Cell-free DNA Fragmentation Profiling for Monitoring Therapeutic Response in Metastatic Colorectal Cancer

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Disclosure Information

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I have the following relevant financial relationships to disclose:
Delfi Diagnostics, Inc.: Employee, Stock, Patent, and Other Intellectual Property

Introduction

- Measurement of mutant allele fraction (MAF) in cell-free DNA (cfDNA) via expensive target panels typically relies on prior tumor tissue analyses or knowledge of specific mutations
- There is an unmet need to develop an effective and inexpensive test to provide predictive information about treatment outcomes in patients receiving a variety of systemic therapies
- The DELFI Tumor Fraction approach (DELFI-TF) is a cfDNA fragmentome-based model capable of accurately detecting circulating tumor DNA fractions without needing genetic information about the tumor of origin
- Here, we evaluate the first version of the DELFI-TF approach for treatment response monitoring in patients with metastatic colorectal cancer (mCRC)

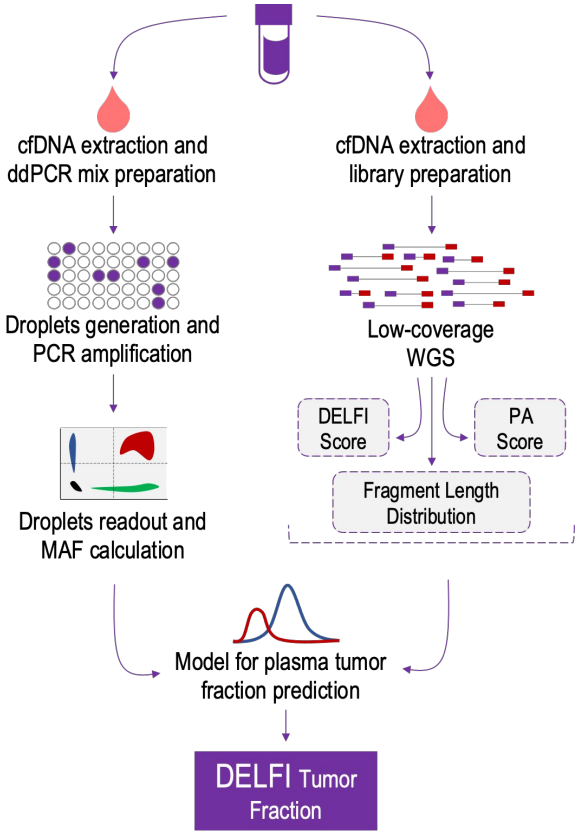
Clinical Cohort Description

- The current study is a planned exploratory analysis of longitudinal plasma samples from mCRC participants enrolled in the phase III study CAIRO5 (NCT02162563)[1]
- Study participants had their tumor tissue specimens genotyped for *KRAS* (exon 2, 3, and 4), *NRAS* (exon 2 and 3), and *BRAF* (codon 600) mutations before enrollment
- All available blood draws at the pre-treatment baseline and on-treatment timepoints were retrospectively processed
- Cell-free DNA tumor fraction was assessed as the mutant allele frequency (MAF) of the tumor-tissue-proven *RAS*/*BRAF* mutations measured by ddPCR
- An external cohort of non-cancer individuals was used for analytical reference [2]

