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Differentially expressed genes in platinum-resistant high-grade serous ovarian cancer

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237 - Poster Session

Did surgical delay due to COVD-19 affect the short- and longer-term mental health of patients?

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Objectives: At the height of the COVID-19 pandemic, the US Surgeon General ordered the cessation of all elective surgical procedures. We evaluated the mental health impact of COVID-19 related surgical delay on patients awaiting procedures for benign, pre-malignant and malignant conditions. We sought to understand the short term impact of surgical delay and to identify potential longer term mental health affects after completion of the delayed procedure.

Methods: All patients over age 18 awaiting surgery for benign, pre-malignant or malignant conditions in the gynecologic oncology, surgical oncology and colorectal services at Northwell Health were eligible. Upon enrollment, participants completed a baseline survey consisting of the Generalized Anxiety Disorder Questionnaire (GAD-7), the Penn State Worry Questionnaire (PSWQ), and Brief-Illness Patient Questionnaire (B-IPQ). Six weeks after their surgery, participants were sent a second survey consisting of the Center for Epidemiologic Studies Depression (CES-D) scale in addition to the GAD-7, PSWQ, and B-IPQ.

Results: 56 patients underwent their procedure and completed the follow-up survey. Patients with suspected benign conditions had a longer delay in scheduling their surgery than patients with suspected/confirmed cancer or pre-malignant conditions (101.4d vs 66.3d, p<0.05). There was no correlation of length of delay with post-operative worry, anxiety, or depression scores. There was no decrease in level of worry, as delineated by the PSWQ, among gynecologic oncology patients when comparing pre-operative to post-operative data. However, surgical oncology and colorectal patients demonstrated decreased post-operative worry. There was no difference in anxiety by surgical specialty.While the surgical delay was ongoing 79% of patients considered it to be moderately to extremely concerning, with 46% indicating the highest possible level of concern. Post-operatively, 47% of the respondents indicated moderate to extreme concern about the surgical delay, while 37% were not concerned. Initially, the surgical delay was considered to have a moderate to severe impact upon daily life by 65% of patients; which decreased to 53% at the time of post-operative follow-up. Interestingly, these relative decreases in patient concern were not significant when comparing pre-operative to post-operative values as a whole, by diagnosis or by specialty. 20% of participants qualified as depressed based on their response to the CES-D. Of these patients, 70% had a post-operatively confirmed cancer or pre-cancer. The incidence of depression was not affected by the post-operative diagnosis.

Conclusions: Many patients experienced distress surrounding surgical delay due to the COVID-19 pandemic. This extended to their post-operative period. Gynecologic oncology patients did not experience decreased post-operative worry, while surgical oncology and colorectal patients did. There was no significant difference in the incidence of post-operative depression by specialty or post-operative diagnosis.

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238 - Poster Session

Differences in tumor sequencing across ethnic groups in the treatment of endometrial cancer

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Objectives: We aimed to identify ethnic differences in genetic mutations associated endometrial cancer (EC), as well as differences in the utilization of sequencing results to direct disease treatment based on actionable mutations among different ethnic groups.

Methods: Patients of interest were identified using the EMERSE program. Inclusion criteria included patients with endometrial cancer who underwent solid tumor genomic sequencing between the dates of April 2014 and January 2019 at our institution. Patients meeting the inclusion criteria with verifiable tumor sequencing results were included in our retrospective cohort. Patients were excluded if they had synchronous cancers and germline or non-solid tumor testing only. Clinical information was abstracted from the medical record. Differences between groups were calculated using descriptive statistics.

Results: 287 patients met inclusion criteria. The majority of patients who underwent genomic sequencing of their tumors were non-Hispanic Caucasian (n=212, 73.9%), followed by non-Hispanic African American (n=55, 19.2%) and Hispanic (n=6, 2.1%), a distribution that accurately reflects the ethnic makeup of our state population. Among patients who underwent tumor sequencing, non-Hispanic Caucasian patients had an 82% likelihood (n=174) of having an actionable mutation, whereas non-Hispanic African American patients had a 60% likelihood (n=33) (p<0.001). PTEN (n=107, 80.5%, p<0.001) and FGFR2 (n=28, 95.8%, p=0.04) mutations were found at a higher rate in non-Hispanic Caucasian patients. When controlling for histological subtypes, however, ethnic variations in these mutations were no longer significant. FBXW7 mutations (n=4, 40%, p=0.03) were found to occur at a lower rate in non-Hispanic African American patients. No significant differences in the rates of genetic mutations were found in Hispanic, Asian, or American Indian/Native Alaskan patients. 21 patients received targeted treatments based on sequencing results. Among ethnic groups, 9.8% (n=17) of non-Hispanic Caucasian and 12.1% (n=4) of non-Hispanic African American patients were initiated on targeted treatments (p=0.68). The majority of patients receiving targeted therapy had endometrioid histology (n=11, 52.4%), followed by carcinosarcoma (n=5, 23.8%) and serous (n=4, 19.0%) histology.

