Objectives: Vitamin D deficiency confers poor outcomes in many cancers. While little data exists regarding the relationship between vitamin D deficiency and ovarian cancer (OC), the vitamin D receptor (VDR) single nucleotide polymorphism (SNP), FokI, is associated with increased OC risk. The relationship between the VDR FokI SNP and circulating serum 25 hydroxycholecalciferol (25(OH)D) is unknown. While vitamin D aids in production of inflammatory hormones such as leptin, the relationship between leptin and 25(OH)D levels in OC patients (pts) has not been studied. This study aimed to characterize 25(OH)D levels at the time of OC diagnosis and its associations with treatment-related morbidity, leptin levels, and VDR SNP status.
Methods: A retrospective review was performed of pts diagnosed with OC treated at a single institution. Pts were grouped by serum 25(OH)D status, with 25(OH)D deficiency defined as < 20 ng/mL and insufficiency 20-29 ng/mL. Demographics, clinical characteristics, treatment-related morbidity, survival, serum 25(OH)D, leptin, and VDR SNP markers were compared between groups.
Results: Of 122 pts included in the study, 82 were 25(OH)D deficient, 21 were insufficient, and 19 were normal. The median age was 67 yrs, and 70% were stage III/IV. There were no differences in demographics, stage, treatment-related morbidities or survival between groups (all p>0.05). There was no difference in serum leptin levels or SNP allele status between groups (all p>0.05). Due to differences in severity of disease and expected disease outcomes, further analysis was restricted to those with stage III/IV OC (n=85, deficient n=59, insufficient n=13, normal n=13). For this cohort, there was no difference in demographics, treatment-related morbidities, or survival (all p>0.05). When adjusted for BMI, there was no difference in serum leptin levels between groups or SNP allele status (all p>0.05, Table). There was no association between SNP allele groups and progression free (p=0.44) or overall survival regardless of 25(OH)D status (p=0.96).
Conclusions: This study did not detect an association between serum 25(OH)D levels and treatment-related morbidity, leptin levels, or VDR SNP status in women with OC in either the overall population or only those with stage III/IV disease. Interpretation is limited by small numbers and the retrospective design. Few patients receiving neoadjuvant chemotherapy were included in this study likely introducing selection bias. Prospective evaluation is ongoing.

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Poster #29

Family history of cancer associated with improved survival in uterine serous carcinoma

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Objectives: Uterine serous carcinoma (USC), a subset of endometrial cancers, accounts for fewer than 10% of cases, but disparately accounts for 50% of uterine cancer related deaths. Prior reports indicate an association between USC and BRCA 1 germline mutations. Our objective was to compare the survival of patients with USC with and without a family history of breast, ovarian, uterine, GI, pancreatic, brain, melanoma or GU cancers (Multiple Organ Hereditary Cancers or MOHC).
Methods: We extracted all genetic alterations in the commonly tested genes during genetic panel testing, progression free survival (PFS), and overall survival (OS) from The Cancer Genome Atlas (TCGA) in all patients with USC. We performed a multi-institutional retrospective review of all patients who were diagnosed with USC from 2005 to 2014. Demographics and clinic-pathologic data were obtained. Disease progression was defined by RECIST criteria. Statistical analysis was performed using the Kaplan-Meier Survival Analysis.
Results: Genetic alterations in the following commonly tested genes were extracted from TCGA in USC patients: BRCA1, BRCA2, CHEK2, BRIP1, RAD51C, BARD1, TP53, RAD50, RAD51D, ATM, NBN, PALB2, MRE11A, MSH6, MLH1, MSH2, PMS2. In those with advanced (stage III/IV) USC (n=69), PFS and OS were worse in patients with a genetic alteration of the above genes versus those without (PFS of 47.7 versus 19 mos and OS of 50.9 versus 30.1 mos; P = 0.01). One hundred ninety patients with USC were included in the retrospective analysis. Greater than 50% of the patients had a personal and/or family history of MOHC. 30% of these patients had a personal history of MOHC. When comparing survival between those with and those without a personal and/or family history of MOHC, patients with a MOHC history had longer PFS (49 versus 20 mos, P = 0.01) and longer OS (65 versus 34 mos, P = 0.01). Although not significant, a difference in overall survival was seen among patients with advanced USC (n=104) with a personal and/or family history of MOHC versus those without (35 versus 20 mos, P = 0.16).
Conclusions: Women with USC with a personal and/or family history of MOHC have improved survival compared to those without. Identification of genetic predisposition may improve treatment options and outcomes in this subgroup of patients. Genetic testing should be considered in patients with USC.