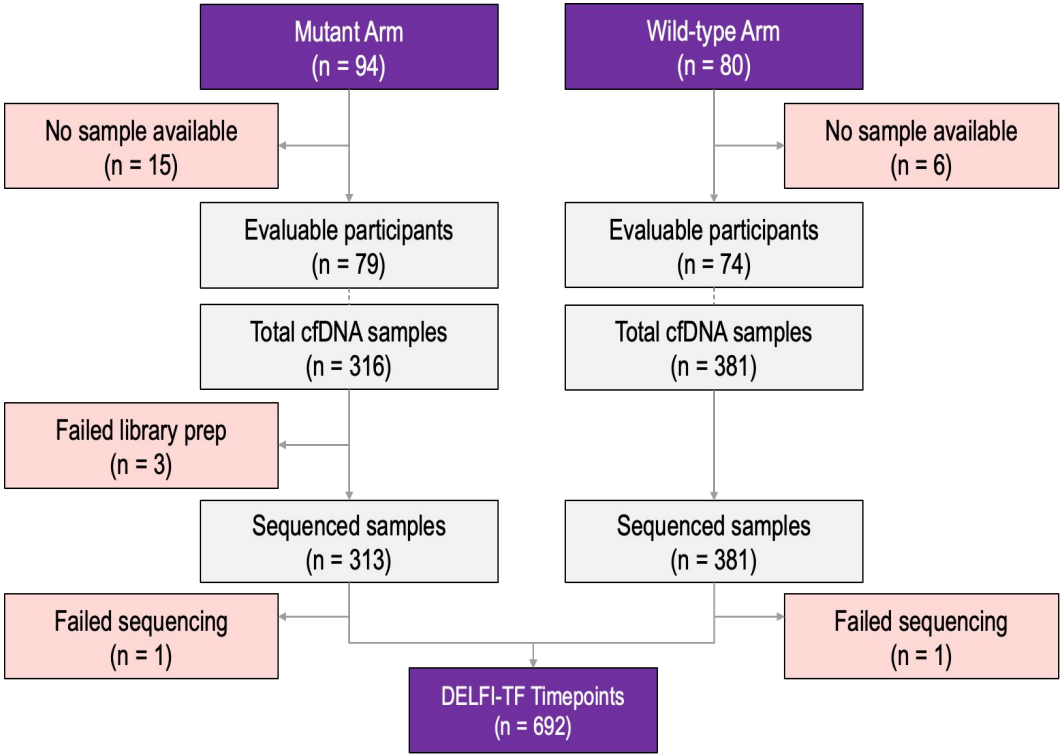
1. Huiskens, *et al*. *BMC Cancer*, 2015. 2. Mathios, *et al*. *Nat Commun*, 2021

Model Development

- Utilized cfDNA aliquots used for whole genome sequencing were obtained from the same plasma volumes used for ddPCR testing
- After aligning the low-coverage WGS data to the reference genome, fragment-based genomic features were obtained from 504 non-overlapping 5Mb bins
- A Bayesian regression model was trained and cross-validated against *RAS/BRAF* MAF using the DELFI scores, PA scores, and fragment length distribution weights
- DELFI-TF slope was defined as the slope of the regression line fitted to the DELFI-TF values across timepoints associated with the response assessment by RECIST1.1



Study Flowchart



DELFI-TF strongly correlates with ddPCR MAF in patients with RAS/BRAF mutant mCRC