Conclusions: Genomic sequencing of solid tumors was utilized in a high percentage of patients with endometrial cancer. When examining ethnic groups, no disparate use of tumor sequencing was found. Similar actionable mutations were seen across ethnic groups when controlling for tumor histology. Overall, utilization of tumor sequencing results to personalize care was used at a low rate among patients with actionable mutations across ethnic groups. This underutilization highlights the need for the continued development of efficacious, targeted therapies for endometrial cancer.

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239 - Poster Session

Differentially expressed genes in platinum-resistant high-grade serous ovarian cancer

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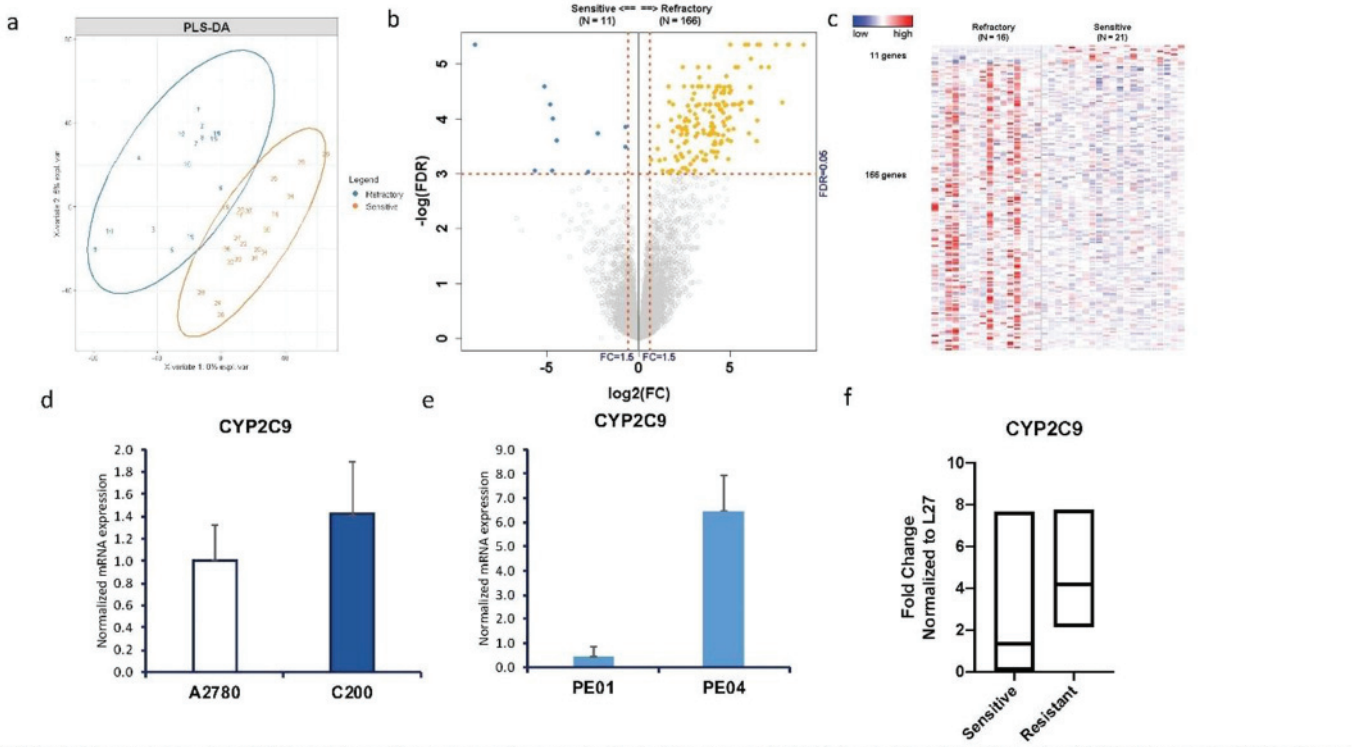
Objectives: The purpose of this study was to identify genes and pathways differentially expressed in platinum resistant high grade serous ovarian cancer (HGSOC) when compared to sensitive HGSOC.

