EP111/#1490 PROTEOGENOMICS DELINEATE PATHOGENESIS, MOLECULAR CHARACTERISTICS, AND PREDICTORS OF PROGESTIN RESPONSE IN EARLY-ONSET ENDOMETRIOID ENDOMETRIAL CANCER

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Introduction Endometrial carcinoma (EC) remains a public health concern with a growing incidence particularly in younger women. Women with early-onset endometrioid EC (EEEC) who wish to maintain fertility are a worldwide concern, and biomarkers for predicting which patients will respond to progestin-based fertility-sparing therapy are a major unmet clinical need.
Methods To comprehensively characterize the proteogenomic characteristics of the early-onset endometroid endometrial carcinoma (EEEC), we conducted a multi-omics study (genomics, and proteomics) with FFPE tissues from paired tumor and normal tissues of 222 endometrioid ECs (including 81 EEECs younger than 40 who mainly received fertility-sparing treatment) and 14 atypical endometrial hyperplasia (AEH) patients from Tongji and Fudan Hospital (TJFD cohort) in China.
Results EEEC was featured by exclusive germline muataions,a higher BMI and downstream dysregualted lipid metabolism signaling. Our integrated multi-omics analysis unexpectedly revealed an exposome-related mutational signature to be associated with EEEC leading to EEEC specific CTNNB1 and SIGLEC10 hotspot mutations and downstream protein pathway disturbance. Interestingly, in EEECs $SIGLEC10^{Q144K}$ mutation resulted in aberrant Siglec-10 protein expression and promoted progestin resistance by interacting with ERα. We identified and validated four (EEF1E1, ILVBL, SRPK1 and NUDT5) biomarkers of progestin resistance.
Conclusion/Implications Our study provides a unique high-quality proteogenomic resource of EEECs, and explicates the distinct clinical and molecular characteristics of EEECs, encompass-ing obesity, genetic susceptibility, and environmental exposure, that are concomitant with pathogenesis and progestin resistance. Furthermore, we identified biomarkers for progestin response in EEEC fertility-sparing treatment. These attributes can be utilized to promote primary prevention and early detection of EEECs

EP112/#1491 PROTEOGENOMICS DECIPHER DISTINCT METASTASIS PATTERNS AND BIOMARKERS OF ENDOMETRIAL CARCINOMA

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Introduction Endometrial carcinoma is a common gynecologic malignancy, and lymph node metastasis greatly affects patient outcomes. Proteogenomics analysis has emerged as a powerful tool for identifying molecular mechanisms involved in cancer progression and metastasis, offering potential for biomarkers discovery and personalized treatment strategies.
Methods In this study, we utilized WES, proteomics, and multiplex immunohistochemistry to investigate the metastasis patterns of different molecular subtypes in a cohort of 96 EC patients with lymph-node metastasis and 126 without metastasis. Our aim was to elucidate the molecular characteristics that distinguish between these two groups and identify potential biomarkers for metastasis.
Results Proteogenomics analysis identified two distinct metastasis patterns of EC associated with TME. One pattern is characterized by an immune-cold phenotype, which is predominantly observed in patients with the MSI subtype. These patients often exhibit JAK1 mutations, defects in immunoproteasome components and HLA complexes, leading to deficiencies in antigen presentation pathways, resulting in immune evasion. The other is characterized by an immune-hot phenotype, mainly distributed in the CNL and few MSI subtype, with significant infiltration of macrophages and upregulation of integrin pathways, promoting tumor cells to undergo mesenchymal transition. Additionally, we explored and validated three consensus biomarkers shared across diffrerent molecular subtypes for predicting lymph-node metastasis.
Conclusion/Implications Our research provides an unprecedented large-scale multi-omics resource of lymphatic metastasis EC, offering novel insights and new biomarkers for effectively stratifying high-risk patients for lymphatic metastasis. We have deciphered two distinct metastasis patterns in EC, which can be exploited for the development of personalized screening and targeting strategies.

EP113/#220 COMPOUND AC1Q3QWB UPREGULATES CDKN1A AND SOX17 VIA INTERRUPTING THE HOTAIR-EZH2 INTERACTION AND ENHANCES THE EFFICACY OF TAZEMETOSTAT IN ENDOMETRIAL CANCER

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Introduction Endometrial cancer (EC) is a common female reproductive system malignant tumor, with increasing incidence rates and poor prognosis in recurrent/metastatic cases. The interaction between long non-coding RNA HOTAIR and polycomb repressive complex 2 (PRC2) causes the abnormal suppression of tumor suppressors, which plays a crucial role in tumor development. This study aims to investigate the potential of AC1Q3QWB (AQB) to interrupt the HOTAIR-EZH2 interaction in EC and evaluate a novel combination therapy of AQB and tazemetostat (TAZ).
Methods RNA immunoprecipitation (RIP) and chromatin isolation by RNA purification (ChIRP) assays were utilized to verify the interference of AQB with HOTAIR-EZH2 interaction in EC cells. The Agilent Human ceRNA Microarray was employed to identify tumor suppressors upregulated by AQB and TAZ, while the chromatin immunoprecipitation (ChIP) assay was performed to investigate the mechanism of genes activation. The combination therapy of AQB and TMZ was used for in vivo experiments.
Results AQB inhibited HOTAIR and EZH2 binding in EC cells, restoring the expression of numerous tumor suppressors. In vitro, the combination of AQB and TAZ produced a

synergistic effect, significantly upregulating CDKN1A and SOX17, which resulted in cell cycle arrest and inhibited the proliferation, migration and invasion of EC cells. Additionally, it showed that AQB can enhance the anti-tumor effect of TAZ in vivo.

