**Methodology** Patients (n=49) undergoing maximal-effort upfront-debulking surgery for advanced HGSOC had a tumour mapping of their tumour dissemination. Tumour biopsies were collected (range 4–15) from patients, and also at time of relapse (n=10 patients). DNA was extracted from tumours (5 per patient, n=49 patients plus paired relapse samples) and Illumina Human OmniExpress genotyping performed. Allele-specific copy number (CN) was quantified using ASCAT. CN signature exposures were determined for all samples. Homologous recombination (HR) scores were estimated using a scarHRD algorithm, applying a cut-off >42 for HR-deficient.
**Results** Extensive genomic variations in CN signature exposures for different patients' tumours were observed, including between matched primary and relapse tumours. Increased CN signature exposure scores for Signatures 2 (p=0.00017), 4 (p=0.0029) and 6 (p=0.001) correlated with poor outcome in platinum-resistant/refractory patients, increased Signature 3 correlated with favourable outcome (p=0.00018) for platinum-sensitive and no-relapse patients. Variations in HR scores were observed across the cohort with one fifth of patients presenting with a mixed HR score profile across their tumour deposits, demonstrating both HR-deficient and HR-proficient tumours within patients.
**Conclusion** Extensive CN variations in CN signature scores and mixed HR-deficiency/proficiency scores indicates that a single tumour biopsy does not accurately depict disseminated HGSOC biology, and therefore should not be used as the basis to derive biomarker profiles for prediction of patient treatment responses or outcomes.

## 2022-RA-1651-ESGO EPITHELIAL OVARIAN CANCER IS INFILTRATED BY ACTIVATED EFFECTOR T CELLS COEXPRESSING MULTIPLE INHIBITORY RECEPTORS AND BY MYELOID CELLS EXPRESSING INHIBITORY RECEPTOR LIGANDS

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**Introduction/Background** Despite evidence suggesting a potential role for immunotherapy in Epithelial Ovarian Cancer (EOC), initial attempts had limited efficacy. A better characterization of tumor infiltrating lymphocytes' (TIL) immunophenotype appears crucial to deeply understand their role in anti-tumor immunity and to set the basis for their potential modulation to optimize adoptive cell therapies approaches. We extensively characterized the composition and phenotype of immune cells in EOC to identify pathways involved in limiting anti-tumor immunity.
**Methodology** Immune infiltrate was investigated for phenotype in 48 EOC specimens by immunohistochemistry (IHC) and flow cytometry (FC). Furthermore, the gene expression of tumor samples was evaluated with a panel of 799 immune and cancer-related genes by the Nanostring platform. FC was also used to compare T cells isolated from tumor, ascites and peripheral blood of 19 patients for memory phenotype and for the expression of multiple inhibitory receptors (IRs) and of activation markers.
**Results** Both IHC and FC revealed a high infiltration by T lymphocytes and myeloid cells, while B cells were scanty. High-dimensional analysis of FC data identified 2 metaclusters of $CD4^+$ and $CD8^+$ T cells exclusively present in tumors, characterized by a $CD137^+CD39^+PD\text{-}1^+TIM\text{-}3^+CD45RA^-CD62L^-CD95^+$ phenotype. Gene expression profile revealed a peculiar microenvironment in samples characterized by high TIL content, with increased expression of immunity- and myeloid-related genes. Accordingly, the ligands for IRs and co-stimulatory molecules were mainly provided by myeloid rather than neoplastic cells.
**Conclusion** Our data suggest that EOC is infiltrated by antigen-experienced T lymphocytes displaying features of both activation and partial exhaustion, possibly driven by IRs ligands expression by infiltrating myeloid cells.

## 2022-RA-1697-ESGO EVALUATION OF ADVANCED LUNG CANCER INFLAMMATION INDEX AS A PROGNOSTIC FACTOR IN PATIENTS WITH OVARIAN CANCER TREATED WITH PRIMARY DEBULKING SURGERY

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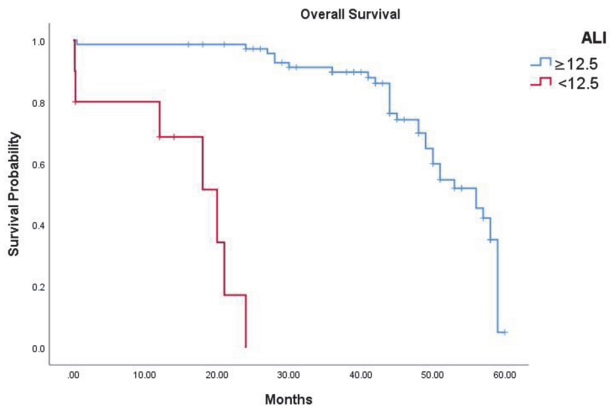
10.1136/ijgc-2022-ESGO.902

