CASE STUDY

ctDNA-guided Change of Therapy Improves Quality of Life of a Lung Cancer Patient

Quick Summary

- Tripti Vasudev*, aged 61 years, was diagnosed with NSCLC.
- Genetic analysis revealed the presence of an *EGFR* mutation - $EGFR^{L858R}$ at the initiation of therapy.
- The patient was prescribed Afatinib as a first-line therapy. However, lung cancer persisted and the patient was advised to undergo a rebiopsy as well as the Strand Liquid Biopsy Test **(Strand Advantage Sense & Resist Tests)** to understand the overall tumor heterogeneity.
- High systemic tumor burden, with a distinct bias towards the $EGFR^{T790M}$ mutation, was noted in the analysis of ctDNA by liquid biopsy.
- The patient was switched to Osimertinib therapy and further progression of the patient is being monitored using periodic liquid biopsies.
- An accurate assessment of overall tumor load as well as tumor clonality is provided by a combination of liquid and solid biopsies.
- Concurrent evaluation of solid tumor tissue as well as liquid biopsy led to comprehensive evaluation of a patient, leading to better therapeutic choices. Genetic analysis of the second lung cancer biopsy **ALONE** would have supported the continuation of Afatinib therapy, eventually leading to failure of therapy.

Introduction

Lung cancer has the distinction of being the cancer with the fastest fatality. In most cases, the overall survival of lung cancer patients is no longer than 9-12 months post-diagnosis (Murali et al. 2017). In India, the prevalence to incidence ratio of lung cancer is the lowest amongst all cancer cases.

CANCER	PREVALENCE / INCIDENCE RATIO (Takiar & Jayant 2013)
Breast	5
Cervix	5
Ovary	3
Stomach	1
Lung	1
Mouth	4
Lifetime	3

Table 1. Prevalence / Incidence Ratio for Lung Cancer is the lowest in India (Takiar & Jayant 2013).

** Name changed to protect patient privacy*

Considering the rapid loss of health of lung cancer patients, prognostic aids that can help to assess the status of a patient during therapy would be of tremendous value. Although imaging techniques like PET-CT are available, newer technologies like liquid biopsy to obtain a sample of tumor DNA (known as ctDNA) can be used very effectively to assess patient status (Marmarelis et al. 2017; Vendrell et al. 2017; Hou et al. 2017).

Patient Profile

Tripti Vasudev, a retired accountant aged 61 years, had moved from Patna to Bhubaneshwar in 2015. She was glad to escape the pollution of Patna and looked forward to a healthy and quiet retirement. Despite relocating to a cleaner environment, she noticed that her persistent low cough had not gone away. In fact, her breathing difficulties had increased slowly but steadily. She consulted a renowned doctor in Bhubaneshwar who advised her to undergo a CT-scan to understand the root cause of her problems. Small areas of abnormal growth (nodules) were evident in the CT-images and hence Tripti was advised to undergo a lung biopsy to withdraw a sample of the tissue.

Histopathological investigations confirmed that Tripti had developed Non-Small Cell Lung Cancer (NSCLC), type adenocarcinoma. A full–body scan revealed the presence of similar nodules all over the body as well.

Treatment Options

Tripti was advised treatment with Afatinib, a targeted therapy molecule. This drug inhibits the activity of the EGFR protein, which is mutated in most adenocarcinoma cases. However, her oncologist noted that the tumor persisted and response to Afatinib therapy waned, a few months into the therapy. A fresh biopsy of the lung tumor was advised to understand the genetic profile of the persistent NSCLC, in a second attempt. The StrandAdvantage 48-gene Test was prescribed for identification of mutant genes as well as other molecular markers.
Tripti's oncologist also advised her to take advantage of novel liquid biopsy tests which can facilitate tracking of the tumor via a blood sample, at any point of time, during the therapy.