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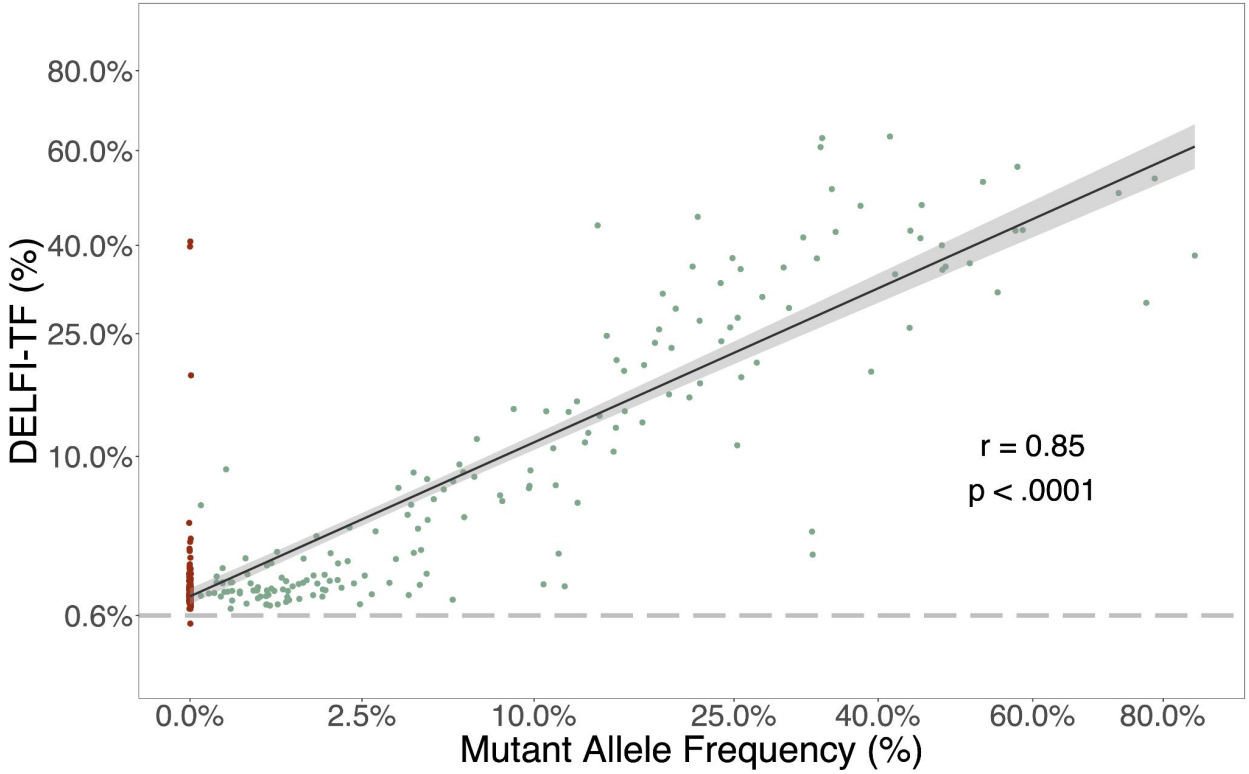

DELFI-TF Values Are High in Patients With Cancer and Reduced After Initiation of Therapy

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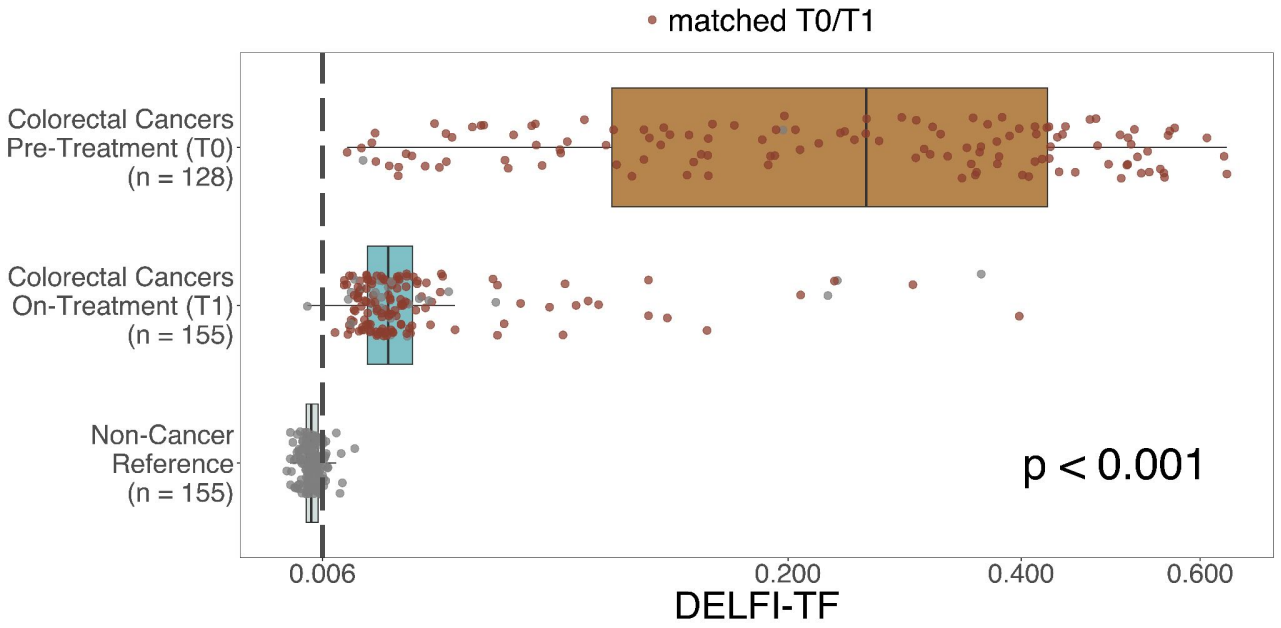

