FPN #588P

PLCRC-PROVENC3 study: Prognostic value of post-surgery liquid biopsy circulating tumor DNA in stage III colon cancer patients

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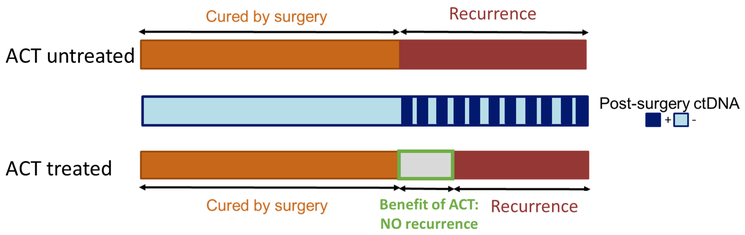
Background

- Current clinical guidelines in the Netherlands recommend adjuvant chemotherapy treatment (ACT) following resection of the primary tumor for all stage III colon cancer patients.
- Only **15-20%** of the patients benefit from ACT: around 55% of stage III colon cancer patients are cured by surgery alone and are being overtreated, and 30% will relapse despite ACT.
- **Prognostic biomarkers** may improve ACT decisions and reduce futile treatment by identifying the patients at a higher risk of recurrence that could benefit from ACT.



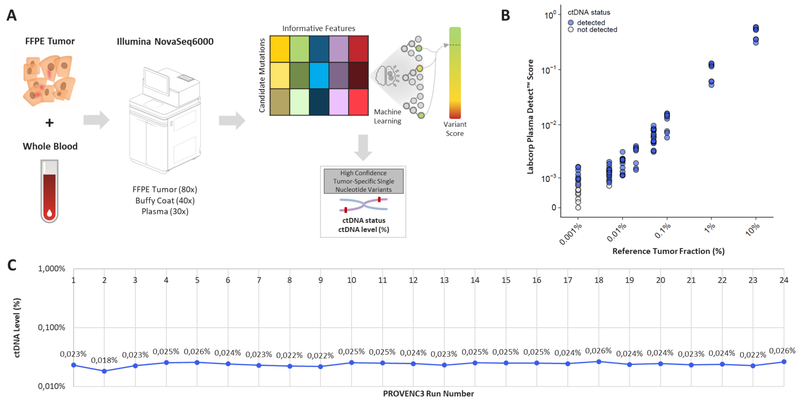
- Post-surgery circulating tumor DNA (**ctDNA**) detection indicates presence of minimal residual disease.

Goal of the study

Investigate the prognostic value of post-surgery ctDNA detection for disease recurrence in ACT treated stage III colon cancer patients

Experimental approach: ctDNA detection method

Tumor-informed detection of plasma ctDNA through integrated **whole genome sequencing (WGS)** analyses:

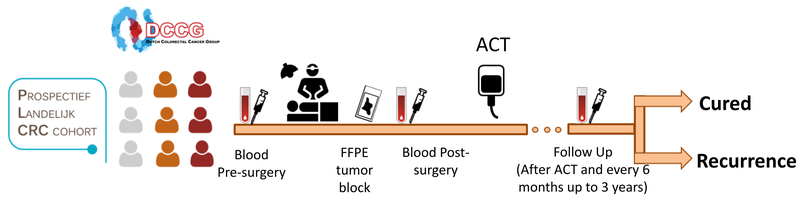


- A) Schematic of the Labcorp Plasma Detect™ assay workflow (adapted from Keefer et al., 2022 Nature Communications and Wood et al., 2018 Science Translational Medicine)
- B) Analytical studies demonstrated a limit of detection (95%) of 0.005% tumor content utilizing contrived reference models derived from commercially available cell lines (including lung cancer, breast cancer, and melanoma), with a specificity of 99.6% (2,015/2,023) observed across 119 noncancerous donor plasma specimens evaluated against 17 reference somatic mutation datasets. The observed tumor fraction was also highly correlated with the reference tumor fraction (Pearson correlation coefficient = 0.96, p<0.001).
- C) Analysis of an external contrived reference control sample demonstrated reproducible results across 24 independent runs evaluated for the PROVENC3 clinical study (CV = 7.2%)

Experimental approach: PROVENC3 study

PROVENC3: (**PRO**gnostic **V**alue of **E**arly Notification by **C**tdna in Colon Cancer stage **3**).

- PROVENC3 is an **observational** study within the Prospective Dutch Colorectal Cancer Cohort (PLCRC, https://plcrc.nl/for-international-visitors).
- 26 Participating hospitals in PROVENC3.
- **210 patients included** (Dec2016-Oct2021): Stage III, ACT treated, post-surgery blood available.



- One post-surgery blood sample is collected from day 3-65 after surgery (Median: 10 days, IQR: 14 days), before ACT.
- All biosamples are sent to a central laboratory (The Netherlands Cancer Institute).
- Clinical data is collected in the Netherlands Cancer Registry by IKNL.

