Poster rounds with the professors: Group E1

1/#337 MOLECULAR CLASSIFICATION OF ENDOMETRIAL CANCERS USING AN INTEGRATIVE DNA SEQUENCING PANEL

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Objectives Molecular classification of endometrial cancers (EC) is critical for prognostication, but adoption into clinical practice remains challenging due to complexity and costs of sequencing. We aimed to develop a simple molecular technique to classify EC using a high-depth targeted sequencing panel.

Methods Leveraging on a prospective study of newly diagnosed EC from three cancer centers, 181 formalin-fixed paraffin-embedded (FFPE) samples were sequenced. Our panel identified somatic mutations, copy number variants, insertions/deletions, loss of heterozygosity, structural rearrangements and promoter methylation from a single aliquot of DNA. Variants were analyzed for pathogenicity and clinicopathologic information was collected.

Results Of 181, 86 (48%) were classified as microsatellite instability-high (MSI-h/MMRd), of which 62 (72%) harbored MLH1 promoter methylation and 24 (27%) had pathogenic variants in MMR genes. Of cases with single classifier, three (1.6%) had POLE mutation (POLEmut), 15 (8%) had p53 variant (p53mut) and 61 (34%) had no specific molecular profile. Sixteen (9%) were multiple classifiers, with 8 (4%) MMRd-p53mut, 6 (3%) MMRd-POLEmut, 1 (0.5%) MMRd-p53mut and 1 (0.5%) POLEmut-p53mut. Survival outcomes stratified similarly to TCGA, but when MMRd group was subclassified, MLH1 methylated group had worse outcomes as compared to POLEmut subtype (p=0.396).

Conclusions Our NGS panel can classify EC into 4 TCGA subgroups through a simplified process. The difference in survival between MLH1 methylated group within MMRd cohort suggests that further subclassification is required for accurate prognostication.

REFERENCE

2/#338 ARE MISMATCH REPAIR DEFICIENT ENDOMETRIAL CANCER RECURRENCES MORE SALVAGEABLE THAN INTACT COHORT?

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Objectives Studies suggest increased radiosensitivity in mismatch repair deficient (MMRd) endometrial cancers (ECs) compared to MMR intact (MMRi) cohort. The aim of the study was to compare the recurrence patterns between MMRd and MMRi EC and assess whether the use of radiation leads to higher salvage in MMRd recurrences.

Methods Newly diagnosed EC of all stages and histology were prospectively recruited from 3 cancer centers in Ontario, Canada between 2015–2018. Tumors were reflexively assessed for MMR by immunohistochemistry. Clinicopathological, survival and recurrence details were compared between the MMRd and MMRi cases.

Results Of 666 cases, there were 83 (12%) recurrences, with 26 (31%) in MMRd and 57 (69%) in MMRi cohort after median follow-up of 26 months. There were no differences in their stage, grades, lymphovascular space invasion or type of molecular classification.
adjuvant therapy. Local vaginal/pelvic recurrences were more common in the MMRd than MMRi cohort (65% vs. 30%) whereas distant recurrences were more common in MMRi cohort (70% vs. 35%). Post-recurrence survival was higher in MMRd cohort (43.8 vs 20 months; p=0.306). Of those with local recurrences, RT with curative intent was used in the majority (9/15 in MMRd and 7/8 in MMRi). All of those with local recurrences with MMRd tumors salvaged with curative intent RT are alive without disease (9 of 9), whereas only 2 with MMRi tumors are alive without disease (2 of 7).

Conclusions MMRd ECs are more likely to recur locally with high rate of salvage with RT, possibly indicating the increased radiosensitivity in this cohort.

**4/#474**

**MOLECULAR LANDSCAPE OF ERBB2/HER2 GENE AMPLIFICATION AMONG PATIENTS WITH ENDOMETRIAL CARCINOMA**

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Objectives Investigate the incidence of ERBB2/HER2 gene amplification among patients with endometrial cancer.

Methods The AACR GENIE v12.0 database was accessed and patients with endometrioid (EEC), serous (USC), clear cell (UCC) and carcinosarcoma (UCS) and data on copy-number gene alterations were selected for further analysis. Incidence of ERBB2/HER2 gene amplification was investigated while the genomic profile of patients with ERBB2 amplification was further explored. Data from the OncoKB database was utilized to determine pathogenic gene alterations.

Results A total of 2784 patients were identified; 1648 with EEC (1708 samples), 573 with USPC (593 samples), 389 with UCS (389 samples) and 93 with UCC (94 samples). Overall incidence of ERBB2 amplification was 4.5% (n=124); 12% (n=71) for UPSC, 8.5% (n=8) for UCC, 7.2% (n=28) for UCS and 1% (n=17) for EEC. Among samples with ERBB2 amplification, the most prevalent alterations involved the TP53 (91%), PIK3CA (47%), CCNE1 (23%), FBXW7 (24%), MYC (13%), PIK3R1 (17%), KRAS (10%), ARID1A (8%), and ERBB3 (8%) genes. For patients with EEC and ERBB2 amplification, 64.7% (n=11) had a TP53 mutation. However, among patients with EEC and a TP53 mutation (n=304), the overall incidence of ERBB2 amplification was 3.6%.

Conclusions While ERBB2 amplification is frequently encountered among patients with USC, a high incidence was also observed among those with UCC, and UCS. For patients with EEC, incidence of ERBB2 amplification is low, especially in the absence of TP53 mutations. Half of tumors with ERBB2 amplification harbored a PIK3CA mutation providing rationale of the combination of transstuzumab with mTOR/AKT inhibitors in future trials.

**5/#274**

**IS REFLEX MLH1 PROMOTER HYPERMETHYLATION TESTING FOLLOWING MLH1 LOSS BY IMMUNOHISTOCHEMISTRY IN ENDOMETRIAL CARCINOMA BEST PRACTICE?**

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Objectives Reflex screening of newly diagnosed endometrial carcinomas (EC) was introduced in Ontario for women <70 in 2018 and regardless of age in 2020. MLH1 deficient (MLH1-d) cases by immunohistochemistry (IHC) are further analyzed to detect MLH1 promoter hypermethylation