Fragmentation profiles show marked heterogeneity at pre-treatment and disease progression timepoints

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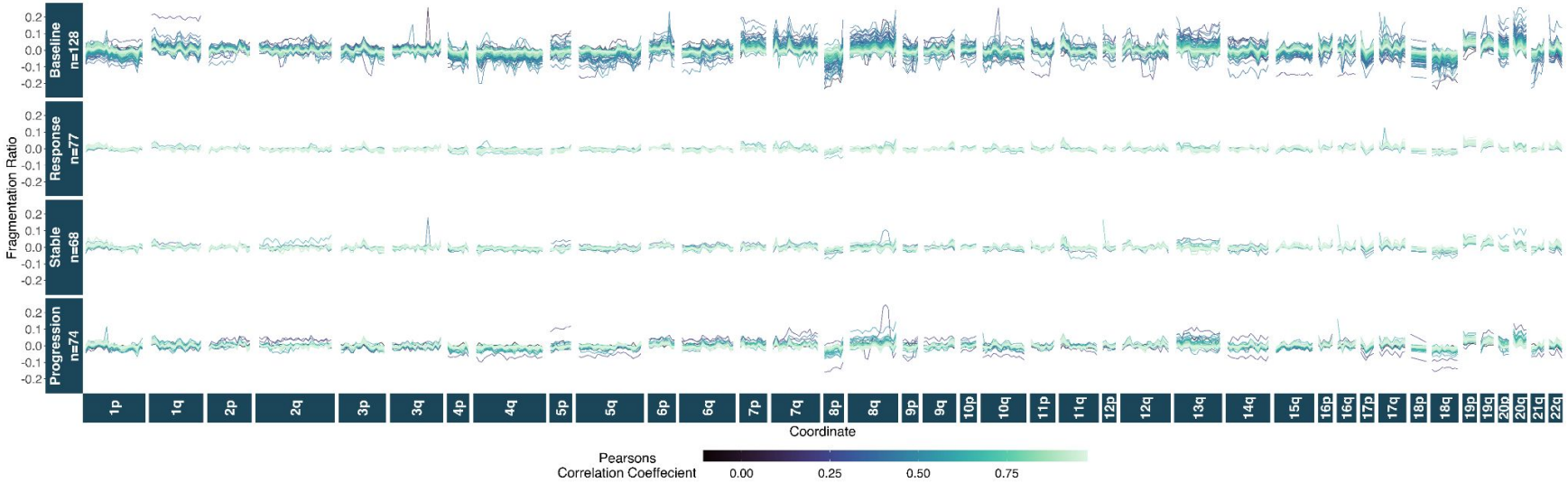

Fragmentation profiles exhibit aberrations even in the context of copy neutral regions in matched tissue

