

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 personalized treatment of patients with prostate cancer. In addition, identification of an inherited mutation in a cancer affected patient can have far-reaching beneficial effects on reducing morbidity and mortality in his family members via implementation of cancer screening and prevention strategies. Currently, the majority of data on DNA repair gene mutational rates has been studied in metastatic castrate resistant prostate cancer patients. As a result, the National Cancer Care Network supports germline genetic testing in metastatic prostate cancer patients with a family history suggestive of the associated syndrome, but there is currently no indication for testing in patients with localized prostate cancer alone. 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 single nucleotide variations and copy number alterations were performed for the 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). Single nucleotide variant burden and the fraction of the genome in copy number alterations were correlated with Gleason score. Phenotypic and genetic analysis is ongoing for prostate cancer patients enrolled in the Penn Medicine Biobank.

Results: Approximately 10% of localized prostate cancers have 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). We are now utilizing the robust resources of the Penn Medicine Biobank to study the relationship of germline DNA repair gene mutations to Gleason score in prostate cancer patients at Penn Medicine. Whole exome sequencing data will be analyzed for 187 prostate cancer patients in the discovery cohort. Targeted sequencing for DNA repair mutations will then be performed in 1559 prostate cancer patients in the validation cohort. Subsequently, genomic predictors of response to targeted therapy will be analyzed in the tumors of patients with germline DNA repair mutations.

Conclusions: Between 12-26% of localized Gleason 9-10 prostate cancers are associated with increased levels of genomic instability. Further studies in the Penn Medicine Biobank will investigate the role of inherited genetic variation as a cause of genomic instability in Gleason 9-10 localized prostate cancers. The results of this study will directly inform the precision medicine treatment of patients with localized prostate cancer.

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