Short Communication
Volume 7:3, 2022

Journal of Molecular Histology and Medical Physiology

ISSN: 2684-494X

Open Access

Diagnosis of Lung Cancer of Gene Analysis using Cytological Specimens

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Introduction

Tissue samples are regarded as the gold standard for genetic panel test samples. However, tissue samples are frequently not available in clinical practise. In order to assess analytical accuracy, nucleic acid yield, and quality utilising cytological specimens, we included patients who had diagnostic procedures and used an amplicon-based high-sensitivity next-generation sequencing panel test capable of detecting eight druggable genes. Due to their simplicity in collection and processing, cytological specimens were suitable for both nucleic acid yield and specimen quality. In 68.7% of lung adenocarcinomas, gene alterations were found through cytological sample analysis, and 99.5% of the time, these samples matched the results of companion diagnostic tests. Additionally, there was a strong association between the allele frequency of gene mutations in cytological specimens and tissue specimens. This is the first study to use cytological samples to prospectively assess the viability of a lung cancer gene panel test.

Description

Immune checkpoint inhibitors and molecularly targeted medications are frequently used in personalised treatment for lung cancer in order to maximise response and long-term prognosis [1-3]. The Food and Drug Administration has so far approved molecular-targeted medications for epidermal growth factor receptor (EGFR) mutation, Anaplastic Lymphoma Kinase (ALK) fusion genes, c-ros oncogene1 (ROS1), v-raf murine sarcoma viral oncogene homolog B1 (BRAF), mesenchymal-epithelial transition (MET) exon14 skipping mutations, and (FDA). EGFR/Human Epidermal Growth Factor Receptor 2 (HER2) exon20 insertion, Kirsten rat sarcoma virus gene (KRAS) mutation, and their related molecular-targeted medications will also soon be accessible.

Traditionally, the single-plex Polymerase Chain Reaction (PCR) approach has been used to detect individual gene changes. This method has good sensitivity and specificity, is relatively cheap, and has a quick turn-around time (TAT). This technique has gained a lot of popularity, primarily for the cobas® EGFR mutation test's ability to detect EGFR mutations (Roche Molecular Systems, Pleasanton, CA, USA). Due to time and sample consumption restrictions, it is not viable to test successive single gene alterations one after the other due to the discovery of numerous lung cancer driver genes in the last ten years. Thermo Fisher Scientific's Oncomine Dx Target Test Multi-CDx system, a gene panel test that simultaneously assesses 46 cancer-related genes, was approved by the FDA in 2017 and is one of the first next-generation sequencing (NGS) panels for non-small cell lung cancer testing [4]. However, this batch test needs a substantial number of malignant cells in the tissue samples that were taken, as well as expert sample management. Due to the tiny sample sizes, specimens obtained via a bronchoscope frequently fail to produce enough malignant cells [5]. Additionally, in some circumstances, insufficient tissue can be obtained to conduct gene batch testing. Examples include significant pleural effusion, malignant lymphangiopathy that bleeds upon examination, and small-sized mediastinal lymph nodes metastasis. Due to the patients' generally poor health, less intrusive procedures and shorter examination times might be necessary. It is anticipated that more cases in the future will allow liquid biopsy to discover gene alterations. However, given their low sensitivity and high cost of use right now, liquid panel tests might not be the best option.

These aforementioned unmet needs for gene batch testing in lung cancer diagnosis exist in practical practise. As a result, we present encouraging findings regarding the creation of the lung cancer compact panel (LCCP), a high-sensitivity NGS lung cancer gene panel, and its use for cytological materials as a prospective validation study. This testing procedure is currently being used as a multi-companion diagnostic kit for lung cancer regulatory affairs with the Ministry of Health, Labor, and Welfare.

In this study, cytological specimens are used to prospectively assess the viability of a lung cancer gene panel test. By comparing tissue samples, we evaluated cytological specimens for nucleic acid quantity and quality as well as gene mutation analysis success rate.