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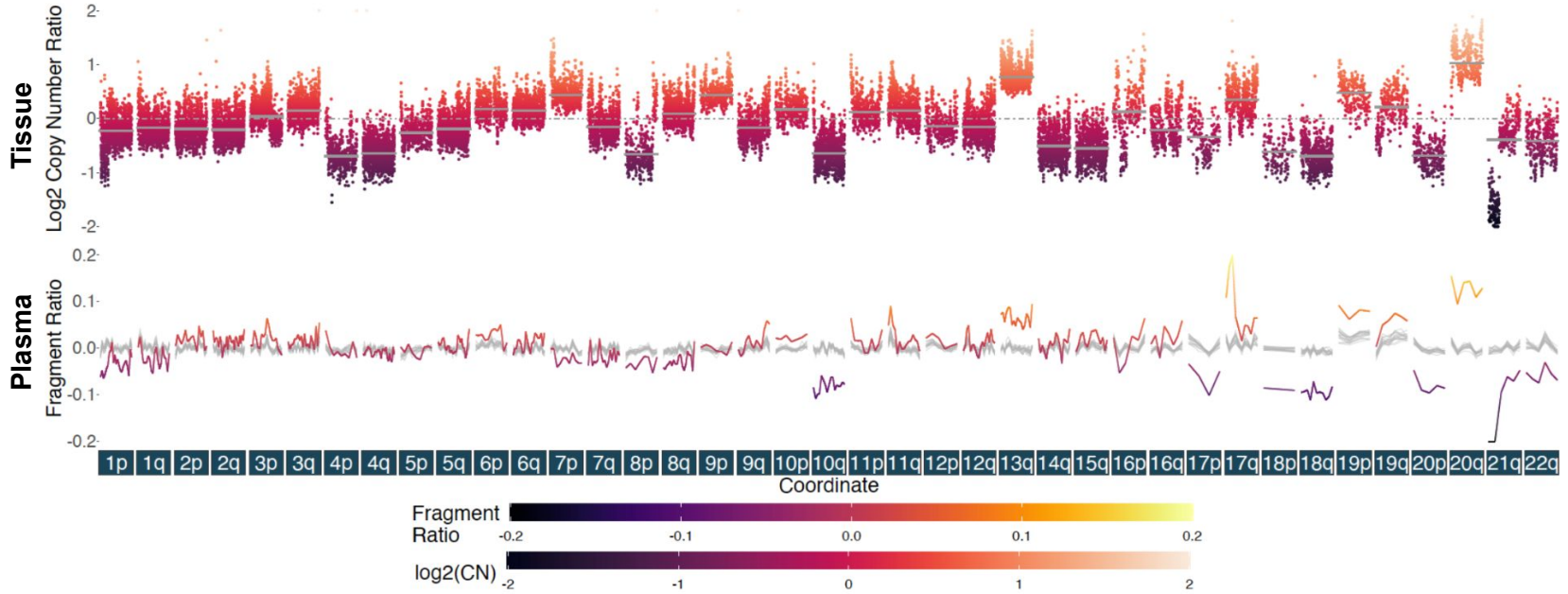

Baseline DELFI-TF and MAF are equivalent in predicting imaging response and resection status

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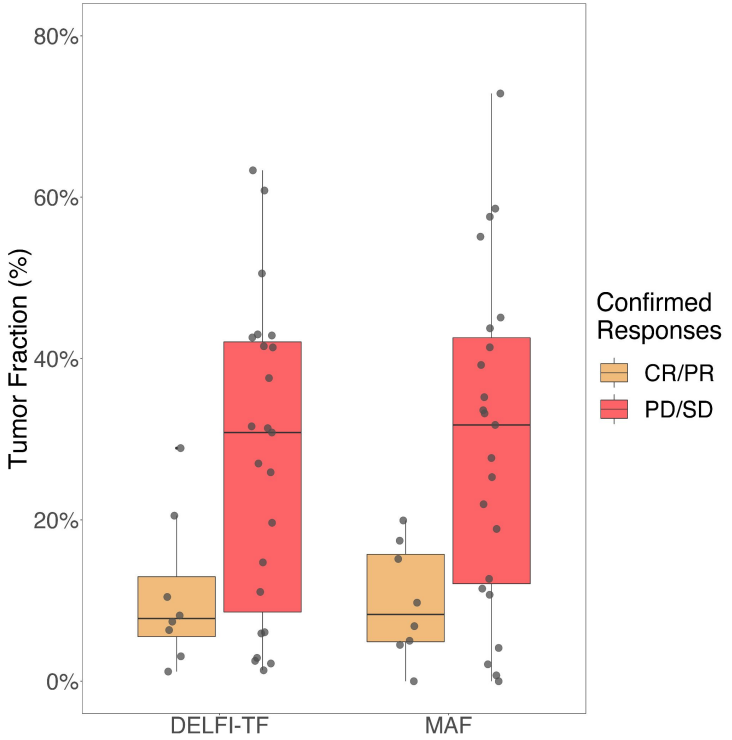

