Circulating Tumor DNA (ctDNA) as a Marker of Residual Disease and Recurrence Risk in Resected Stage I-IV Epithelial Ovarian Cancer (EOC).

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BACKGROUND

Patients with epithelial ovarian cancer (EOC) often relapse despite surgery and chemotherapy. Current prognosis estimates, based on FIGO staging +-/ molecular features, lack precision.

Standard of care for stage I-III EOC is 6 cycles of adjuvant chemotherapy, which may include 3 cycles of neoadjuvant treatment. Many treated patients do not benefit from chemotherapy because they had no residual disease post-operatively or because treatment did not eradicate disease that was present.

Studies in multiple solid tumor types have demonstrated that after curative intent surgery detectable ctDNA, a marker of minimal residual disease (MRD), predicts a very high risk of recurrence.[1-5]

Our primary aim was to explore the association between detectable ctDNA following debulking of primary EOC and recurrence free survival (RFS). Secondary aims included exploring the relationship between ctDNA and RFS at EOCdiagnosis, following neoadjuvant therapy and post adjuvant chemotherapy.

METHODS

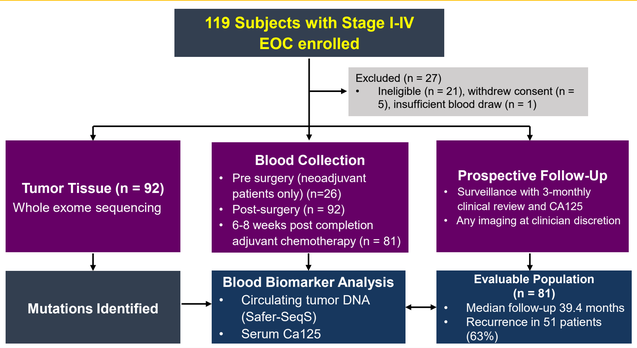
In this prospective, multi-centre, observational study, we collected blood samples for ctDNA analysis post-surgery, and 6-8 weeks post-chemotherapy completion, from patients with debulked stage I-IV EOC planned for adjuvant chemo. In addition, pre-cycle 1 and pre-operation blood samples were collected from some patients who received neoadjuvant chemotherapy.

We used a tumor-informed approach for ctDNA analysis, with whole exome sequencing of tumor tissue followed by detection of up to 50 variants in the plasma with the SaferSeqS assay.[6] The primary study endpoint was recurrence-free survival (RFS), calculated from the date of surgery, using the Cox proportional-hazards model.

Patients received standard of care platinum-based chemotherapy. Surveillance included at a minimum three monthly CA125's for the first two years. Data including patient demographics, pathology details, treatment details, timing and nature of surveillance investigations, date of recurrence, details of recurrence and date of death were prospectively recorded.

RESULTS

Patient Population and Evaluable Patients



Demographics of evaluable population

	Total	Post op ctDNA positive	Post op ct DNA negative	pvalue
Total	81	63	18	
Adjuvant Rx only	62 (76%)	49	13	P=0.011
Neoadjuvant Rx	19 (24%)	14	5	
High grade serous	68 (84%)	53	15	P=0.482
Other Histology	13 (16%)	10	3	
Stage I-II	26 (32%)	18	8	p = 0.011
Stage III-IV	55 (68%)	45	10	
Zero residual disease	50 (62%)	33	17	P=0.001
Any residual disease	31 (38%)	30	1	
BRCA mutant	19 (23%)	9	10	P=0.027
BRCA Wildtype	62 (73%)	53	8	

Median number of tumor informed variants analyzed in plasma = 44 (range 3-60)

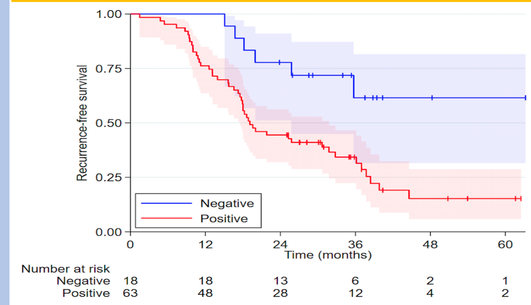
ctDNA +ve in 63/81 pts (78%)

