The Continued Relevance of the Seed and Soil Hypothesis to Metastatic tumor Dissemination, Distribution, and Therapy Resistance with an Emphasis on Liver Metastasis in Castration-Resistant Prostate Cancer

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Abstract:

Background: Patients with liver metastasis have a poor prognosis and liver metastasis have been associated with the emergence of neuroendocrine prostate cancer post androgen receptor (AR) pathway inhibitors (ARPIs), such as enzalutamide and abiraterone. Leveraging the prostate cancer post-mortem rapid tissue collection program at the University of Washington, we set out to determine (i) the distribution of metastasis in patients, (ii) the prevalence of liver metastasis, (iii) when they occur in the disease history, (iv) whether abiraterone treatment is effective in patients with liver metastasis, (v) whether the emergence of AR negative disease in castration-resistant prostate cancer (CRPC) is associated with liver metastasis, and (vi) if there is a biological event that promotes liver metastasis in patients with CRPC.

Methods: Tissue samples were obtained from patients who participated in the post-mortem rapid tissue collection study and gross and microscopic analyses of metastatic sites were performed. Patients were grouped based on sites of metastasis. To identify the AR negative tumor phenotype, RNASeq was conducted on metastases with confirmatory immunohistochemistry (IHC). Clinical histories were used to identify differences between patients with and without liver metastasis at death. RNASeq, ctDNA methylation, and IHC were used to identify differentially expressed genes and proteins.

Results: Sixty-one percent of patients in our cohort (n=143) had liver metastasis at death. The median occurrence of liver metastasis was 177 days prior to death. There was an association of liver metastasis with increased incidence of visceral metastasis including lung (62% vs. 34%), adrenal (34% vs. 13%) and spleen (11% vs. 2%) metastasis. AR negative disease was predominantly observed in patients who had liver metastasis (30%) versus no liver metastasis (5%) at death. Patients who died without liver metastasis were more responsive to abiraterone treatment than patients with liver metastasis ($p=0.0286$). Patients with AR negative disease had shorter survival compared to AR positive disease ($p=0.0325$). Cytokeratin 19 was identified as a biomarker associated with liver metastasis independent of AR status ($p<0.0001$).

Conclusions: There are distinct metastatic molecular phenotypes that grow in distinct organ sites. Prevalence of liver metastasis at death is significantly higher than documented in premortem scans and clinical trials. Loss of AR expression in response to ARPIs is confined to patients with liver metastasis, signifying a marker for the AR negative phenotype and predicted for lower response to AR-targeted

agents. The expression of cytokeratin 19 may be a biomarker for metastasis to the liver independent of AR status.

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