Analysis of Circulating Tumor DNA for Early Relapse Detection in Stage III Colorectal Cancer After Adjuvant Chemotherapy

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Background

- Circulating tumor DNA (ctDNA) has emerged as a promising biomarker for early prediction of relapse across different tumor types.[1-5]
- In patients with colorectal cancer (CRC), multiple studies have analyzed ctDNA to monitor tumor burden using fixed gene panels and droplet digital PCR.[6]
- Here we use a highly sensitive and specific, bespoke, whole exome-based next generation sequencing (NGS) approach (Signatera™) for ctDNA monitoring.

Methods

- The study included a cohort of 33 patients (16 males and 17 females) with a median age of 56 (32-73) years stage III CRC who underwent surgery and were treated with at least 4 months of adjuvant chemotherapy.
- Plasma samples were collected during extended adjuvant therapy.
- Mutational profiles derived from primary tumor tissue and germline DNA whole exome were used to design assays targeting tumor-specific somatic variants.
- The bespoke assays were used for ctDNA detection in plasma samples. Relapse-free survival (RFS) was calculated for patients stratified by ctDNA status

Figure 1. Signatera Molecular Protocol

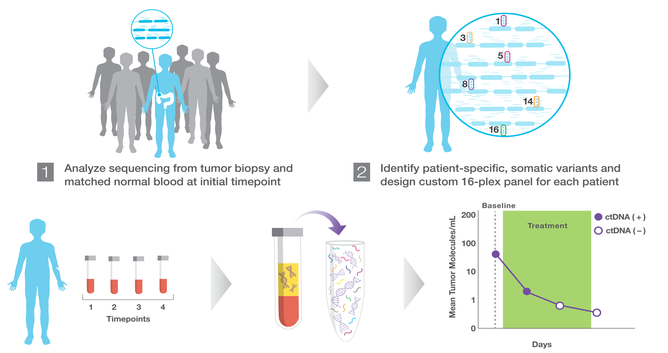
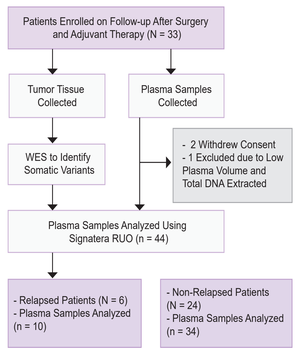


Table 1. Patient Demographics

Characteristics	Patients (N = 33)	ctDNA-Positive	ctDNA-Negative
Clinical Disease Stage, n (%)			
IIIB	20 (60)	4 (20)	16 (80)
IIIC	13 (40)	1 (8)	12 (92)
Pathologic T stage, n (%)			
T3	19 (59)	3 (16)	16 (84)
T4a	10 (29)	1 (10)	9 (90)
T4b	4 (12)	1 (25)	3 (75)
Pathologic N stage, n (%)			
N0	2 (6)	0	2 (100)
N1	13 (40)	4 (31)	9 (69)
N2	18 (54)	1 (6)	17 (94)
Recurrence at Any Site, n (%)			
Yes	6 (20)	3 (50)	3 (50)
No	24 (80)	0	24 (100)

Figure 2. Study Design



N, number of patients; n, number of plasma samples

Figure 3. Patient Overview and Patient-Specific Plots

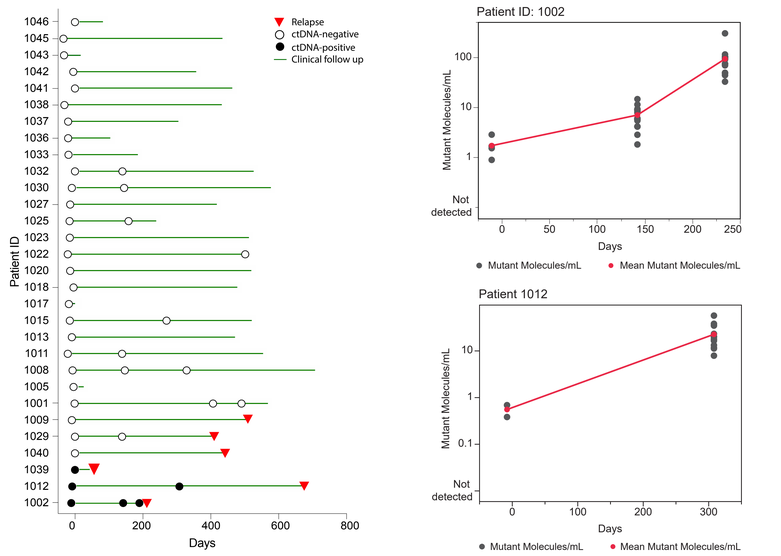


Figure 3. (Left) Plasma samples (n = 44; average volume = 1.8 mL) from patients (N = 33) collected during extended adjuvant treatment were analyzed for the presence of ctDNA. (Right) Of the five ctDNA-positive patients, clinical follow-up was available for three patients, all of whom relapsed (100%; 3/3); three of 27 ctDNA-negative patients (11%) also clinically relapsed.

Figure 4. Association of ctDNA with Relapse Free Survival

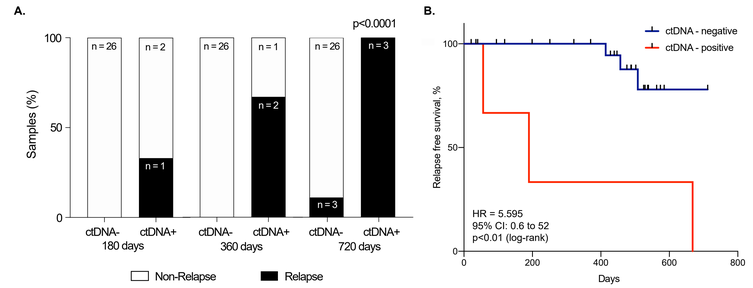


Figure 4. (A) Molecular relapse through ctDNA analysis was detected up to 668 days ahead of radiological imaging with an average lead time of 305 days. The majority of relapses in ctDNA-positive patients (67%; 2/3) occurred within a year of follow-up, whereas no relapses were observed in ctDNA-negative patients during the one-year time frame. (B) All plasma samples (n = 33) from 24 non-relapsing patients were ctDNA-negative, corresponding to a specificity of 100%. The presence of ctDNA was associated with a markedly reduced RFS compared to ctDNA-negative patients.

Conclusions

- The study results indicate that ctDNA status is associated with high relapse risk in patients with CRC (positive predictive value = 100%) and can serve as a predictor of patient outcome.
- Molecular relapse through ctDNA analysis was detected up to 668 days ahead of radiological imaging with an average lead time of 305 days.
- Despite low plasma volumes (<4 mL) and lack of longitudinal samples for analysis, ctDNA was detected in 50% of relapse cases.

References

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