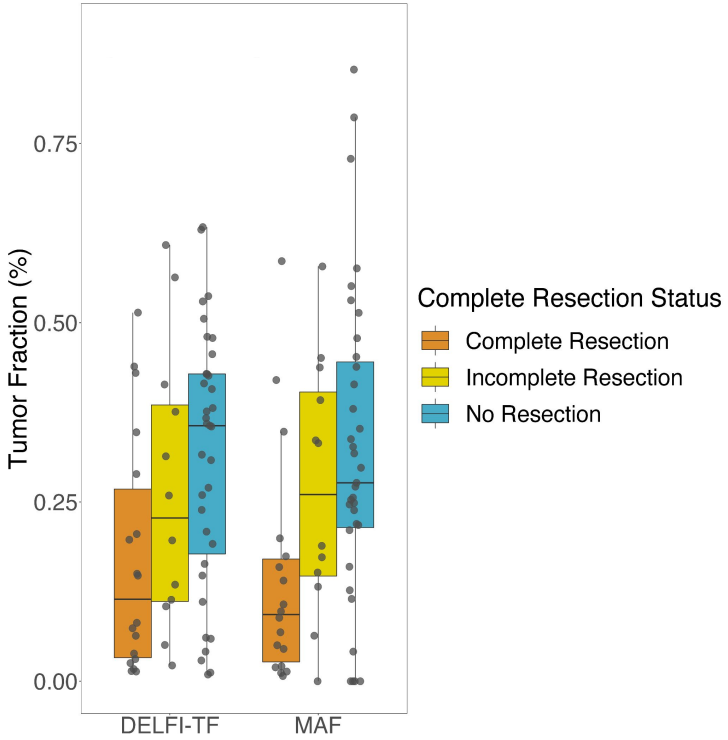

Baseline DELFI-TF and MAF analogously predict survival outcome in *RAS/BRAF* mutant patients

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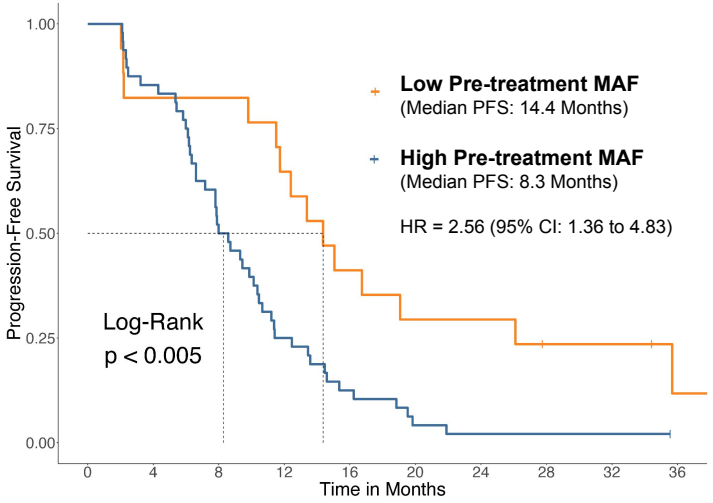
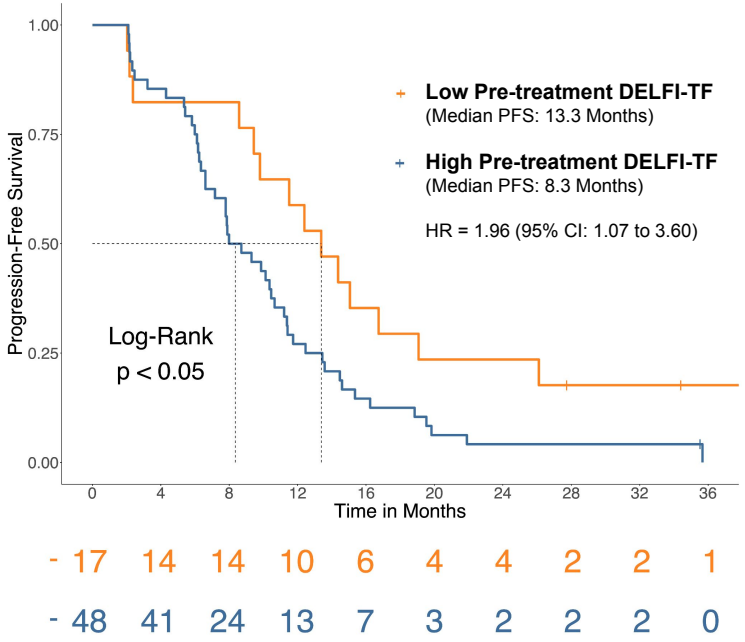
Pre-treatment MAF and DELFI-TF are categorized as Low (< first 25th %) and High (> first 25th %)





