

Frequent homologous recombination deficiency in high-grade endometrial carcinomas

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Purpose of the Study: High-grade endometrial cancers (EC) generally have a poor prognosis with limited treatment options. The high levels of genomic instability including high somatic copy number alterations (sCNA) in a subset of these EC are reminiscent of defects in pathways governing genome integrity. Here, we assessed the occurrence of homologous recombination deficiency (HRD) in EC in relationship to the underlying aetiology.

Methods: Fresh tumor tissue of 36 EC was prospectively collected between 2015-2017. The ability of replicating tumor cells to accumulate RAD51 protein at DNA double strand breaks (RAD51 foci) induced by ionizing radiation was used as a functional read out for HR capacity. Tumors were molecularly characterized by comprehensive genetic analysis (next generation sequencing and array comparative genomic hybridization). Additionally, we determined the prevalence of *BRCA*-like sCNA-profiles (surrogate marker HRD) in the TCGA-EC cohort.

Summary of results: HRD was observed for 24% of EC and was significantly associated with non-endometrioid morphologies (46% HRD, $p=0.014$). None of the low-grade endometrioid EC were HRD. HRD was exclusively found in TP53-mutant EC, and genetic characterization revealed either pathogenic variants in *BRCA1* or significant somatic copy number losses in HR-genes. TCGA data supported our finding, as *BRCA*-like profiles were present in 42% (81/192) of NEEC and 8% (33/404) of EEC.

Conclusions: Homologous recombination deficiency is a frequent event in EC, particularly in non-endometrioid, TP53-mutant EC. This finding supports treatment strategies for these patients that exploit HRD, like platinum and PARP inhibitors.