Baseline clinicopathological characteristics

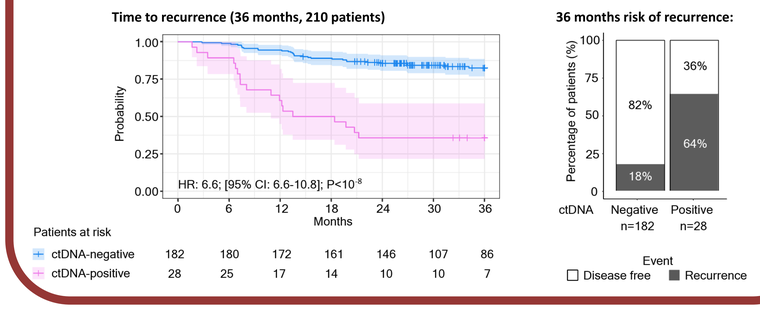
Results for **210 patients** with post-surgery ctDNA analyzed and clinical follow up (FU) information available. Median FU: 40 months, IQR: 29-48 months.

		ctDNA positive	ctDNA negative	Total	p.value 0.05 sig. lev.
		28	182	210	
Median age (years)		68 (43-83)	63 (32-79)	63 (32-83)	0.08
Sex	Female	9 (32%)	88 (48%)	97 (46%)	0.15
	Male	19 (68%)	94 (52%)	112 (54%)	
Clinicopathological risk	Low risk (T1-3, N1)	17 (61%)	110 (60%)	127 (60%)	1
	High risk (T4 and/or N2)	11 (39%)	72 (40%)	83 (40%)	
T status	T1	0 (0%)	4 (2%)	4 (2%)	0.81
	T2	3 (11%)	26 (14%)	29 (14%)	
	T3	18 (64%)	107 (59%)	125 (60%)	
	T4	7 (25%)	45 (24%)	52 (24%)	
N status	N1	19 (68%)	136 (75%)	155 (74%)	0.49
	N2	9 (32%)	46 (25%)	55 (26%)	
MSI status	Stable (MSS)	26 (93%)	154 (85%)	180 (86%)	0.38
	Instable (MSI)	2 (7%)	28 (15%)	30 (14%)	
Differentiation grade	Well differentiated	0 (0%)	0 (0%)	0 (0%)	0.77
	Moderately differentiated	22 (79%)	150 (82%)	172 (83%)	
	Poorly differentiated	4 (14%)	25 (14%)	29 (13%)	
	Undifferentiated	0 (0%)	0 (0%)	0 (0%)	
	UNK	2 (7%)	7 (4%)	9 (4%)	
Tumor location	Left	13 (46%)	106 (58%)	119 (57%)	0.31
	Right	15 (54%)	76 (42%)	91 (43%)	
RAS	WT	13 (46%)	113 (62%)	126 (60%)	0.15
	mut	15 (54%)	69 (38%)	84 (40%)	
BRAF	WT	21 (75%)	147 (81%)	168 (80%)	0.46
	mut	7 (25%)	35 (19%)	42 (20%)	

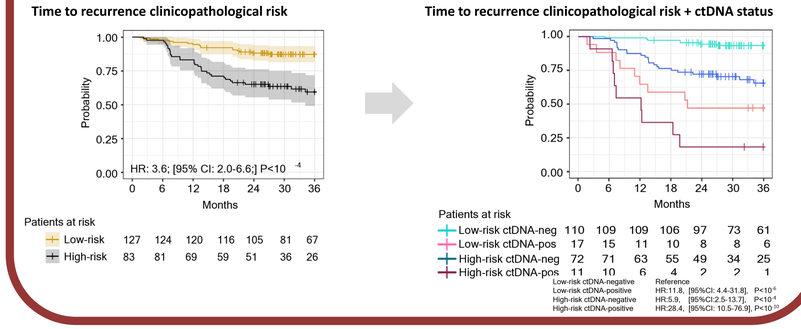
Post-surgery ctDNA status was independent of all clinicopathological risk characteristics evaluated.

Post-surgery ctDNA detection has a strong prognostic value

Post-surgery ctDNA-positive patients are at a higher risk of experiencing a recurrence than ctDNA-negative patients.

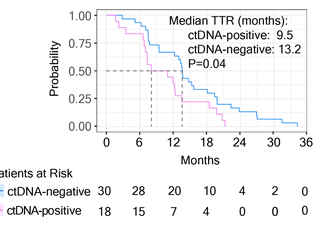


Post-surgery ctDNA status improves risk stratification in stage III colon cancer patients compared to other clinicopathological risk factors:



Time to recurrence is shorter for ctDNA positive patients

Shorter time from surgery to recurrence may provide an opportunity for earlier and potentially more effective intervention than is possible when the recurrence manifests clinically.



Conclusions

- Post-surgery ctDNA testing improves the stratification of stage III colon cancer patients for disease recurrence on top of current clinicopathological risk factors.
- There is a substantial but limited time window between ctDNA detection and radiological recurrence identification.

Next steps

- Based on the results of this study, a health technology assessment will be conducted, and we will design an interventional study towards implementation of ctDNA testing for stage III colon cancer patients.

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