**Introduction/Background** Advanced Lung Cancer Inflammation Index (ALI) reflects systemic inflammation and has been shown to be a prognostic factor for lung cancer patients undergoing surgery. No previous study has assessed the prognostic significance of ALI in patients with ovarian cancer (OC). This study aimed to explore the relationship between ALI and prognosis of OC.
**Methodology** Electronic records of 83 patients with OC who underwent primary debulking surgery (PDS) at Tata Medical Center between 2017 and 2018 were reviewed. Patients treated with primary chemotherapy and those treated with palliative intent were excluded. The ALI score was calculated as body mass index x serum albumin/neutrophil to lymphocyte ratio. A web-based programme [Cutoff Finder (http://molpath.charite.de/cutoff/)] was used to deduce the appropriate cut-off value for ALI. The Kaplan-Meier method and Cox Proportional Hazards model were used to compare survival among prognostic groups.
**Results** The optimal cut-off value of ALI was determined as 12.5. Among the 83 patients, 10 had low ALI (<12.5), and 73 had high ALI (≥12.5). The low-ALI group had more complications of Clavien-Dindo grade 3 or higher after PDS (P=0.04). The patients with low ALI had higher chances of 30-day-mortality following PDS compared to the high-ALI group (P=.005). Median relapse-free survival (RFS) in the low-ALI group was 9 months compared to 32 months in the high-ALI group (hazard ratio [HR] for relapse, 0.16; P <0.001). Median overall survival (OS) in the low-ALI group was 20 months, and in the high-ALI group median OS was 56 months (HR 0.12, P<0.001).




**Abstract 2022-RA-1697-ESGO Figure 1**

**Conclusion** Low ALI was associated with higher perioperative complications and poorer survival in ovarian cancer. The utility of preoperative ALI as a prognostic marker in ovarian cancer should be assessed in prospective studies.

## 2022-RA-1709-ESGO A PREDICTIVE MODEL FOR DETECTION OF EPITHELIAL OVARIAN CANCER BASED ON METHYLATION LANDSCAPE

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**Introduction/Background** More than 75% of individuals with ovarian cancer (OC) are diagnosed at an advanced stage, given that early-stage disease is usually asymptomatic. Epigenetics studies are emerging in cancer research and diagnostics with encouraging outcomes. Recent developments in large-scale DNA methylation profiling have shown that those changes are at the very early stage of carcinogenesis, indicating that the detection of such markers would drastically increase patient outcome. In OC, that would potentially represent early detection for the majority of patients. Here, we **(1) investigated a large-scale methylation landscape of OC, (2) devised a predictive model based on the discovered targets**, and **(3) sought to validate its performance on independent external cohorts**.
**Methodology** Fresh-frozen tissues were collected from **29 OC patients and 14 benign pelvic mass** patients. Samples were submitted to global DNA methylation profiling, comprised of **~850,000 targets**. For the **design of the predictive model** we performed: (1) univariate linear model; (2) LASSO-penalized multivariate analysis; (3) cross-validation; and (4) group assignment by centroid approach followed by principal component analysis (PCA). The predictive model was **trained with our own samples and validated in 2 external cohorts**.
**Results** We **identified 21 targets** that showed a clear distinction for the OC patient group, with clustering analysis showing two independent groups. Furthermore, the two main components explained 66% of the variance shown by PCA. **The validation of our model in 2 independent cohorts showed classification concordance of 81.1% and 85.2%, respectively.**
**Conclusion** Our current findings showed that OC presents an unique methylation landscape represented by a signature of 21 targets. Our **predictive model algorithm showed considerable concordance with external cohorts**. Noteworthy, due to the relatively small cohort used to train our model, we are currently collecting more samples to further improve its prediction efficiency, which may be relevant in diagnostic settings.

# Trophoblastic diseases

## 2022-RA-701-ESGO ELUCIDATING MECHANISMS UNDERLYING METHOTREXATE RESISTANCE VIA QUANTITATIVE PROTEOMICS ANALYSIS OF GTN PATIENT SAMPLES AND CHORIOCARCINOMA CELL LINES: A CRUCIAL ROLE FOR SERINE METABOLISM

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10.1136/ijgc-2022-ESGO.904

**Introduction/Background** Choriocarcinoma is an aggressive type of Gestational Trophoblastic Neoplasia (GTN). Patients with low-risk GTN following a molar pregnancy frequently commence therapy with single-agent methotrexate (MTX). Unfortunately, many develop resistance (MTX-R) and require either another single agent or more toxic combination agent chemotherapy to achieve remission. Understanding the molecular mechanisms of MTX-R may identify interventions to prevent or reverse this.
**Methodology** We employed proteomics profiling to identify changes that accompany MTX-R in post molar GTN patient samples and in choriocarcinoma cell lines that were either MTX sensitive (MTX-S) or resistant (MTX-R).
**Results** Quantitative mass spectrometry (MS) analysis revealed that the de novo serine synthesis pathway was one of the most downregulated pathways both in the MTX-R patients and in the resistant choriocarcinoma cell line. Decreased glucose-derived serine synthesis is supported by our findings that choriocarcinoma MTX-R cells have a less active glycolytic pathway. Concomitant de novo serine synthesis inhibition and serine deprivation from the growth medium promoted MTX-R in cell lines. Moreover, examination of the expression levels of 1-Carbon metabolism enzymes suggested a different utilization of serine, the major 1-Carbon donor, between sensitive and resistant cells. In particular, MTX-R cells may be channeling serine into pathways crucial for cell survival, such as the synthesis of glutathione (GSH), as indicated by the increased levels of this metabolite in resistant cells.
**Conclusion** Upon MTX-R, choriocarcinoma cells favor redirection of serine to GSH production and this may help with combating chemotherapy-induced reactive oxygen species (ROS) accumulation and hence participate in the resistant phenotype. In contrast, MTX-sensitive cells utilize serine for nucleotide synthesis and the maintenance of proliferation. Hence, targeting upstream pathways or molecules that block the synthesis of serine in combination with or without MTX treatment could improve therapeutic response in patients with MTX resistance.