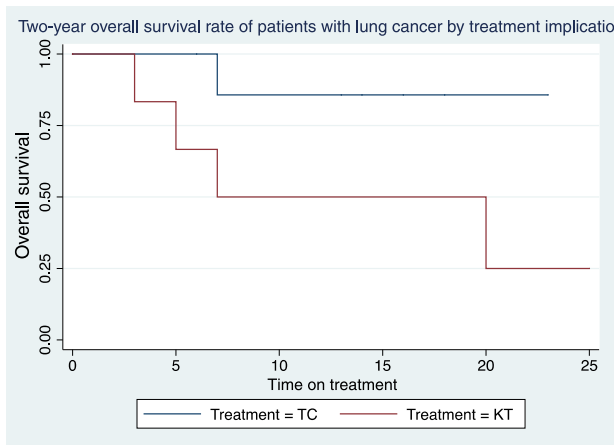


Figure 3. Treatment change implication on survival. KT, kept treatment; TC, treatment changed.

other than community-based health insurance; hence, findings cannot entirely represent the rest of Rwandan patients with lung cancer. Complete smoking history was only available for two patients in the study, underlining the issues encountered with medical reporting. In addition, not all international guideline-recommended molecular testing was made, mostly on the basis of affordability and relevance of testing. Toxicity data were also not analyzed for both the initial systemic therapy and targeted or immunotherapy.

In conclusion, there is still little known on lung cancer in African settings. Our study is one of the few in a Sub-Saharan African setting revealing survival benefits for patients with advanced lung cancer placed on targeted therapy, but the paucity of diagnostic tools and the generally high costs of the subsequent treatment remain an obstacle in achieving similar survival rates found in resource-rich settings..

CRediT Authorship Contribution Statement

Achille Van Christ Manirakiza: Conceptualization, Data curation, Methodology, Visualization, Investigation, Supervision, Validation, Writing - original draft, Writing - review & editing.

Fidel Rubagumya: Data curation, Writing - review & editing.

Eulade Rugengamanzi: Methodology, Software, Data curation, Writing - original draft.

Alphonsine Mukandekazi: Methodology, Data curation, Writing - review & editing.

Jessica Beneyo: Conceptualization, Writing - review & editing.

Maurice Musoni: Writing - review & editing.

Thierry Zawadi Muvunyi: Writing - review & editing.

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