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**Introduction & Objectives:** High-risk PCa (HRPCa) remains very heterogeneous with an unacceptable variation in outcome after radical prostatectomy (RP). We need a better understanding of tumor biology to identify lethal PCa and allow more patient-specific treatments. As the objective of this study was to identify potential drivers of metastatic disease of HRPCa, we found that XPO1 was down-regulated in non-metastatic HRPCa and investigated the role of XPO1 as driver of metastases.

**Materials & Methods:** A retrospective matched case-control study with long-term follow-up of two clinically identical HRPCa groups, both treated with RP but with one developing metastatic recurrence (n=19) and the other not (n=25) was designed. DNA and RNA of the primary tumor were extracted and somatic copy number aberration (CNA) and MicroArray based gene expression analysis identified XPO1 as gene of interest. Subsequent in vitro analyses as well as treatment with a XPO1 inhibitor (KPT-8602) were performed to evaluate the effect of XPO1 on the metastatic potential of PCa cells. For in vivo analyses, subcutaneous xenografts of PC3-FLuc were induced. Tumor growth and metabolic activity was evaluated via caliper measurements and bioluminescent scanning (IVIS Spectrum).

**Results:** A focal deletion of 2p15 and lower expression of the XPO1 gene was unique for non-metastatic patients. Treatment of different PCa cell lines with KPT-8602 inhibits both proliferation and migration. Our in vivo experiments show that KPT-8602 treatment result in a significantly inhibition of tumor growth of subcutaneous xenografts.

**Conclusions:** Inhibition of XPO1 induces a lower proliferation and migration rate in PCa cells as well as a reduced tumor growth in our subcutaneous xenografts. The development of stable cell lines by CRISPR/Cas9, mimicking our clinical findings as well as the effect of KPT8602 treatment on the development of metastases via intravenous xenografts are under development. These findings suggest that lower XPO1 has a potential protective effect against metastases development in HRPCa.