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Poster #30

Chromobox 2 protein identified as driver of anoikis-escape and disease progression in high grade serous ovarian cancer

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Objectives: Chromobox 2 (CBX2), a polycomb repressor complex subunit, plays an oncogenic role in a variety of cancers. In prostate cancer, CBX2 is a driver of metastatic progression. We sought to investigate the hypothesis: CBX2 upregulation promotes advanced high grade serous ovarian carcinoma (HGSOC) by promoting a stem-like transcriptional profile and inhibiting anoikis.
Methods: Gene Expression Omnibus (GEO) and The Cancer Genome Atlas (TCGA) were queried to establish CBX2's role. In vitro evaluation of CBX2 occurred in PEO1, OVCAR8, and OVCAR4 HGSOC cell lines. PolyHEMA-coated plates forced cells to grow in suspension and simulated anoikis-escape. Quantitative polymerase chain reaction and immunoblots evaluated CBX2 expression. Small hairpin RNAs (shRNAs) knocked down CBX2 for loss-of-function studies. To mimic HGSOC progression several culture conditions (2D, colony formation, and 3D, spheroid) were examined. Secreted luciferase (gLuc) activity was utilized as a proliferation indicator. Stemness was tested with the Aldefluor assay, measuring aldehyde dehydrogenase activity (ALDH). Using patient tumors from the Gynecology Tissue and Fluid Bank (GTFB) and a HGSOC tissue microarray (TMA) with matched primary, metastatic, and lymph nodes, a CBX2 expression profile was established. Student's t-test was used to define statistical significance, with a p value of < 0.05.
Results: GEO/TCGA analyses established CBX2 is upregulated in HGSOC tumors compared to benign tissues and CBX2 expression conveyed worse disease-free survival (11.7 vs 17.6 months, Log-rank test p-value < 0.005) and overall survival (34 vs. 44.8 months, Log-rank test p-value <0.005). PEO1, OVCAR8 and OVCAR4 cells upregulate CBX2 when grown in suspension compared to adherent conditions. CBX2 knockdown led to a significant inhibition of proliferation in all culture conditions. Forced suspension promoted increased ALDH

activity and CBX2 knockdown led to a decrease in ALDH activity. Examination of primary samples from the GTFB and TMA revealed CBX2 expression is increased in HGSOC and is upregulated in approximately 58% of metastases when compared to the primary tumor.
Conclusions: CBX2 directly impacts proliferation and is overexpressed in HGSOC, indicating CBX2 may be associated with advanced disease. Elucidation of the mechanism is ongoing, however, a stem-like phenotype seems to play a role. This work expands our understanding of HGSOC progression and identifies a novel therapeutic target.

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Poster #31

Salvage treatment in recurrent endometrial cancer of the pelvis and peritoneal cavity

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Objectives: Regional recurrence of endometrial cancer (EC) is uncommon but represents a challenging yet potentially curable group of patients. Here we seek to determine optimal methods of salvage therapy for regionally recurrent EC.
Methods: A single institution database was analyzed from 2007 to present with 22 cases identified of nodal, pelvic, or peritoneal cavity recurrences of EC treated with curative intent. Patient, tumor, and treatment characteristics were identified and analyzed for both initial and recurrent treatment. Univariable Cox proportional hazards models were used to estimate the risk of a second recurrence. Due to sparse event rates, conclusions were confirmed with Fisher's exact tests.
Results: At diagnosis, 73% were endometrioid histology, 73% stage 1, and 27% with LVSI. Of 22 cases of recurrent EC, 13 recurrences (59%) were regional including the pelvic and paraaortic nodes, while 9 recurrences (41%) were to the abdomen. Twelve patients experienced remission from last treatment to most recent follow up ranging from 20 days to over 6 years. Nine (75%) of the patients currently in remission underwent surgery, EBRT, and chemotherapy. Nine of 22 patients experienced a second pelvic or peritoneal recurrence (41%). Three of the 4 patients with distant metastases had regional or abdominal recurrences. The overall probability of survival two years after a regional or abdominal recurrence treated with salvage therapy was 69% (95% CI: 38% - 86%). The overall probability of progression-free survival at 2 years was 51% (95% CI: 26% - 72%).
Conclusions: In this sample, we found no meaningful association of a definitive salvage regimen and survival for recurrent EC of the pelvis and peritoneal cavity. Aggressive use of multimodality therapy with surgery followed by tumor-directed radiotherapy and chemotherapy has favorable progression-free and overall survival in this very high-risk population of recurrent EC patients.

