Topics: cfNA (circulating free nucleic acid)

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Copy Number Variation analysis in circulating-tumor DNA in advanced stage high-grade serous epithelial ovarian cancer patients.

Introduction

High-Grade Serous Epithelial Ovarian Cancer (HGS-EOC), the most common and lethal ovarian cancer sub-type, is a systemic disease defined by high level of somatic copy number alteration (SCNA) (i.e the clonal gain in 8q24) (1) (2) and by marked spatial and temporal tumor heterogeneity (3) (4). The lack of biomarkers for treatment response monitoring and for the early detection of disease recurrence is limiting the clinical management of HGS-EOC. In the present study, we considered the SCNA data generated by low pass whole genome sequencing analysis (sWGS) to: *i*) evaluate the SCNA concordance profile between circulating free tumor DNA (ctDNA) and matched tumor gDNA obtained from tissue biopsies at time of diagnosis (T0). *ii*) exploit the presence of clonal SCNA in the ctDNA (gain in 8q24) to longitudinally monitor the dynamic changes in the amount of ctDNA during patients follow up. *iii*) use ctDNA as a non-invasive biomarker to detect disease recurrence earlier than radiological imaging assessments.

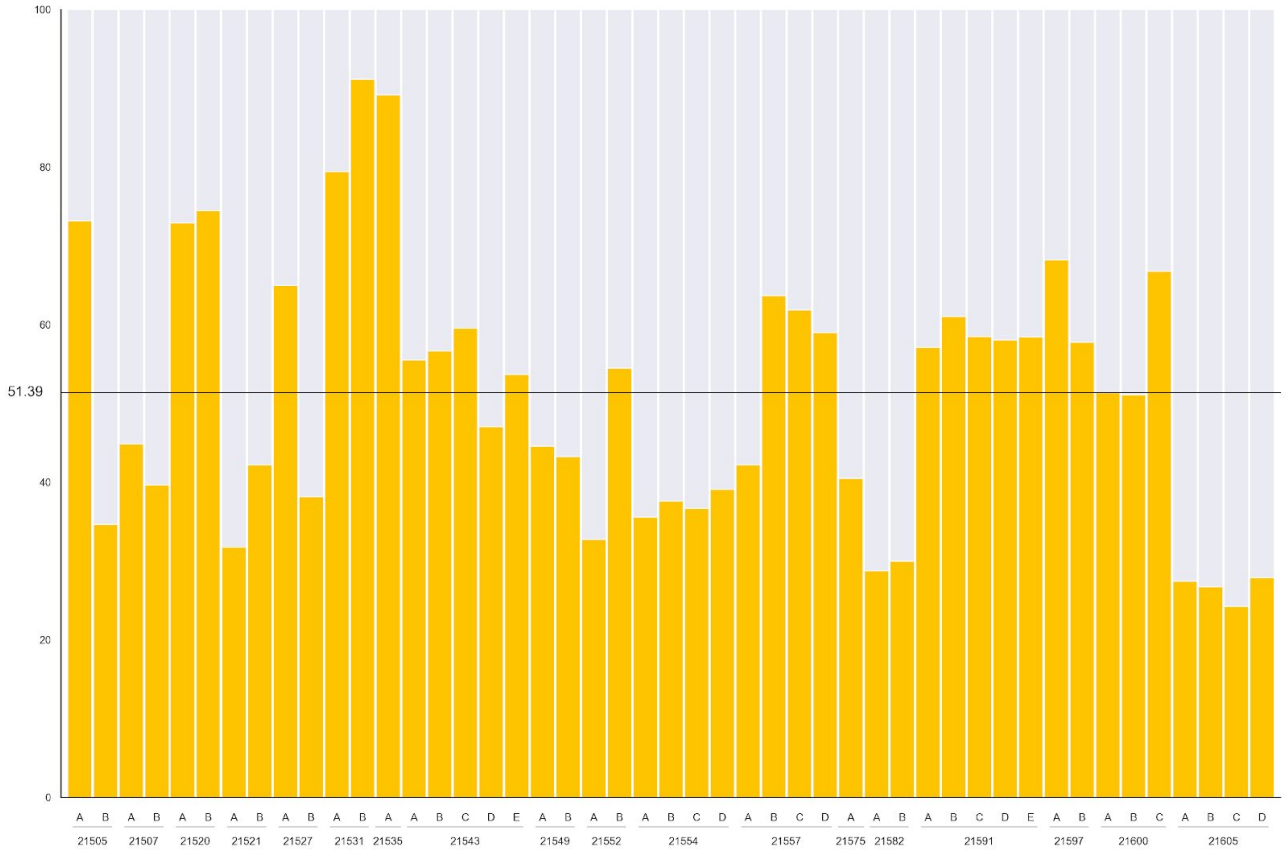
Methods

A cohort of 45 HGS-EOC patients was retrospectively selected for the study. For each patient the following specimens were available: i) two or more snap-frozen tumor biopsies obtained at T0 ii) plasma samples collected at T0 and different time points during the follow up (Tn). DNA purified from plasma samples and tissue biopsies was quantified and the number of genome equivalent calculated. Whole-genome libraries were prepared

(KAPA hyper plus, Roche) and sequenced (Nextseq-500, Illumina) at 0.5X (sWGS). NIPT pipeline (5) was exploited to analyze SCNAs in cfDNA.

Results

The median of cfDNA yield extracted from 1 ml of plasma was 8.7 ng (5-12.5 ng) with a genome equivalent values ranging from 457 to 2592 GE/ml. At T0: i) clonal gain in the 8q24 region was detected in both ctDNA and biopsies ii) the Tumor Fraction (TF) of ctDNA ranges between 0.8% and 5% iii) the copy number burden (CNB) for cfDNA and biopsies showed a median concordance of 51.39% (figure 1).



The presence of 8q24 clonal amplification and the TF in ctDNA was also used for disease monitoring in comparison with the standard serum biomarker (CA125 protein level).

Conclusion

Our results support sWGS as a tool for genomic analysis of ctDNA in HGS-EOC patients as i) it appears to able to recapitulate the biological features of the systemic disease at time of diagnosis and ii) it could anticipate disease recurrence in comparison with CA125 protein levels

References:

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