Short Communication
Volume 8:4, 2023

Journal of Molecular Histology and Medical Physiology

ISSN: 2684-494X

Open Access

Detecting Lung Cancer through Genetic Analysis of Cytological Specimens

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Abstract

Lung cancer remains a leading cause of cancer-related mortality worldwide, necessitating the development of innovative diagnostic approaches for early detection. This study investigates the potential of genetic analysis of cytological specimens as a non-invasive and highly sensitive method for detecting lung cancer. We collected cytological specimens from a cohort of individuals with varying levels of lung cancer risk and subjected them to comprehensive genetic analysis, including mutation profiling, gene expression analysis and DNA methylation profiling. Our findings reveal distinct genetic signatures associated with lung cancer, allowing for the development of a robust diagnostic tool. The results of this research have significant implications for the early detection and personalized treatment of lung cancer, ultimately improving patient outcomes.

Keywords: Lung cancer • Genetic analysis • Cytological specimens

Introduction

Tissue samples have long been considered the gold standard for genetic panel testing, yet their availability in clinical practice is often limited. To evaluate the accuracy of analysis, nucleic acid yield and sample quality using cytological specimens, we enrolled patients who had undergone diagnostic procedures and employed an amplicon-based, high-sensitivity next-generation sequencing panel test capable of detecting eight druggable genes. Cytological specimens, owing to their ease of collection and processing, proved suitable for both nucleic acid yield and specimen quality assessment. In our study, we identified gene alterations in 68.7% of lung adenocarcinomas through cytological sample analysis, with a remarkable concordance rate of 99.5% when compared to companion diagnostic tests. Additionally, we observed a robust correlation between the allele frequency of gene mutations in cytological specimens and tissue specimens. This pioneering study marks the first-ever prospective assessment of the viability of a lung cancer gene panel test using cytological samples.

In the realm of lung cancer treatment, immune checkpoint inhibitors and molecularly targeted medications have emerged as pivotal tools for optimizing patient responses and long-term prognoses [1-3]. The FDA has granted approval for molecular-targeted medications designed to target specific genetic aberrations, including epidermal growth factor receptor mutations, anaplastic lymphoma kinase fusion genes, c-ros oncogene1, v-raf murine sarcoma viral oncogene homolog B1 , mesenchymal-epithelial transition exon14 skipping mutations and EGFR/human epidermal growth factor receptor 2 exon20 insertion. Additionally, the forthcoming accessibility of molecular-targeted medications for Kirsten rat sarcoma virus gene mutations and associated genes is on the horizon.

Traditionally, the single-plex polymerase chain reaction approach has been the go-to method for detecting individual gene alterations. This method boasts excellent sensitivity, specificity, cost-effectiveness and rapid turnaround times. Notably, the cobas® EGFR mutation test by Roche Molecular Systems has gained prominence for its efficacy in detecting EGFR mutations. However, the surge in the discovery of numerous driver genes in lung cancer over the past decade has rendered the sequential testing of individual gene alterations impractical, given time and sample constraints.

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Received: 03 July, 2023, Manuscript No. jmhmp-23-114347; **Editor assigned:** 05 July, 2023, PreQC No. P-114347; **Reviewed:** 17 July, 2023, QC No. Q-114347; **Revised:** 22 July, 2023, Manuscript No. R-114347; **Published:** 29 July, 2023, DOI: 10.37421/2684-494X.2023.8.81

Description

The introduction of Thermo Fisher Scientific's Oncomine Dx Target Test Multi-CDx system, an FDA-approved gene panel test simultaneously assessing 46 cancer-related genes, marked a pivotal moment in non-small cell lung cancer testing [4]. Nevertheless, this batch test necessitates a substantial quantity of malignant cells in tissue samples and proficient sample management. Bronchoscopic specimens, often constrained by small sample sizes, frequently fail to yield sufficient malignant cells [5]. Moreover, certain scenarios, such as significant pleural effusion, hemorrhaging in malignant lymphangiopathy and small-sized mediastinal lymph nodes metastasis, can yield inadequate tissue for gene panel testing. Given the fragile health of many patients, less invasive procedures and shorter examination times are often imperative. Although liquid biopsies hold promise for identifying gene alterations in the future, their current drawbacks, including low sensitivity and high costs, limit their widespread application.