Results of Genetic Testing

The StrandAdvantage 48-gene Test, a pan-cancer test was prescribed for Ms. Tripti Vasudev, in the second biopsy of her lung cancer. This test is designed to identify mutations in genes that are mutated in most solid tumors.

Therapy	*Tested Marker(s)*	*Relevant Marker(s)*	*Likelihood of Response***
Osimertinib	*EGFR*	*EGFR* ^{T790M}	*Enhanced*
Afatinib	*EGFR, ERBB2, KRAS, MET*	*EGFR* $^{L858R, T790M}$	*Limited - Enhanced*
Gefitinib	*EGFR, ERBB2, KRAS, MET*	*EGFR* $^{L858R, T790M}$	*Poor*
Erlotinib	*EGFR, ERBB2, KRAS, MET*	*EGFR* $^{L858R, T790M}$	*Poor*

Table 2. Genetic Analysis of the Second Lung Biopsy- Solid Tissue Sample

Tripti's lung cancer tissue showed two mutations in the *EGFR* gene, namely *EGFR*^{L858R} and *EGFR*^{T790M}. Tumors bearing these mutations can be effectively targeted with drugs like Afatinib and Osimertinib, respectively. Afatinib therapy had already been administered to her, during the preceding months.

In order to assess the tumor burden present in other organ systems as well, a liquid biopsy test for detection of tumor DNA in the blood was also performed.

A Liquid Biopsy for cancer is a novel 'Blood Test' for cancer. Cancer cells, like normal cells, shed DNA into the blood as a part of regular tissue turnover. This DNA is known as 'cell-free DNA' (cfDNA). It is possible to extract cfDNA from blood and then check for the presence of DNA released by cancer cells. DNA derived from cancer cells is called 'circulating tumor DNA' (ctDNA). The amount of ctDNA present in the blood is a good indicator of the total tumor burden, present in a patient.

Analysis of ctDNA from the Liquid Biopsy

Sample Collection Date	Test	Gene	Mutation	Result	Copies/ ml plasma
19-May-2017	Strand Liquid Biopsy*	*EGFR* *EGFR*	L858R T790M	Detected Detected	1,195,000 253,000

Table 3. EGFR-Sense and Resist Tests- Liquid Biopsy Sample

The *EGFR* mutations identified in the solid tumor sample were also detected in the liquid biopsy sample that had been taken from the patient at the same time. Moreover, the number of copies of ctDNA present per ml of plasma indicated that the tumor burden in Tripti is very high. In fact, Tripti is one of the rare patients who were able to survive despite having such a high tumor load.

Since Tripti had been undergoing Afatinib therapy, the prevalence of the $EGFR^{L858R}$ mutation was lower than that of the $EGFR^{T790M}$ mutation. These results indicated that her lung cancer was changing its genetic profile and cells with the $EGFR^{T790M}$ mutation were becoming more dominant than cells which respond to Afatinib treatment.