Conclusion/Implications AQB has demonstrated a promising inhibitory effect on EC cells. When combined with TAZ, the expression of CDKN1A and SOX17 was significantly upregulated, resulting in more potent anti-tumor effects. This combination therapy could provide a novel strategy for treating EC.

EP114/#688 EVALUATING CDK 4/6 INHIBITORS IN COMBINATION WITH ENDOCRINE THERAPY IN ENDOMETRIAL CANCERS: A RETROSPECTIVE STUDY

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Introduction CDK 4/6 inhibitors (CDK4/6i) with endocrine therapy (ET) has promising phase II results in estrogen receptor (ER)+ recurrent/advanced endometrial cancer (EC). The purpose of our study is to evaluate characteristics and clinical outcomes of patients with ER+EC who have received a CDK4/6i+ET at our institution.

Methods This is a multi-center institution retrospective chart review, which included patients diagnosed with endometrial cancer and treated with CDK4/6i+ET between 2016- March 2023 for $\geq$1 month in duration. Outcomes evaluated included time to treatment failure (TTF) and progression free survival (PFS).

Results Thirteen patients were identified, with an average age of diagnosis at 61 years (IQR: 50–68). The most common histopathologic diagnosis was endometrioid (n=8, 61.5%), followed by endometrial stromal sarcoma (ESS) (n=4, 30.8%). The median follow-up after CDK4/6i was 8.6 months (IQR 4.7–17.5). The median number of treatments since recurrence was 2, including 9 with prior ET. The TTF in the endometrioid group was 5.1 months (95% CI 3.8-NR), where PFS was not reached (NR) (95% CI 5.4-NR). The TTF and PFS in the ESS group was the same at 9.8 months (95% CI 7.9-NR). Four patients were still on treatment upon study completion, five patients discontinued due to disease progression, and four discontinued because of toxicity.

Conclusion/Implications Patients with ER+EC have reasonable responses to CDK4/6i+ET with the majority of patients with endometrioid histology discontinuing due to toxicity rather than progression. This data supports the findings from the previously published clinical trials that CDK4/6i+ET should be considered as a treatment option in recurrent ER+EC.

EP115/#847 CORRELATION BETWEEN MISMATCH REPAIR STATUS AND LYMPH NODE METASTASIS IN ENDOMETRIAL CANCER

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Introduction Endometrial cancer is the most common gynecologic malignancy worldwide, and lymph node metastasis is a major prognostic factor for patients with this cancer. Mismatch repair (MMR) deficiency is known to play a critical role in the development of endometrial cancer, but its association with lymph node metastasis and recurrence remains unclear. In this study, we aimed to investigate the correlation between MMR status and lymph node metastasis/recurrence rate in endometrial cancer.

Methods We retrospectively analyzed 59 patients with endometrial cancer who underwent surgery and received MMR testing at out institution between 2010 and 2022. Immunohistochemistry was performed to assess the expression of MMR, including MLH1, PMS2, MSH2, and MSH6.

Results Of these patients, 14 (23.7%) had MMR deficiency. The MMR deficient group had a higher proportion of early stage (stage I and II) compared to the MMR proficient group (78.6% vs. 64.4%). However, lymph node metastasis was more common in the MMR deficient group (21.4%) compared to the MMR proficient group (13.3%) (p=0.038). Furthermore, the recurrence rate was higher in the MMR deficient group (21.4% vs. 15.6%).

Conclusion/Implications Therefore, MMR status may serve as a useful biomarker to predict the risk of lymph node metastasis and recurrence in patients with endometrial cancer. Based on our findings, knowing the MMR status before surgery may help in determining an appropriate surgical plan, which could potentially improve the prognosis and quality of life of the patients. Further studies with larger sample sizes are needed to validate our findings.

EP116/#189 RADIOGRAPHER LED INSERTION OF POST-OPERATIVE VAGINAL APPLICATOR FOR ENDOMETRIAL CANCER BRACHYTHERAPY: CLATTERBRIDGE CANCER CENTRE EXPERIENCE

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Introduction Vaginal vault brachytherapy (VBT) using post-operative vaginal applicator (POVA) has been a standard adjuvant treatment for endometrial cancer and reduces the risk of local recurrence. The Clatterbridge Cancer Centre (CCC) has offered VBT since the start of the service. Radiographer-led delivery of POVA was implemented to free up clinician time and improve service delivery. Historically all POVA insertions were carried out by the clinicians. More recently clinicians have performed the initial assessment and applicator placement for the first insertion and the subsequent insertions were then carried out by competent radiographers. The aim of this study was to evaluate the safety and effectiveness of radiographer-led delivery for subsequent treatments.

Methods This is a retrospective audit of endometrial cancer patients treated with VBT between 31st March 2020 and 28th February 2023. The aim is to identify the frequency of clinician input for the subsequent treatments and identify any complications.

Results During the specified time period, 278 patients were treated with VBT amounting to a total of 724 treatments. All of the 278 planned first fractions were carried out by the clinicians and only 15 of the subsequent 446 treatments