Methods: A total of 37 patients with HGSOC tissue samples underwent RNA sequencing performed by TEMPUS (N=37, 21 platinum sensitive, 16 resistant; 85% Stage III-IV; 58% received neoadjuvant chemotherapy). RNA gene expression data and significantly impacted pathways were analyzed using Advaita Bio's iPathwayGuide. Differentially expressed (DE) genes were identified using FDR of 0.05 and fold-change of 1.5. Genes from several impacted canonical



a. PLS-DA blot of all 37 samples; b. Volcano Plot of 177 Differentially Expressed Genes; c. Heat map of gene expression intensity of DE genes separated by individual sample; d. Normalized mRNA expression of CYP2C9 of platinum sensitive (A2780) cell lines and platinum resistant (C200) cell lines; e. Normalized mRNA expression of CYP2C9 of platinum sensitive (PE01) cell lines and platinum resistant (PE04) cell lines; f. CYP2C9 expression in human plat-resistant versus sensitive OC normalized to L27

metabolic pathways were validated by PCR against external data sets in a separate ovarian cancer sample group (n=15), platinum resistant ovarian cancer mouse tumor model, and wild-type sensitive and platinum resistant ovarian cancer cell lines. Relative gene expression was calculated using the comparative Ct method, also referred to as the "2 DDCT", using L27 as internal control gene.

Results: We identified 177 differentially expressed (DE) genes out of a total of 16,607 genes (1.1%) with measured expression. 15 pathways were found to be significantly impacted. Of the 15 canonical pathways, all were up regulated in the resistant HGSOC and the majority of the most significantly altered (5/10) were related to metabolism (Retinol metabolism (p-value = 0.002); Tyrosine Metabolism (p-value = 0.005); Tryptophan Metabolism (p-value = 0.009); and Phenylalanine Metabolism (p-value = 0.012); CYP Drug Metabolism (p-value = 0.022)). A total of 3 separate genes from the CYP family and two from the Dopa Decarboxylase family of genes were validated against an external data set of human ovarian tissue samples, cell lines, mouse ovarian tumor model, and found to have similarly increased gene expression in the genes tested in the platinum resistant groups. Compilation of KEGG analysis and the common network genes revealed pathways associated with amino acid metabolism to be most significantly altered.

Conclusions: We describe the identification of a unique transcriptomic profile associated with platinum resistance. Interestingly, the main pathways identified are related to metabolism, suggesting that the survival to chemotherapy demands a major metabolic adaptation. These findings also represent a first step towards the identification of biomarkers for the detection of chemo-resistant disease and metabolism-based drug targets specific for chemo-resistant tumors. Further validation of this model is required in order to determine its clinical value.

240 - Poster Session

Differentiated vulvar intraepithelial neoplasia has a high-risk of recurrence and progression to invasive vulvar cancer

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Objectives: Differentiated vulvar intraepithelial neoplasia (dVIN) is implicated as a precursor to HPV-negative squamous cell carcinoma of the vulva (SCCV). It has a variable clinical course that has not yet been fully characterized. Data on the clinical and histopathologic features of dVIN, risk of recurrence and progression to SCCV is limited. Our objective was to describe the natural history of dVIN and evaluate predictors of recurrence and disease progression to carcinoma in a cohort of women with histologically confirmed disease.

Methods: Under an IRB-approved protocol, we retrospectively identified 27 patients with biopsy-proven dVIN from 2011 to 2020. Cases were independently reviewed by 2 gynecologic pathologists. Demographics, histopathologic features including immunohistochemical (IHC) staining for p16, p53, ER/PR and GATA 3 and clinical course were abstracted. Patients were followed with semi-annual exams and biopsies at the discretion of their gynecologic provider.

Results: Median age of the cohort was 70 years (range 43-91). Median follow-up time was 4 months (range 1-21). All women were Caucasian. The majority of women had concurrent lichen sclerosus (LS) adjacent to dVIN (81%). No specific primary treatment (topical versus surgical excision) was superior in preventing recurrence or progression to SCCV. 67% of women had recurrent dVIN at a median of 8 months from the initial diagnosis. 10 women had SCCV during the study period: 4 (15%) at primary diagnosis adjacent to dVIN, and 6 (22%) progressed to SCCV. Median time to progression was 34 months (range 1-120). P53 mutation (including p53 overexpression or p53 null) was associated with progression to SCCV ($p<0.01$). Decreased GATA 3 staining was associated with both recurrence ($p=0.03$) and progression to SCCV ($p<0.01$).