The relevance of estrogen-driven tumor growth within molecular subgroups of endometrial cancer

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Introduction

- The presence of estrogen -, and progesterone receptor expression (ER/PR) is determined by immunohistochemistry.
- In endometrial cancer (EC), ER/PR expression is prognostically relevant.
- ER/PR expression ≠ estrogen driven tumor growth.
- ER-pathway activation (ERPAS) can be determined by measuring RNA levels of activated ER genes. (OncoSIGNal, InnoSIGN B.V., The Netherlands)
- ER/PR expression is present across all TCGA-based subgroups.
- Yet, whether ER-pathway is activated in the TCGA molecular subgroups is unclear

Primary objective

To identify ***estrogen driven tumor growth*** by ERPAS in the TCGA-based molecular subgroups of endometrial cancer.

Methods

72 endometrial cancer cases with >36 months follow-up.

ER/PR-IHC expression analysis
Cut-off value of 10%

ERPAS
was inferred from ER-target gene activity using OncoSIGNal in isolated RNA from tumor tissue. An active ERPAS was defined as a score >29,7.

TCGA molecular classification
was performed using Next Generation Sequencing with single-molecule Molecular Inversion Probes (smMIPs) and subsequently grouped in the *POLE*-mutant, MSI, *TP53*-mutant or no specific molecular profile (NSMP) group.

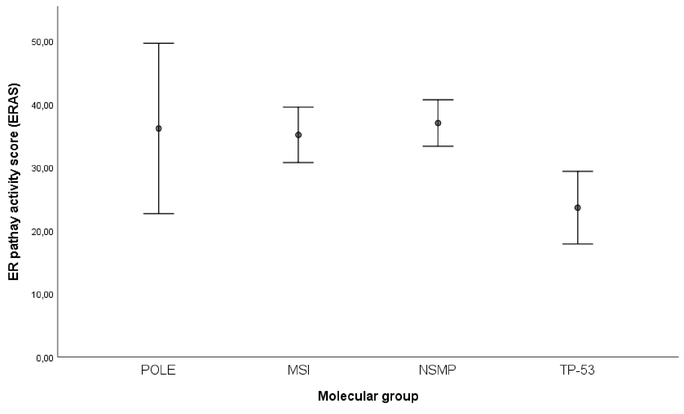
Results

The *TP53* group had significantly worse outcome compared to other subgroups.
ER pathway was active in the majority of *POLE*, MSI and NSMP subgroups.

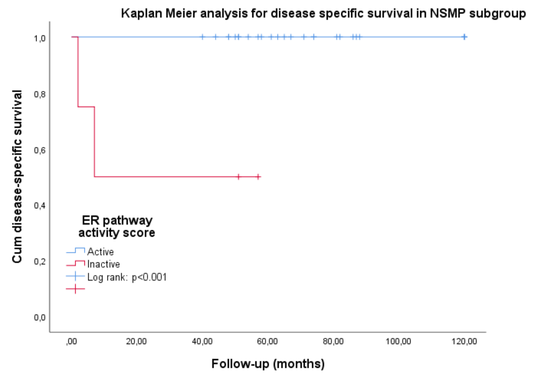
	***POLE* (n=4)**	**MSI (n=18)**	**NSMP (n=32)**	***TP53* (n=18)**
ER pathway Inactive Active	 25% **75%**	 16,7% **83,3%**	 12,5% **87,5%**	 61,1% **38,9%**
Death by disease	0%	5,6%	9,4%	55,6%

POLE = polymerase epsilon mutated, MSI: microsatellite instable, NSMP: no specific molecular profile, TP-53: tumor protein-53 mutated. ER: estrogen receptor, IHC: immuno-histochemical expression, PR: progesterone receptor, ERPAS: ER pathway activity score (OncoSIGNal)

The mean ERPAS was significantly higher in MSI and NSMP groups compared to the *TP53* subgroup



ER pathway activity was significantly associated with disease-free and disease-specific survival in the complete cohort and NSMP subgroup:



Kaplan Meier curve of disease specific survival according to ERPAS in the subgroup with no specific molecular profile (NSMP). Analyses of the other subgroups were not possible due to limited number of cases.

Conclusion

The majority of *POLE*-mutant, MSI and NSMP tumors showed an active ER pathway, indicating relevance of estrogen driven tumor growth in the TCGA subgroups

In the NSMP subgroup, ERPAS could be used for stratify patients for prognosis.

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