Case study: dynamic changes of DELFI-TF and MAF compared to imaging assessment

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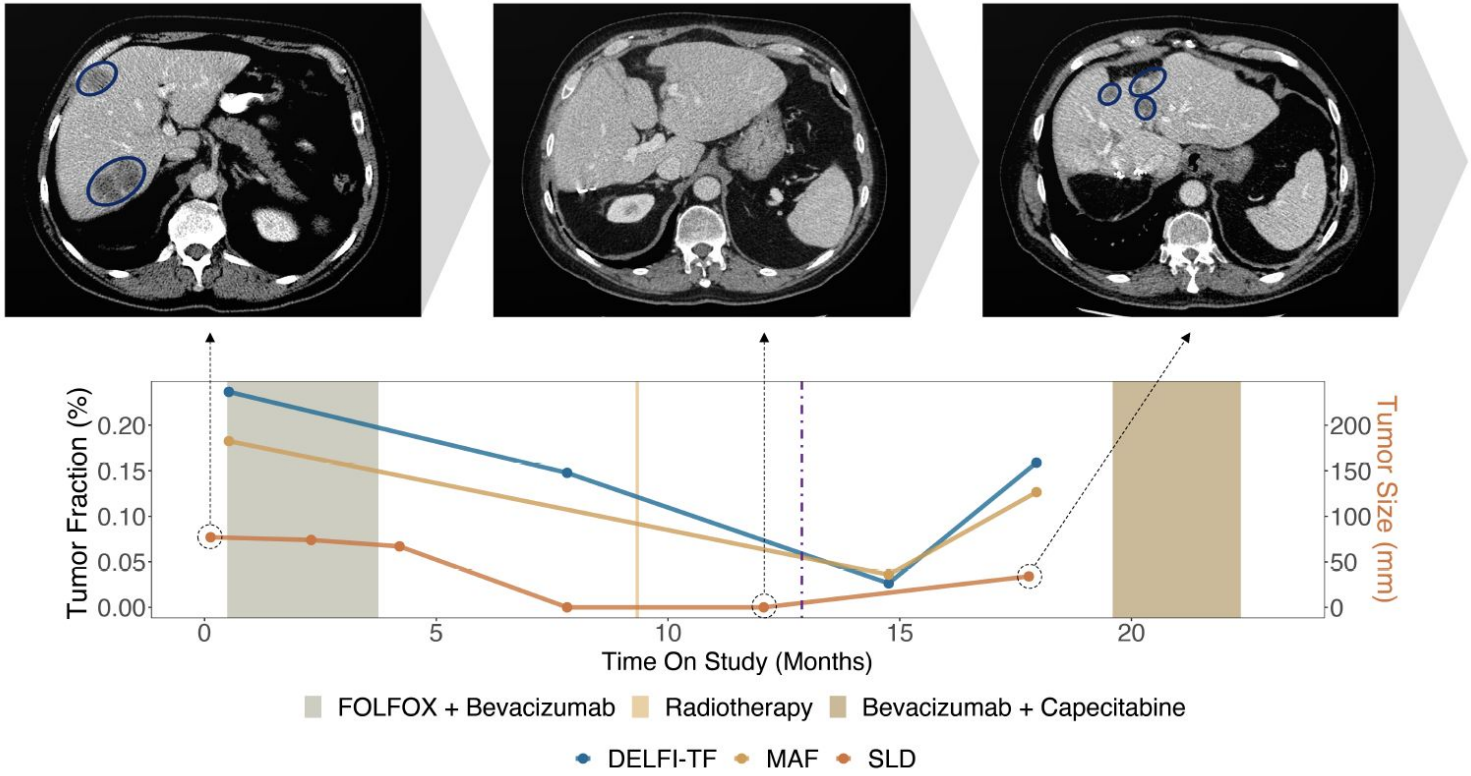