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Poster #32

Determining the methylation patterns of clinically normal endometrium and multiple tumor regions from uteri containing endometrial cancer

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Objectives: Aberrant DNA methylation occurs early in carcinogenesis and is being explored as a biomarker for early detection of endometrial cancer (EC). Methylation can be present as a field effect in histologically normal tissues and can be associated with future cancer development. Additionally, molecular diversity or intratumoral heterogeneity (ITH) within a cancer can be related with a higher risk of recurrence. Here we explore the field effect and ITH of EC through methylation analyses of normal and tumor regions.
Methods: Cases of hysterectomy for EC from 1/2011-12/2013 were retrospectively identified. Women with germline genetic mutations, presence of synchronous cancers, or history of chemotherapy or radiation receipt were excluded. Normal endometrium (NE), pre-cancerous lesions (PC), and up to 3 separate tumor regions from within each hysterectomy specimen were selected by a single gynecologic pathologist. Extracted DNA from each area underwent pyrosequencing of 4 genes previously identified as methylated in type I (RASSF1A, CDH13) or type II (HTR1B, ADCYAP1) EC. Methylation percentage was evaluated individually across CpG sites and averaged across each gene. The CpG sites of each gene were noted to have consistent methylation using hierarchical clustering. Differences in methylation between NE and EC for each gene were assessed using paired t test. Patterns of methylation across the tumor regions within the patient and between patients were assessed using principal component analysis.
Results: Among 24 EC cases, 4 were clear cell (CC), 6 grade 1 or 2 endometrioid adenocarcinoma (EA1/2), 4 grade 3 endometrioid adenocarcinoma (EA3), and 10 serous. The mean age of this cohort was 64 years. In the hysterectomy specimens, NE areas were available in 14/24 (58%), PC lesions in 11/24 (45%) and 3 separate tumor regions in 22/24 women (91%). NE had significantly lower methylation than tumor regions for all the 4 genes (all $p<0.005$). Tumor methylation did not appear to be is associated with age for any of the genes tested. Intratumoral variation in methylation was observed, though the level of magnitude was smaller than the difference in tumor vs. NE or tumor vs. PC lesions. Fig 1
Conclusions: Normal endometrium did not exhibit epigenetic changes identified in EC tumor regions and methylation ITH was observed in EC tumors. Both of these findings suggest molecular changes associated with EC development are focal but heterogeneous.

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Poster #33

Clinicopathologic factors associated with increased risk of recurrence in stage IA grade 1 endometrial cancer

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Objectives: Endometrial cancer (EC) recurrence risk generally depends on pathologic prognostic factors such as stage, grade, depth of myometrial invasion (MI), and lymph node (LN) involvement. FIGO Stage IA grade 1 (IA G1) endometrial cancers lack most adverse features and are categorized in the low recurrence risk group, however, the factors associated with recurrences in this group are not clearly defined though recurrences have been reported in about 5% of cases. The purpose of this study was to identify clinical and pathologic factors that predict for tumor recurrence in IAG1 EC.
Methods: We retrospectively reviewed clinical records for EC patients diagnosed between January 1996 and July 2017 at our institution. 127 patients with FIGO 2009 Stage IA grade 1 EC who underwent surgical resection were included. Baseline characteristics were analyzed with chi-square tests. Univariate logistic regression analysis was performed to test for factors that associate with recurrence.
Results: Median follow up was 22 months (m). Tumor recurrence was recorded in 12 (8.6%) of patients with median time to