P2.203: A Dual-Compartment Multi-Omics Liquid Biopsy Strategy Enhances Tumor DNA Detection in Operable Early-Stage Lung Cancer

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INTRODUCTION

In early-stage lung cancer, limited circulating tumor DNA (ctDNA) shedding constrains the sensitivity of plasma ctDNA–based mutation detection.

We investigated whether genomic analysis of DNA derived from circulating tumor cells (CTC) isolated using the highly sensitive ISET platform could enhance tumor DNA detection in operable early-stage lung cancers.

METHODS

Design:

50 patients undergoing surgery for lung cancer at Gemelli Hospital (Rome, Italy) were prospectively enrolled. Among them, 30 were stage I, 14 stage II, 4 stage III, and 2 stage IVa ; 42 adenocarcinoma, 4 squamous carcinoma, 2 large-cell neuroendocrine carcinoma, and 2 carcinoid tumors. **The primary endpoint was comparison of variants detection using CTC-derived DNA (CTC-DNA) and plasma ctDNA using an identical next-generation sequencing (NGS) workflow**. Peripheral blood (10 mL) was collected in Streck tubes. Plasma (2 mL) was used for cfDNA extraction, and CTCs were isolated using the ISET platform followed by bulk CTC-DNA extraction. Matched tumor tissue and leukocyte DNA were obtained. Dual-indexed, UMI-enabled libraries were prepared and subjected to high-depth targeted Illumina sequencing optimized for low variant allele frequency detection. Variants were filtered using quality, depth, population frequency, and functional annotation criteria, with additional filtering using an in-house panel of normals and public variant databases to remove artefacts and germline events. Clinically relevant variants were annotated using established cancer knowledgebases.

RESULTS

Clinically relevant variants were detected in **70% (35/50)** of patients using CTC-DNA, **46% (23/50)** using ctDNA, and **82% (41/50)** using combined CTC-DNA + ctDNA (Figure 1). In stage I patients, detection rates were **70% (21/30), 50% (15/30), and 80% (24/30)**, respectively, with similar results in stage II disease (Figure 2).
In adenocarcinoma, detection rates were **69% (30/42), 52.4% (22/42), and 83.3% (35/42)** for CTC-DNA, ctDNA, and combined analysis, respectively; corresponding rates in squamous carcinoma were **100% (4/4), 25% (1/4), and 100% (4/4)** (Figure 3).
CTC-DNA yielded substantially more clinically relevant variants than ctDNA (**82 vs 30**). Overall, **112 variants were detected by liquid biopsy versus 113 in tumor tissue**. Most liquid-biopsy variants had very low VAFs (**<1%**), whereas tumor-tissue variants showed higher VAFs (median 1.8%; mean 7.6%; IQR 0.36–12.9%).

Figure 1

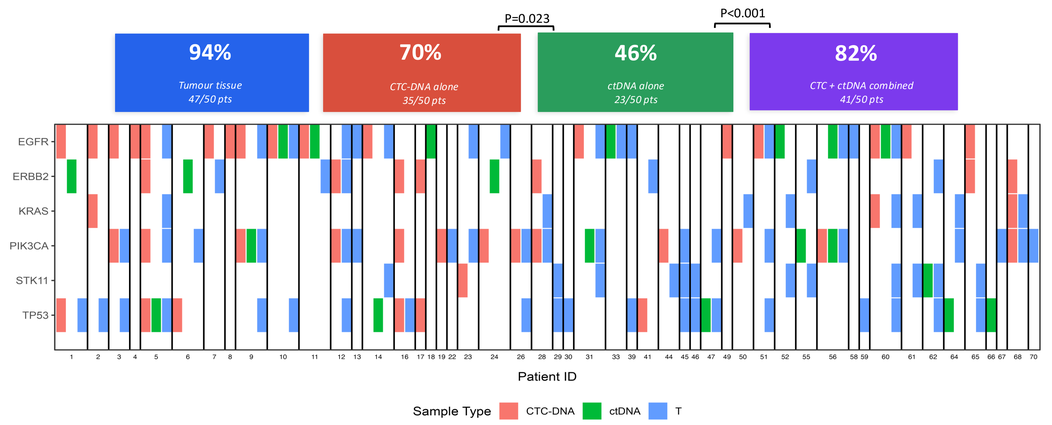


Figure 2

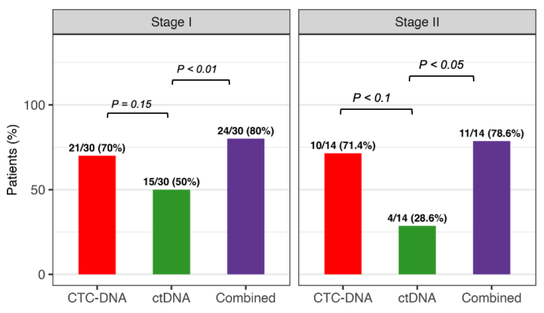
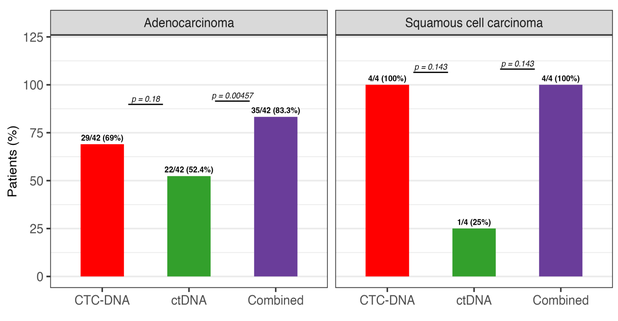


Figure 3



DISCUSSION AND CONCLUSION

Actionable Take Away Message

- In operable lung cancer, CTC-DNA analysis following hypersensitive CTC isolation using ISET showed statistically significant higher sensitivity than plasma ctDNA and provided complementary information on tumor heterogeneity.
- Combining CTC-DNA and ctDNA improved clinically relevant variants detection across stages and histological subtypes, including in the the most challenging stage I and adenocarcinoma histology.

Future Direction for Research

These findings support further evaluation of multi-compartment scalable liquid biopsy strategies to enhance variants detection in early-stage lung cancer, where ctDNA-only approaches remain limited.

REFERENCES & ACKNOWLEDGEMENTS