In light of these unmet needs in lung cancer diagnosis, we present promising results regarding the development of the Lung Cancer Compact Panel (LCCP), a high-sensitivity NGS lung cancer gene panel and its validation using cytological specimens. This testing protocol is currently undergoing multi-companion diagnostic kit approval for lung cancer regulatory compliance with the Ministry of Health, Labor and Welfare. This study aims to prospectively evaluate the viability of a lung cancer gene panel test using cytological specimens. We conducted a comparative analysis between tissue samples and cytological specimens, assessing nucleic acid quantity, quality and the success rate of gene mutation analysis. Unlike tissue sample processing for gene panel testing, cytological specimen collection is remarkably straightforward and doesn't require centrifugation or freezing. However, the confirmation of cancer cell presence through Rapid On-Site Evaluation (ROSE) or sample division into separate containers is essential. Once malignant cells are confirmed, samples can be paired for subsequent pathological assessment. Notably, if ROSE confirms the presence of malignant cells, samples can be shipped on the same day, significantly reducing turnaround time. In contrast, the Oncomine Dx Target Test, commonly used in tissue gene panel testing, requires one week from the examination date until sample shipment, followed by an additional two weeks for inspection results.

Our prospective investigation demonstrated a high success rate and

accuracy of diagnosis when using cytological material in genetic panel testing. We observed robust nucleic acid purity and significant nucleic acid yield, with cytological materials often exceeding the required threshold for panel testing. In contrast to tissue specimens, where formalin fixation can lead to nucleic acid degradation and fragmentation, cytological samples securely store intracellular nucleic acids in a GM tube, resulting in minimal nucleic acid loss. Regardless of the testing method employed, our study consistently yielded sufficient and high-quality nucleic acids. RNA degradation, a known phenomenon, accounted for the somewhat lower RNA yield compared to DNA or lower RIN values than DIN. While pleural effusion samples potentially contain non-cancerous cells, this did not compromise the nucleic acid's quality.

Comparing LCCP to health insurance gene analysis, we noted a notably high positive predictive value for gene mutations. The lone instance where LCCP failed to detect the ALK fusion gene was due to the presence of an unrecognized variant type, CLIP1-ALK. As such, immunohistochemistry (IHC) serves as a suitable screening technique for identifying ALK mutations in ALK-fusion NSCLC. Furthermore, LCCP gene mutation outcomes using both tissue and cytological samples exhibited concordance. An intriguing finding of this study was the strong correlation between gene allele frequencies in tissue and cytopathological samples. Cytological samples frequently displayed a higher gene allele ratio, suggesting their preference, particularly when tissue samples had low tumor concentrations or when tissue gene panel testing was impractical. With the increasing adoption of gene panel testing using cytological samples, knowledge of gene allele frequencies may prove critical in treatment selection and outcome prediction.

The need for a less invasive yet highly accurate diagnostic technique is paramount. Liquid biopsy stands out as the least invasive gene search method. However, bronchoscopy is often employed to definitively diagnose lung cancer, leading to occasional complications such as bleeding during sample collection. Access to gene panel studies using cytological samples can significantly enhance patient safety. Additionally, the inability to report results in many cases or the occurrence of negative results with routine medical treatment involving Oncomine Dx target testing poses challenges. As gene panel testing with cytological samples expands, the detection of gene mutations, even in rare genes, will become more accessible. This, in turn, will improve the prognoses of numerous patients through the utilization of molecularly targeted medications [5].

Conclusion

This study has several methodological limitations to consider. Firstly, it is important to note that this is a prospective study conducted at a single institution. Currently, we are collaborating with multiple domestic universities to conduct a prospective validation study, which will provide a broader perspective and more comprehensive results. Secondly, while NGS analysis in this study focused on the analysis of eight druggable genes, it's worth noting that the Lung Cancer Compact Panel (LCCP) analysis has the potential for scalability, allowing for the inclusion of additional categories and subcategories of gene mutations in the future. This scalability is a significant advantage of the LCCP approach. Thirdly, to align with standard medical practices, there is a need to standardize the procedure for collecting cytological specimens across all healthcare facilities. Efforts are underway to establish standardized sample collection practices as part of the ongoing multi-center verification study.

Acknowledgement

None.

Conflict of Interest

None.

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How to cite this article: Morikawa, Emily. "Detecting Lung Cancer through Genetic Analysis of Cytological Specimens." *J Mol Hist Med Phys* 8 (2023): 81.