RRSO. Further study of cancer risks associated with gHRD/non-BRCA mutations is necessary to guide recommendations for risk-reducing surgery.

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Abstract #34

Exploratory analysis of somatic BRCA mutations in endometrial cancer and its clinical implications

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Objectives: Germline BRCA mutations in ovarian cancer patients are associated with improved response to chemotherapy and survival. With the increased use of molecular profiling, many women with endometrial cancer (EC) have been found to harbor somatic BRCA mutations, the significance of which is unknown. The goal of this study is to evaluate the prognostic and predictive features of somatic BRCA mutations (sBRCA+) in EC.

Methods: An IRB-approved, retrospective review of patients with molecularly profiled, EC from 3 academic institutions between 2010 – 2017 was performed. Summary statistics were used to describe demographic and clinical characteristics. Analysis included a comparison of response and survival following treatment with platinum-based chemotherapy among sBRCA+ and somatic BRCA wild-type (sBRCAwt) patients.

Results: Of the 109 patients included, 12.8% were sBRCA+ (Table). Of these, the median age was 47.5 yrs and 62% were endometrioid. This was not statistically different from the 95 sBRCAwt patients, of which the median age was 50 yrs and 66% were endometrioid (all $p>0.05$). sBRCA+ pts were more likely to have microsatellite instability-high (MSI-H) tumors than sBRCAwt (50% vs 17%, $p=0.01$). Of the 45 patients with complete chemotherapy data available, the median progression-free survival (PFS) was 26 mo. There was no difference in the distribution of sBRCA+ patients above and below the median PFS (23% vs 18%, $p=0.69$). The median overall survival (OS) for the 108 pts with evaluable data was 30.4 mo. There was no statistical difference in the distribution of sBRCA+ patients above and below the median PFS (19% vs 8%, $p=0.11$). Of the 14 sBRCA+ patients, 4 had germline mutation testing and all 4 were negative.

Conclusions: Among EC patients, somatic BRCA mutations are relatively uncommon. sBRCA+ patients are more likely to have MSI-H tumors, but no other clinical factors were associated with these mutations. While there appears to be a trend towards improved OS among sBRCA+ patients, this was not statistically significant, likely due to the small numbers in our cohort. Data collection continues with recruitment of additional sites to improve the power of this study.

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Abstract #35

Pilot early detection trial of longitudinal combined biomarker assessment for ovarian cancer risk among BRCA affected women

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Objectives: Screening for ovarian cancer with CA-125 using a set cut off for normal values has inadequate sensitivity for clinical use. A risk of ovarian cancer algorithm which systematically interprets longitudinal changes in CA-125 values to detect the first significant rise above a woman's baseline has shown promise. The objective of this pilot early detection study was to assess personalized risk using an expanded longitudinal algorithm that detects the first significant rise above a woman's baseline in either CA-125 or HE4.

Methods: BRCA1/2 affected women who had chosen to defer prophylactic oophorectomy were recruited to participate in a prospective early detection trial. Patients self-allocated into two groups: 1. standard of care surveillance according to NCCN recommendations and 2. combined biomarker surveillance using CA-125 and HE4 assayed every 4 months. Biomarkers were evaluated using the Risk of Ovarian Cancer Algorithm (ROCA) which calculates the probability of having a change-point in the biomarker, used as a surrogate for having undetected ovarian or fallopian tube cancer. ROCA risk scores were calculated for the individual markers as well as for the combination. Risk estimates were categorized as normal, intermediate, and elevated. Post-test follow up for elevations in any individual risk score (CA-125, HE4 or combination) was trans-vaginal sonography (TVS) for intermediate risk, and TVS and review by gynecologic oncologist for elevated risk.

Results: 149 BRCA 1 and 2 affected women enrolled in the ROCA biomarker arm of the screening study and 409 blood draws over 1.4 years provided 409 time points for analysis. Abnormal individual risk scores were identified in 95 (23%) of 409 time points; 68 (16.7%) were intermediate and 27 had elevated risk scores (6.7%). Retrospective analyses of the combination CA125/HE4 ROCA score showed that 50 time points (12.2%) had a rise over time in one or both markers with an elevated combined risk score. One stage IIA fallopian tube cancer with serous tubal intra-epithelial cancer (STIC) was identified from the study group at patient-initiated risk reducing salpingo-oophorectomy (RRSO). Nonetheless, in that case the combined ROCA and the individual HE4 ROCA reported elevated risks.

Conclusions: Combination biomarker risk scoring is feasible, and this preliminary evaluation appears to show improved specificity compared with individual risk scoring, reducing the number of false positives by about one-half. Further evaluation, particularly to clarify potential confounders, is needed before firm judgments can be made about mitigating the clinical imprecision of CA 125 testing when using this novel testing method.

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Poster Presentations

Poster #1

Predictive factors of genetic referral for advanced, epithelial ovarian cancer patients at a Single-Institution Cancer Center

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Objectives: Given 15-20% of invasive epithelial ovarian cancer (EOC) cases are attributed to genetic mutations, the Society for Gynecologic Oncology (SGO), National Comprehensive Cancer Network (NCCN)

and National Society of Genetic Counselors (NSGC) recommend genetic counseling and testing (GC/GT) for 100% of EOC patients.

Methods: We analyzed data from 557 women who were diagnosed with advanced EOC from 2001-2015 treated at a single-center cancer center. Information on demographics and socioeconomic status (age, race, education, marital status, children, insurance type), tumor characteristics (site of origin, grade, stage, histotype, debulking status, platinum sensitivity), treatment (sex of gynecologic oncologist, type of chemotherapy provider, clinical trial enrollment, number of therapy lines), survival (progression-free and overall), and referral to genetics counseling was abstracted from medical records. We used logistic regression models to estimate age-adjusted odds ratios and 95% confidence intervals for referral to genetics counseling according to each variable. Stepwise logistic regression was used to identify the most important predictors of genetics counseling referral, with $p<0.3$ as the model entry criterion and $p<0.2$ as the criterion for staying in the model.