Stage III/IV patients more likely to have +ve post operative than Stage I/II (82% vs ctDNA 69%, p=0.011)

Patients with zero residual disease were less likely to have ctDNA post op (OR 12.36, 95% CI 1.54 to 99.4, p=0.018)

Patients with BRCA mutations were less likely to have detectable post op ctDNA (OR 0.12, 95% CI 0.036 to 0.39, p<0.01)

Recurrence Free Survival – Association with post operative ctDNA status



Patients that were ctDNA negative had a longer RFS (HR 3.28, 95% CI 1.38-7.72, p < 0.01)

The estimated 2-year RFS based on post operative ctDNA was 78% for patients that were ctDNA negative and 44% in patients that were ctDNA positive

Unstratified Univariate Analysis for RFS

	Hazard ratio	p-value	95% confidence interval
Post-surgery ctDNA positive	3.20	0.008	1.36 –7.50
Serous histology	1.31	0.48	0.62 – 2.76
Non-zero residual disease	2.43	0.001	1.41 – 4.18
BRCA mutant	0.41	0.027	0.19 -0.90
Stage III-IV	2.21	0.015	1.17-4.17

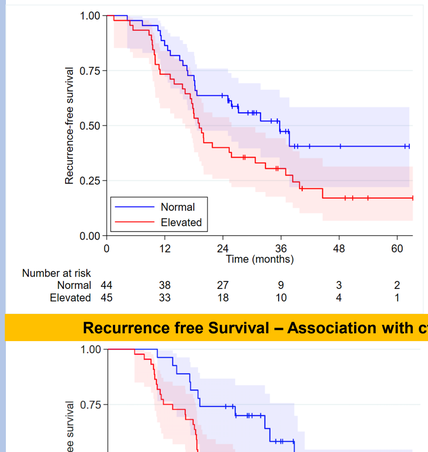
ctDNA results in neoadjuvant patients

Pre-treatment ctDNA was detected in 17 of 18 patients (94%).

Two patients (12%) had clearance of ctDNA after neoadjuvant chemotherapy. Both (100%) had residual disease at surgery.

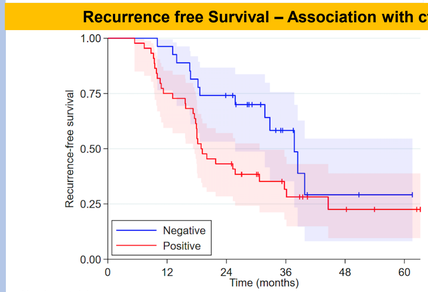
15 patients (88%) had persistently +ve ctDNA post operatively. 7 of these (47%) had zero residual disease histologically.

Recurrence Free Survival – Association with post operative CA125



Patients with an elevated CA125 had shorter RFS compared to those with normal Ca125 (HR 1.99), 95% CI 1.15 to 3.42, p=0.013

Recurrence free Survival – Association with ctDNA status post Adjuvant Chemotherapy



Post chemotherapy, the estimated RFS at 2 years was 74% in the ctDNA negative patients versus 43% in the ctDNA positive group. This difference was not statistically significant (HR 1.64, 95% CI 0.84 - 3.18, p=0.15)

CONCLUSIONS

In a prospective cohort of patients with epithelial ovarian cancer analysed for ctDNA

- Neoadjuvant therapy cohort
  - ctDNA was detectable pre-treatment in most patients
  - Most pre-treatment ctDNA +ve patients remained ctDNA +ve despite chemotherapy
- Post cancer cytoreduction surgery cohort
  - ctDNA was more likely to be detected in patients with stage III/IV disease, those with residual disease, and those without a BRCA mutation
  - ctDNA detection was associated with 2 year RFS
- Post adjuvant chemotherapy cohort
  - ctDNA detection was associated with a trend to inferior 2 year RFS

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