High-Sensitivity ctDNA Analysis Uncovers Relevant Signals Missed by Next-Generation Sequencing in Pancreatic Cancer

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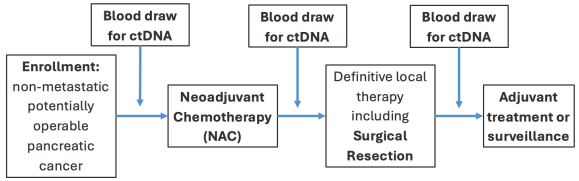
Background

- Pancreatic ductal adenocarcinoma (PDAC) is the third leading cause of cancer-related death in the United States.[1]
- Circulating tumor DNA (ctDNA) is a promising blood-based biomarker with prognostic relevance in various cancers, but its clinical utility in localized PDAC remains unclear.[2]

Research Objectives

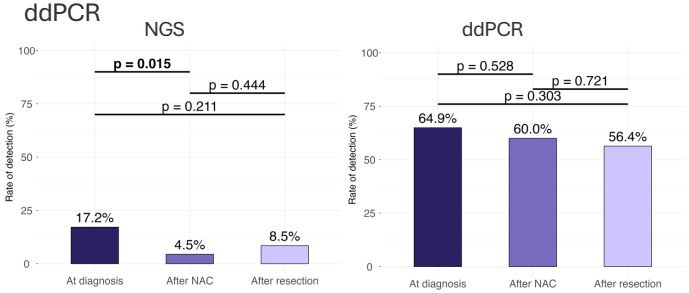
The primary objective was to evaluate the prognostic significance of *KRAS*-mutant circulating tumor DNA (ctDNA) detected by next-generation sequencing (NGS) and digital droplet PCR (ddPCR) in localized PDAC.

Methods



- Patients with localized PDAC were enrolled in a prospective study at Northwestern Medicine between October 2020 and October 2024.
- Samples underwent commercial, tumor-agnostic NGS and ddPCR targeting *KRAS* G12D/V/R mutations .
- Analyses were conducted using RStudio.

Figure 1: *KRAS* ctDNA detection rates by NGS and ddPCR



- ddPCR had higher ctDNA detection rates, while NGS-detected ctDNA decreased over treatment

Figure 2: Overall survival stratified by *KRAS*-specific ctDNA detection by NGS and ddPCR

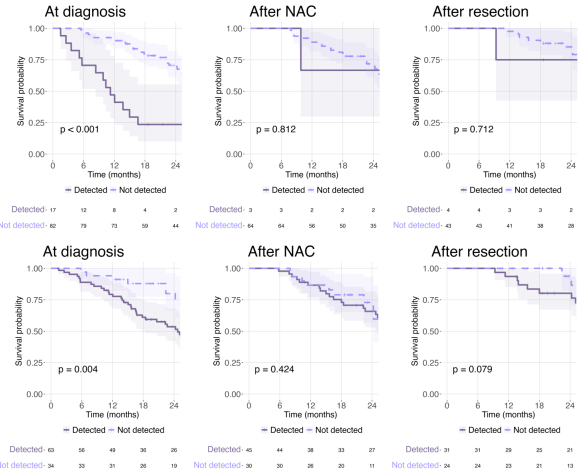
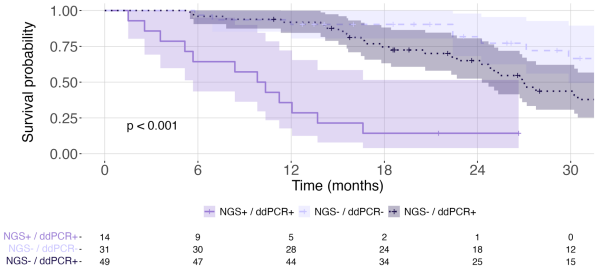


Figure 3: Overall survival by combined NGS and ddPCR status



Limitations

- Modest sample size (106 patients)
- Limited follow-up time (median 22.4 months)
- Limited ability to conduct subgroup analyses

Conclusions

- Higher-sensitivity ctDNA assays may provide additional prognostic information not captured by standard NGS-based approaches
- ddPCR may identify an intermediate-risk subset of patients that could be candidates for *KRAS*-targeted therapies
- Integrating ddPCR with NGS may improve perioperative risk stratification

References

1. Owens DK, Davidson KW, Krist AH, et al. Screening for Pancreatic Cancer: US Preventive Services Task Force Reaffirmation Recommendation Statement. *Jama*. Aug 6 2019;322(5):438-444. doi:10.1001/jama.2019.10232
2. Dang DK, Park BH. Circulating tumor DNA: current challenges for clinical utility. *J Clin Invest*. Jun 15 2022;132(12)doi:10.1172/jci154941