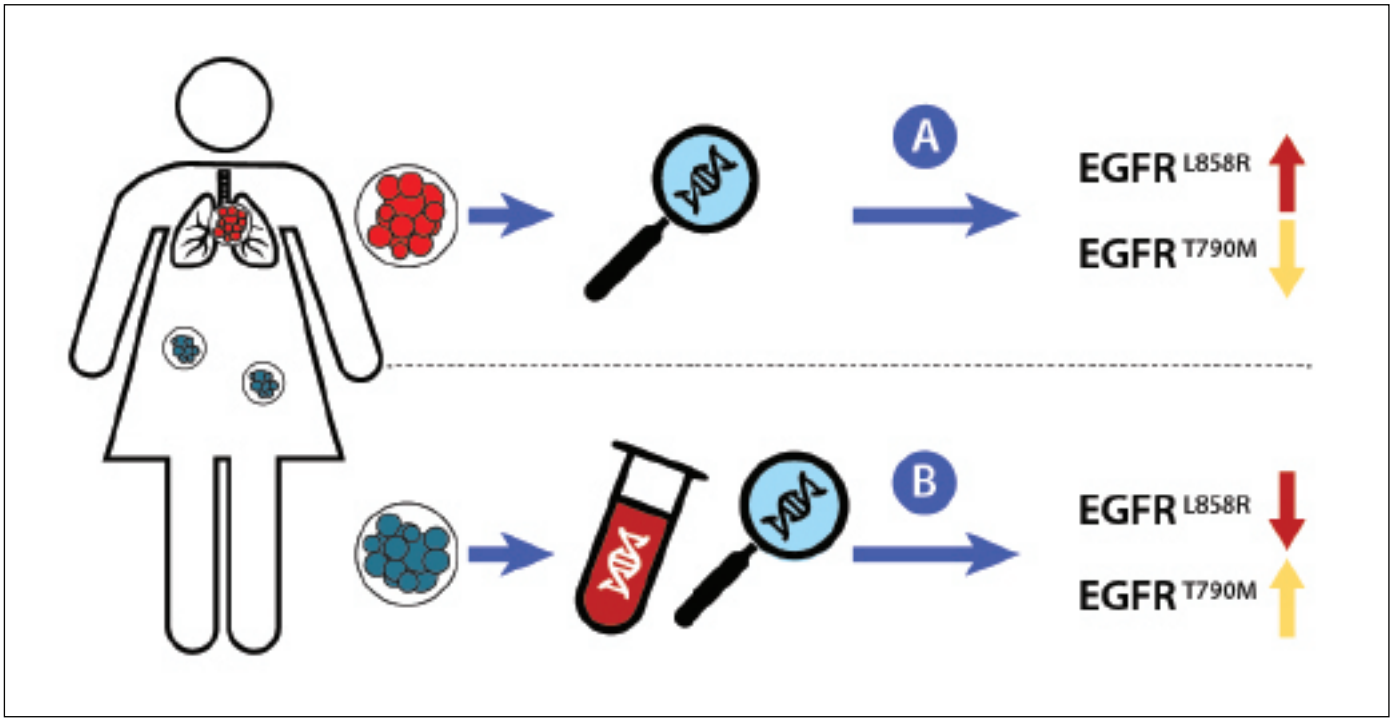

Figure 1. Simultaneous Genetic Analyses of Solid & Liquid Biopsies

The parameter marked with an * are not accredited by NABL and CAP.

Comparison with Lung Biopsy

The prevalence of the same mutations in the second lung tissue biopsy was also assessed.

Sample Collection Date	Test	Gene	Mutation	Result	Copies/ ml plasma
Solid Tumor Result (DNA Source: FFPE)					
06-May-2017	Strand Advantage TST Lung*	*EGFR* *EGFR*	L858R T790M	Detected Detected	54.48% 23.76%

Table 4. Prevalence of EGFR Mutations in the Second Solid Lung Biopsy

Genetic analysis of the solid tumor (second lung biopsy sample) shows that the *EGFR*^{L858R} mutation is the more prevalent one compared to the *EGFR*^{T790M} mutation.

However, since the cancer is metastatic, the overall tumor burden and the predominant tumor genotype present in the rest of the body were assessed with greater accuracy via the liquid biopsy test.

Change in Therapeutic Regimen

The evolution of lung cancer from Afatinib sensitivity to resistance has been documented in several studies. Emergence of the *EGFR*^{T790M} mutation is one of the mechanisms that can make lung cancer resistant to Afatinib therapy (Xiong et al. 2017; Facchinetti et al. 2017).

Considering the high prevalence of the *EGFR*^{T790M} mutation in the liquid biopsy result, Afatinib therapy was terminated for Tripti in August 2017. Instead, she is now undergoing therapy with Osimertinib – a drug that is designed to target cells with the *EGFR*^{T790M} mutation. As of November 2017, Tripti is responding well to the new treatment.

Monitoring Progression

Tracking the progression of possible resistance to Osimertinib as well as development of other genomic rearrangements is now possible using subsequent Liquid Biopsy tests.