DELFI-TF dynamics predict survival outcomes in the overall study population

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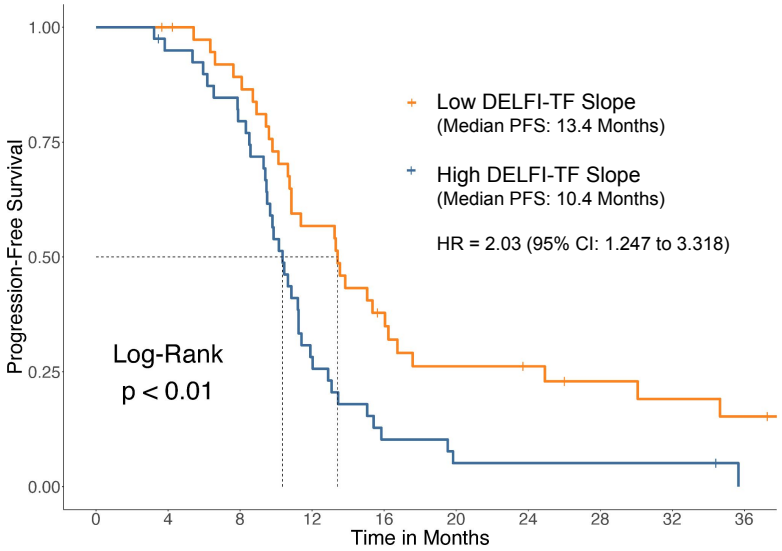
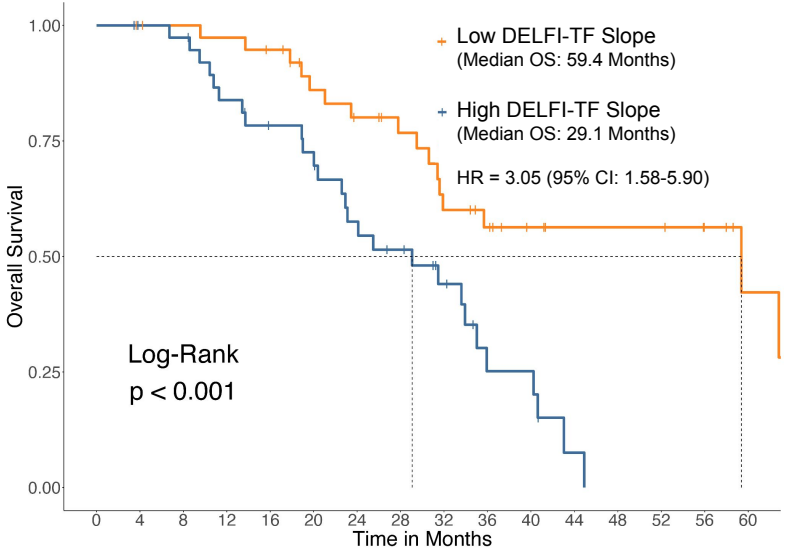
DELFI-TF slope is categorized as Low (below median) and High (above median)





Conclusions

- In this proof-of-concept study, we present DELFI-TF as a model that utilizes low-coverage whole genome sequencing and cfDNA fragment-based statistics to predict tumor fraction in a non-invasive manner
- DELFI-TF strongly correlates with standard MAF testing in patients with mCRC, allowing equivalent prediction of imaging response and liver metastases resection status
- Tumor fractions at baseline and their dynamic changes predicted by DELFI-TF correlate with survival outcomes in mCRC regardless of the presence of known driver mutations
- The development of a tissue-independent approach that does not rely on mutation detection has the potential to expand the use of tumor-agnostic models for both early and advanced disease monitoring

Acknowledgements

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