Tumor-informed ctDNA as an objective marker for postoperative residual disease in epithelial ovarian cancer

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Background

- Complete tumor resection after primary surgery is the most important predictor of prognosis in patients with high-grade serous ovarian cancer (HGSOC)
- Postoperative residual disease is classified by the physician at the end of surgery, an objective marker for tumor residual is not available so far

Methods and Study Schema

Objective: To assess the association between ctDNA levels pre and post surgery and macroscopic residual disease evaluation by the surgeon

- Prospective multi-center feasibility study
- 52 patients with advanced HGSOC who underwent surgery
- Primary debulking surgery: assessment of tumor tissue
- Blood samples: 284 plasma samples
- Time points: preoperatively, d2, d10 post-op and during follow-up
- Future analysis: longitudinal ctDNA detection and patient outcome

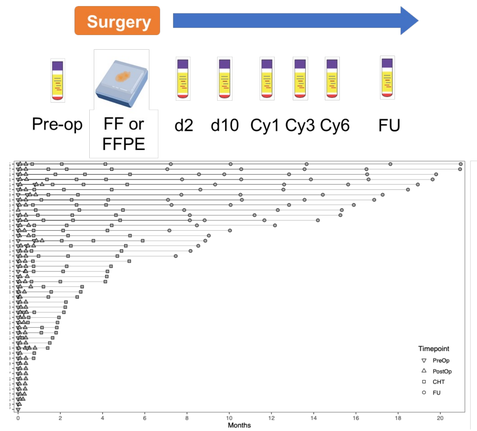


Figure 1. Plasma samples collected pre- and post-operatively and during follow up

How to evaluate minimal residual disease in ovarian cancer after surgery

Circulating tumor DNA is a promising approach

Detection of a high number of SVs ensuring a personalized fingerprint for every patient with a median of 7 biomarkers tracked

Characteristics	Details		n=47 (%)
Age (years)	Mean 65 (39 – 80)		
FIGO	< IIIC	IIA	1 (2.1%)
		IIIA1 +IIIB	11 (23.4%)
	≥ IIIC	IIIC	25 (53.2%)
		IVA +IVB	10 (21.3%)
sBRCA status	mutant		12 (25.5%)
	wildtype		35 (74.5%)
Postoperative residual disease	no		31 (66.0%)
	yes		16 (34.0%)

Table 1. Patient characteristics

Characteristics	
#SVs detected (median)	78 (range 3-345)
#Biomarkers per fingerprint (median)	7 (range 1-8)
% VAF (median)	1.5% VAF (range 0.0000986%-63.8%)
ctDNA detection rate at baseline	96% (45/47)
ctDNA detection rate post-surgery (d10)	89% (39/44)
ctDNA input PreOp (median) PostOp d10 (median)	98ng (range 18-1,104) 334ng (range 21-1,068)

Table 2. Key facts of SV testing

Results

High ctDNA detection rates pre- and post-operatively

- 96% (n = 45/47) of pts preoperatively
  89% (n = 39/44) of pts at d10
- Significantly higher ctDNA levels at d10 in pts with residual disease
- Comparable ctDNA levels pre- and postoperatively in pts with tumor residuals →17% decrease in median ctDNA levels from 3.92% to 3.25% VAF
- 98% decrease in median ctDNA levels between preoperatively and d10 in pts with complete resection →median ctDNA levels 3.40% and 0.07% VAF

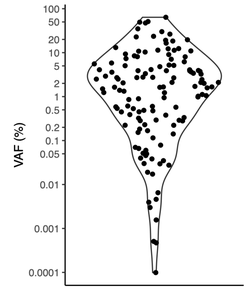


Figure 2. Range of ctDNA detection levels (% variant allele frequency) in all pre- and postoperative plasma samples

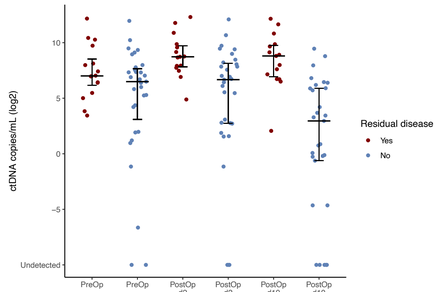


Figure 3. ctDNA levels pre- and postoperatively (d2 and d10) by postoperative residual disease evaluatedby the surgeon

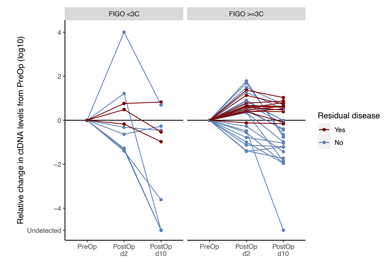


Figure 4. Relative change in ctDNA levels (copies/mL) from pre- to postoperative d2 and d10 by postoperative residual disease and tumor stage (FIGO)

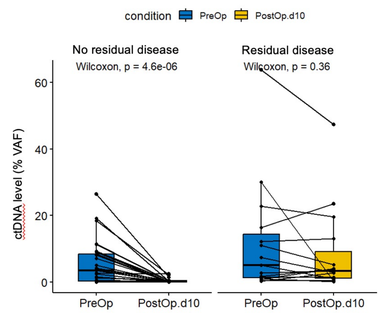
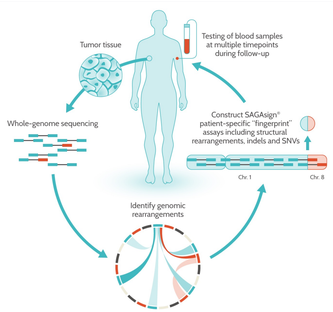


Figure 5. Decrease in ctDNA levels depending on residual disease, demonstrating highly significant decrease after total tumor resection

Workflow



- Whole genome sequencing (WGS) used to identify
  - structural variants (SV)
  - single nucleotide variants (SNVs)
  - indels in tumor tissue

  to develop personalized digital PCR (dPCR) fingerprint assays
- Up to 8 biomarkers in each personalized fingerprint applied to multiple plasma timepoints for ctDNA identification

Conclusions and Future Direction

- Tumor-informed dPCR SV fingerprint ctDNA approach reveals remarkably high detection rates pre- and postoperatively
- ctDNA represents a quantitative and persistent biomarker in the majority of HGSOC patients who have undergone debulking surgery
- In future, ctDNA may be used as an indicator for response to adjuvant therapy

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