First off, in contrast to the processing of tissue samples for gene panel testing, the sample collecting method is incredibly straightforward and does not call for centrifugation or freezing. However, in order to determine whether the GM tube contains cancer cells, ROSE must be performed simultaneously or the sample must be split into two distinct containers. Once the presence of malignant cells has been determined, the samples must be paired for subsequent pathological assessment. It is feasible to ship the sample on the day of the test, which significantly cuts down on turnaround time, if malignant cells can be confirmed with the ROSE method, in particular. On the other hand, it takes the Oncomine Dx target test [4], which is frequently used in tissue gene panel testing, one week from the day of the examination until the sample is shipped, and an additional two weeks after the sample is submitted for the inspection findings.

This prospective investigation found that cytological material used in genetic panel tests had a high success rate and rate of correct diagnosis. High nucleic acid purity and a significant nucleic acid yield confirmed these findings. For panel testing in tissue biopsy, a nucleic acid output of 10 ng is required [4], while for cytological materials, the nucleic acid yield typically far exceeded the need. Contrarily, cytological specimens occasionally exhibited an adequate output of nucleic acids when compared to tissue specimens. While it is thought that during the formalin fixation process of tissue specimens, nucleic acid deterioration and fragmentation frequently occur, resulting in a reduction in nucleic acid yield, in cytological samples, the collected intracellular nucleic acid is stored safely in a GM tube, resulting in little loss for nucleic acid yield.

No matter the test method used in this investigation, sufficient and high-quality nucleic acid yields were produced. The quick degradation of RNA is thought to be the reason why the yield of RNA is somewhat lower than that of DNA or that the RIN value is lower than that of DIN. Although it is believed that cells other than cancer cells are to blame for the high nucleic acid yield of pleural effusion, it is also true that the nucleic acid's quality is quite high.

Between LCCP and health insurance gene analysis, the positive predictive

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Date of Submission: 03 May, 2022; Manuscript No: jmhmp-22-73987; **Editor assigned:** 05 May, 2022, PreQC No: P-73987; **Reviewed:** 17 May, 2022, QC No: Q-73987; **Revised:** 22 May, 2022, Manuscript No: R-73987; **Published:** 29 May, 2022, DOI: 10.37421/2684-494X.2022.7.36.

value of gene mutations was quite high. Due to the uncommon ALK fusion mutation CLIP1-ALK, which was not acknowledged as a detectable variant type, the ALK fusion gene was not discovered by LCCP in only one instance. Therefore, immunohistochemistry (IHC) is a suitable screening technique for finding ALK mutations in ALK-fusion NSCLC. Additionally, the outcomes of LCCP gene mutation using tissue samples and cytological samples agreed with one another.

It is also interesting that this study found a strong association between the frequency of gene alleles found in tissue specimens and cytopathological samples. A larger gene allele ratio was found in the cytological sample, and it was thought that the cytological sample was preferable, in particular when the tumour concentration was low in tissue samples, or in circumstances when the tissue gene panel test was inappropriate. There have been reports of several gene mutations being expressed as the number of gene batch tests rises. Therefore, knowledge of gene allele frequency may be crucial for both choosing treatments and predicting their outcomes.

Currently, a less intrusive and extremely accurate inspection technique is needed. Liquid biopsy is without a doubt the least intrusive gene search method. However, because bronchoscopy is frequently employed to make a conclusive diagnosis of lung cancer, we frequently encounter negative outcomes, such bleeding when taking samples. Patient safety can be significantly improved by having access to gene panel studies on cytological samples. The fact that many instances cannot be reported or that test results for Oncomine Dx target testing in routine medical treatment are negative is also problematic. An increase in gene mutations, even those in rare genes, will be easier to identify with the growth of gene panel testing employing cytological samples. As a result, many patients' prognoses will be improved by the use of molecularly targeted medications [1].

Conclusion

This study's methodological restrictions include the fact that it is a prospective study at a single institution. We are currently working at several domestic universities on a prospective verification study. In spite of being a gene batch test, NGS analysis is only able to analyse eight druggable genes. However, LCCP is a method of analysis that can eventually include more categories and subcategories of gene mutations because it is scalable in terms of mutation measurement items. Third, in order to be consistent with routine medical care, the procedure for gathering cytological specimens must be standardised across all facilities. Additionally, there are plans to standardise sample collecting practises for the ongoing multi-center study's verification.

Conflict of Interest

None.

References

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How to cite this article: Morikawa, Emily. “Diagnosis of Lung Cancer of Gene analysis using Cytological Specimens.” J Mol Hist Med Phys 7 (2022): 36.