EVOLUTIONARY STUDY IDENTIFIES POOR PROGNOSIS HGSC PATIENTS AND REVEALS CLINICALLY RELEVANT TARGETS AT DIAGNOSIS AND RELAPSE

Introduction/Background Ovarian high-grade serous carcinoma (HGSC) is commonly diagnosed at an advanced stage, showing multiple genetically heterogeneous clones existing prior to therapeutic intervention.

Methodology Clonal composition and topology were estimated from whole-genome sequencing data from 510 samples of 148 patients in the prospective, longitudinal, multiregion DECIDER study. Detected subclones were followed in 152 longitudinal circulating tumour DNA (ctDNA) samples, by using targeted sequencing. Multiomics data included H&E-stained images and RNA sequencing data.

Results Based on phylogenies, patients were stratified into three evolutionary states with distinct subclonal heterogeneity within and between metastases:
1) Evolving state is mostly monoclonal and shows only some differences between sampled sites.
2) Maintaining state is highly polyclonal within sites, but shows similar, stable subclonal patterns between sampled sites.
3) Adaptive state has high heterogeneity between metastases that show parallel evolution, making them the most divergent.

Tumours belonging to maintaining state had worst prognosis (p=0.008). Prognosis difference was independent of homologous recombination (HRD), which was found equally in each of the three states.

States were characterized by distinct molecular pathways and morphological features. PI3K/AKT pathway was enriched in maintaining state tumours, and it was shown to be targetable with alpelisib in patient-derived organoids.

After treatment, most patients revealed heterogenic subclonal composition with acquired mutations and only few cases underwent selection. Evolutionary states were modified by the changing selection pressure caused by treatments.

Conclusion Our results revealed that HGSC tumours are not all highly heterogenic and genomically unstable at the time of diagnosis. We showed that prognosis is worst for maintaining tumours that grow in mixtures of multiple clones that remain genomically similar between metastases. These tumours had enriched PI3K/AKT alterations, which were successfully targeted by alpelisib monotherapy in organoids. Multiple lines of treatments altered diagnostic states and most tumours revealed acquired mutations at relapses, making the relapsed disease a moving target.

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A RESTRICTIVE STOMA POLICY AFTER COLORECTAL ANASTOMOSIS? YES WE CAN!

Introduction/Background Anastomotic leak remains the main concern after colorectal anastomosis in ovarian cancer. Our objective was to compare the use of three different management approaches after colorectal resection and anastomosis in patients with ovarian cancer.

Methodology Patients who underwent colorectal resection during cytoreduction for FIGO stage II–IV ovarian cancer were identified (n = 273). Those with terminal colostomy were excluded (n = 22).

We compared 2 time periods with different diversion stoma policy: non-restrictive stoma use (2010–2018) vs restrictive stoma use (2018–2023) for colorectal anastomosis protection.

Univariate analyses were performed for qualitative variables by using the χ² test or Fisher’s test.

Results A total of 252 patients were identified: 133 (52.7%) in the non-restrictive group and 119 (47.3%) in the restrictive group. The rate of procedures per year was 16.6/yy for the non restrictive group vs 24.8/yy for the restrictive group. There was no differences in the rate of anastomotic leak between both groups (5.2% vs 3.3%; p = 0.117). Regarding the the approach followed after colorectal anastomosis, patients were stratified into three groups. Statistic differences were found in the rate of conservative management and observation (55% vs 83%; p < 0.00001) and diverting ileostomy (13% vs 60%; p < 0.00001) and ghost ileostomy technique (32% vs 83%; p < 0.00001).