AN ALGORITHM BASED ON CD8 AND CD68/PD-1 EXPRESSION WITHIN THE TUMOUR IMMUNE MICROENVIRONMENT DETECTED BY MULTIPLEXED IMMUNOFLUORESCENCE CAN DISCRIMINATE FIGO IA AND IB ENDOMETRIOID ENDOMETRIAL CARCINOMAS

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Introduction/Background Most low-risk, early-stage disease endometrioid endometrial carcinomas (FIGO stage 1 EEC) have a good clinical outcome. 5–10% of these patients will suffer recurrence. The tumour immune microenvironment is closely associated with the tumour biology and has been shown to be a powerful prognostic tool in several tumour types.

Methodology A retrospective cohort of hysterectomy specimens (n=75) with FIGO stage 1 EEC from our institution were identified. 77.8% were stage IA and 22.2% stage IB. MELF (Microcystic, elongated, and fragmented) pattern of myoinvasion was detected in 21%. A TMA with 3 regions of interest (ROI) was constructed. Multiplexed immunofluorescence was used to assess staining for CD3, CD8, CD20, CD68, PD-1, PD-L1, FOXP3 and pan-cytokeratin on the Vec- tra Polaris™ platform and analyzed using QuPath software. Discriminant function analysis was performed to classify patients in ‘Stage IA’ vs. ‘Stage IB’, according to invasion. All the analyses were performed with IBM SPSS version 20 and OpenEpi. We fit a logarithmic curve to predict invasion in mm based on CD8.

Results Statistical analyses (chi-square test) showed that CD20, CD68, Foxp3, Foxp3/PD1, CD68/PD1 and CD/PD1 were associated (p<0.05) with MELF but not with depth of invasion (mm). The discriminant model (Stage IA vs IB) obtained the following equation: Classification score = 1.081 + 0.002 (mean_CD8) – (0.005* mean_CD68_PDL1). Sensitivity and specificity for the score were: 68.42% (95% CI 52.54, 80.92) and 57.14% (95% CI 32.59–78.62). Positive Predictive Value was 81.25%. We fitted a logarithmic curve for the prediction of invasion the model was the following mm invasion = 13.725 – 1.446 (ln(mean_CD8)) (figure).

Conclusion An algorithm based on combined CD8 and CD68/PD1 expression can discriminate the likelihood of Stage IA or stage IB tumours from a small tissue sample. In addition, mean of CD8 expression was associated with mm of invasion [AG1] (curve, figure).

FREQUENCY OF MMR DEFICIENCY FOR PRIMARY ENDOMETRIAL NEUROENDOCRINE CARCINOMA AND ITS THERAPEUTIC OUTCOME IN JAPAN

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Introduction/Background Primary endometrial neuroendocrine carcinoma (PENEC) is a histological type with a very poor prognosis compare to the other histological type in endometrial cancer. However because of the rarity, an effective adjuvant chemotherapy regimen has not been established. In recent years, it has been reported that the mutation frequency of mismatch repair (MMR) genes is as high as 44% in 8 of 18 cases. Since PENEC is extremely rare, there is no accumulation of cases or additional reports, and there is also no study in Japan.

Methodology In this study, we investigated the frequency of MMR gene mutations and its treatment outcomes in 15 cases of PENEC diagnosed between 2011 and 2021 at 7 institutions approved by the Juntendo University Institutional Review Board.

Results The histological types of 15 cases were pure large cell NEC (LCNEC) 2 cases, pure small cell NEC (SCNEC) 4 cases, endometrioid carcinoma + LCNEC 3 cases, endometrioid carcinoma + SCNEC 4 cases and carcinosarcoma + SCNEC 2 cases. Of the 15 cases, 46.7% of the 7 cases presented with MMR gene mutations. The patterns of MMR gene mutations were MLH-1+PMS-2 mutation in 6 cases and MSH-2 mutation in 1 case. The PFS was 8.5 months and 10 of 15 cases had recurrence within 3 years. Of the 7 patients with MMR gene mutations, 2 patients who received pembrolizumab both showed partial response. This study suggests that MMR gene mutations are also recognized at a high rate of 46.7% in PENEC in Japan.

Conclusion In the case of PENEC, we should investigate the microsatellite instability (MSI) at the time of recurrence, and if ishowed MSI-high, pembrolizumab administration should be considered. In addition, it will be necessary to plan clinical trials to examine the additional effect of pembrolizumab at the first adjuvant chemotherapy.

IMPACT OF MOLECULAR PROFILING ON ENDOMETRIAL CANCER STAGING: TOWARDS A PERSONALIZED SURGERY

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Introduction/Background Molecular profiling in endometrial cancer (EC) is a consistent information that we may obtain from the pre-operative specimen. Nevertheless, its use for making surgical decisions has been barely explored. We aimed to analyze the impact of molecular profile in EC from a...
surgical perspective, to identify which tumors will most benefit from an extensive surgery and in which it could be avoided safely.

Methodology A cohort of 689 patients with EC treated at Hospital Vall d’Hebron, Barcelona, from 1992–2022 were retrospectively recruited. Clinical, surgical and pathological data were reviewed, and molecular profiling was performed in surgical specimen or preoperative biopsy. Tumors were classified according recommendations for molecular classification reported in ESGO-ESTRO-ESP 2020 Guidelines on EC.

Results The distribution of the cohort was as follows: 47 patients were POLEmut EC(6.8%), 104 patients p53abn EC (15.1%), 242 patients MSI EC(35.1%) and 296 patients NSMP(43%). Patients with POLEmut EC were significantly younger (57 y) and p53abn EC were elderly (67 y) than the rest of the cohorts(64 y, p=0.026). Patients with p53abn EC showed a higher proportion of non-endometrioid histologies (table 1).

Conclusion p53abn EC represents a subset of patients diagnosed with high rates of lymph-node involvement and peritoneal spread, and shows the worst oncological results in terms of survival.

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TARGETING ANDROGEN AND ESTROGEN RECEPTOR SIGNALING IN PATIENT-DERIVED ENDOMETRIAL CANCER ORGANOIDs

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Introduction/Background Alternative treatment options for endometrial cancer (EC) when chemotherapy fails are few. We have previously demonstrated the prognostic impact of Androgen receptor (AR) expression in EC (Tangen et al., 2016). However, the therapeutic potential of targeting AR in EC is not known. Patient-derived cancer organoids have recently developed as valuable tools for drug testing as they better represent the genetic background of the patient cohort. We recently reported a collection of patient-derived EC organoids (Berg et al., 2021), and have expanded this series to include models with distinct pattern of hormone receptor (HR) expression. Here we report preliminary data on the therapeutic effect on targeting AR and ER signaling pathways in a panel of EC organoids representing all subtypes and molecular subgroups of EC.

Methodology Patient-derived EC organoid models, representing the main histological subtypes of EC and distinct patterns of HR expression, were treated both short-term (48 hours) and long-term (18 days) with AR and ER agonists, R1881 and Estradiol, and the AR and ER antagonists, Enzalutamide and Fulvestrant. Response to treatment was evaluated using CellTiter-Glo 3D assay and Incucyte Live Cell System. Protein expression of AR and ER pre- and post-treatment was evaluated by immunohistochemistry.

Results EC organoid models with distinct hormonal expression of AR and ER showed model-specific response to short-term exposure to hormonal therapy. Modulation of expression and