Conclusions

- In Tripti's case, the prognostic technique that provided greater insight into her overall tumor load was the assessment of ctDNA in the liquid biopsy sample.
- Genetic analysis of the second lung cancer biopsy ALONE would have supported the continuation of Afatinib therapy, eventually leading to failure of therapy.
- An accurate assessment of overall tumor burden as well as the emerging dominance of the *EGFR*^{T790M} mutation was provided by liquid biopsy based detection and quantification of ctDNA.
- Liquid biopsy tests can be performed, at physicians' discretion, without the encumbrance of radioactive tracers and specialized imaging equipment.
- Rapid change of therapy from one targeted therapy drug to the next appropriate one has improved the quality of life of the patient and provided further options for therapy. The combination of genetic analysis of the solid tumor and the liquid biopsy sample proved to be highly advantageous to the patient. If the liquid biopsy test had been overlooked, Tripti would have continued to receive ONLY Afatinib treatment with the result that Afatinib –resistant lung cancer cells would have continued to grow in her body. Massive metastasis would have increased her risk for fatality. Instead, the liquid biopsy results proved to be a warning, just in time. The comprehensive genetic profile of the tumor, in the lungs as well as from all over the body, was the deciding factor in the choice of another targeted therapy drug that increased her quality of life.

The parameter marked with an * are not accredited by NABL and CAP.

References

Facchinetti, F. et al., 2017. Mechanisms of Resistance to Target Therapies in Non-small Cell Lung Cancer. In Handbook of experimental pharmacology. Available at: http://www.ncbi.nlm.nih.gov/pubmed/28332047 [Accessed November 28, 2017].

Hou, H. et al., 2017. Discovery of targetable genetic alterations in advanced non-small cell lung cancer using a next-generation sequencing-based circulating tumor DNA assay. Scientific reports, 7(1), p.14605. Available at: http://www.ncbi.nlm.nih.gov/pubmed/29097733 [Accessed November 21, 2017].

Marmarelis, M. et al., 2017. Emerging uses of circulating tumor DNA in advanced stage non-small cell lung cancer. Annals of translational medicine, 5(18), p.380. Available at: http://www.ncbi.nlm.nih.gov/pubmed/29057240 [Accessed November 22, 2017].

Murali, A.N. et al., 2017. Outcomes in Lung Cancer: 9-Year Experience From a Tertiary Cancer Center in India. Journal of Global Oncology, 3(5), pp.459–468. Available at: http://www.ncbi.nlm.nih.gov/pubmed/29094084 [Accessed November 27, 2017].

Takiar, R. & Jayant, K., 2013. A model approach to calculate cancer prevalence from 5 year survival data for selected cancer sites in India. Asian Pacific journal of cancer prevention: APJCP, 14(11), pp.6899–903. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24377623 [Accessed November 20, 2017].

Vendrell, J. et al., 2017. Circulating Cell Free Tumor DNA Detection as a Routine Tool forLung Cancer Patient Management. International Journal of Molecular Sciences, 18(2), p.264. Available at: http://www.mdpi.com/1422-0067/18/2/264 [Accessed March 13, 2017].

Xiong, L. et al., 2017. Dynamics of EGFR mutations in plasma recapitulates the clinical response to EGFR-TKIs in NSCLC patients. Oncotarget, 8(38), pp.63846–63856. Available at: http://www.ncbi.nlm.nih.gov/pubmed/28969034 [Accessed November 28, 2017].

Strand Life Sciences Pvt. Ltd.
5th Floor, Kirloskar Business Park, Bellary Road, Hebbal, Bangalore - 560 024
Phone: 1800-1022-695, support.strandx@strandls.com, www.strandls.com

#StayAheadOfCancer

Strand Center for Genomics & Personalized Medicine is accredited by

CAP ACCREDITED COLLEGE of AMERICAN PATHOLOGISTS # 8750941

Certificate No. MC-2434

Strand ID: LB-47403012018