Implication of Gleason score for the precision medicine treatment of patients with localized prostate cancer

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Background: Recent studies have shown that 4-20% of prostate cancers are associated with germline mutations in DNA repair genes. Identification of these alterations may have clinical implications for the personalized treatment of men with prostate cancer and additional far-reaching beneficial effects on reducing morbidity and mortality in his family members. Currently, the majority of data on DNA repair gene mutational rates has been studied in metastatic castrate resistant prostate cancer patients as compared to men with localized disease. Prior studies suggest a lower rate of DNA repair gene mutation positivity in localized prostate cancer patients, but few explore the differences in gene mutation rate for different subsets of localized prostate cancer, for example by Gleason score.
Methods: Analysis of publically available data for localized prostate cancer cases reported by the MSKCC IMPACT study (Abida et al, JCO Precision Oncology 2017) and The Cancer Genome Atlas (TCGA, Cell 2015) was performed. Phenotypic and genetic analysis is ongoing for 1,852 prostate cancer patients enrolled in the Penn Medicine Biobank (PMBB).
Results: Approximately 10% of localized prostate cancers have evidence of genomic instability. While mutational burden is not correlated with Gleason score, Gleason 9-10 prostate cancers have significantly higher fractions of their genomes in copy number alterations compared to Gleason 6-7 tumors (12.1% versus 8.6%, $p=0.007$ for IMPACT and 26.3% versus 8.4%, $p<10^{-29}$ for TCGA). Given this result, we are now completing an analysis of the association of germline mutation rate in DNA repair genes with Gleason score and other pathological features in prostate cancer patients. Deep oncological phenotyping in the PMBB was completed using a combination of manual chart abstraction with natural language processing based methods to mine unstructured data in the Electronic Health Record (EHR). We have now extended our phenotyping to completion of the following variables: ethnicity, family history of prostate cancer, localized versus de novo metastatic at diagnosis, T and N stage at diagnosis, and pathological variables of extraprostatic extension, seminal vesicle invasion, positive surgical margins and lymphovascular invasion. We are currently completing exonic sequencing of germline DNA from the PMBB cohort of 1852 localized prostate cancer patients for 80 known or proposed prostate cancer germline genes and for single nucleotide polymorphisms to construct a prostate cancer polygenic risk score.
Conclusions: Between 12-26% of localized Gleason 9-10 prostate cancers are associated with increased levels of genomic instability. Our germline sequencing project aims to identify whether the higher genomic instability in Gleason 9-10 prostate cancers is related to inherited mutations in DNA repair genes. The results of this study will directly inform the precision medicine treatment of patients with localized prostate cancer.

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