Results: Overall, 29% of the ovarian cancer patients had been referred for genetic counseling. Higher educational level, female gynecologic oncologist, clinical trial participation, >1 line of therapy and longer survival were associated with greater likelihood of genetics counseling referral in age-adjusted models. Older age, non-serous histotype, suboptimal debulking status, platinum resistance and medical oncologist as chemotherapy provider were associated with lower likelihood of genetic counseling referral. Ten variables were selected as the most important predictors of referral during stepwise regression: younger age, white race, not having private insurance, professional school education, stage IV vs. III cancer, platinum sensitivity, being treated by a female gynecologic oncologist, having chemotherapy provided by a gynecologic oncologist, clinical trial enrollment, and longer overall survival.

Conclusions: Only 20-30% of EOC patients are referred to GC/CT on a nationwide level and similar results were found at our institution. Unique predictive factors will contribute to quality improvement and should be validated at a multi-institutional level to ensure the gold standard of care is provided to all EOC patients.

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Poster #2

Treatment with paclitaxel causes upregulation in resistance protein tubulin beta III in a type 2 human endometrial cancer cell line

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Objectives: The goal of this study is to test the hypothesis that paclitaxel-encapsulated microparticles (PMPs) are a feasible cytotoxic treatment modality in an in vitro model of a Type 2 uterine carcinoma cell line. Poly(lactic-co-glycolic acid)-based (PLGA) microparticles (MPs) are a promising new tool for delivery of cytotoxic chemotherapies. These MPs have the benefit of eluting drugs over a period of weeks for sustained pharmacokinetic effect, which may have a benefit in treating Type 2 endometrial adenocarcinomas that are associated with chemoresistance. Part of this evaluation included evaluating the cell line for resistance to paclitaxel. Overexpression of tubulin beta 3 (TUBB3) has been linked to paclitaxel resistance in many cancers including uterine carcinomas.

Methods: PMPs were prepared using established laboratory procedure to encapsulate 15mM paclitaxel in DMSO using a water/oil/water (W/O/W) method. Blank microparticles (BMPs) were formulated by repeating the process with DMSO only and used as a control. The human endometrial adenocarcinoma type 2 cell line KLE were plated in 6 well plates at a density of 2x10^5 cells and treated with BMPs and varying volumes of the 15mM PMPs (20, 40, and 60 μL). Cells were incubated for 6 days then harvested and underwent western blot analysis for cleaved PARP and TUBB3 with GAPDH loading control. Western Blot intensity was compared to controls for significance using t-test.

Results: Cells treated with PMPs showed decrease in cell density with morphologic changes consistent with apoptosis. For PMPs, increasing volumes showed an intensifying effect. Western Blot analysis for cleaved PARP, a byproduct of apoptosis, showed significant 9-17-fold increase in cells treated with PMPs compared to the control group. WB analysis also revealed an absence of TUBB3 in the controls. After treatment with PMPs, there was a statistically significant increase in TUBB3 for 40 μL ($p=0.02$) and 60 μL ($p=0.01$). There was an increase in TUBB3 at 20 μL of PMPs, but this did not show significance ($p=0.09$)

Conclusions: PLGA encapsulated paclitaxel is a feasible method to deliver cytotoxic chemotherapy in an in vitro model, as evidenced by gross morphologic changes and activation of apoptosis. This study also represents the first demonstration biochemically of upregulation of a resistance marker for paclitaxel as a response to treatment in a cell line that is negative for tubulin beta 3 prior to treatment.

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Poster #3

Does A1c predict surgical complications? A retrospective chart review of patients with Type II Diabetes Mellitus and Endometrial Cancer

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Objectives: The purpose of this study is to determine if patients diagnosed with Endometrial Cancer (EC) and Type II Diabetes Mellitus (DMII) are at increased risk for postoperative complications when compared to EC patients without DMII, and if preoperative A1c level influences risk.

Methods: This retrospective chart review included all women with EC ICD9 codes who underwent surgery and had follow up within 3 months at one of our facilities between Jan 2009- May 2017. Exclusion criteria included use of neoadjuvant therapies, and patients with a diagnosis of prediabetes receiving treatment. We defined DMII via past medical history documentation, an A1c > 6.5% at any time, or a day of surgery fasting blood glucose >126 mg/dL. We extracted A1c levels within 90 days of the surgery date to assess correlation with post-operative outcomes based upon A1C <8.0% and A1C ≥8.0%. We used EC patients without DMII as controls. Post-operative complications included readmission, transfusion, urinary tract infection, wound infection, wound dehiscence, wound seroma, wound hematoma, intrabdominal hematoma, facial dehiscence, vaginal cuff dehiscence, vaginal cuff infection, intrabdominal abscess, ileus, fever, VTE, psychosis, pneumonia, recurrence of disease, and mortality. Complications are listed in table 1 and were manually extracted from chart review. Multi variable models were used to compare the groups.

Results: We included 400 women with EC: 86% had Type I disease and 85.4% were Stage I. Overall, 44% of cases were laparotomies and 56% were laparoscopic. DMII was diagnosed in 29% (n=114) cases. In patients with DMII, 51% (n=58) of cases were laparoscopic and 49% (n=56) were laparotomies. DMII patients who underwent laparotomies were at significant risk for overall complications (OR 4.97, 95% CI: 1.96-12.64) and infectious/wound complications (OR 5.32, 95% CI: