Medical University of Graz

Circulating tumor DNA for the detection of localized prostate cancer

Summary

Diagnostic & Research Institute of Human Genetics, Medical University of Graz

Supervisor:	Prof. Dr. Michael Speicher
Availability:	This position is available.
Offered by:	Medical University of Graz
Application deadline:	Applications are accepted between February 15, 2022 00:00 and March 28, 2022 23:59 (Europe/Zurich)

Description

Background:

Prostate cancer (PC) is the most diagnosed cancer type in men [1]. Most tumors of the prostate grow slowly and may not cause serious harm. However, some types are aggressive and can spread quickly. Patients with metastatic castration-resistant prostate cancer (mCRPC) have an average survival of only 13 months, making early PC detection extraordinarily important. Screening asymptomatic men employing Prostate-Specific Antigen (PSA) testing in serum has been widely adopted and substantially increased the detection and incidence of prostate cancer. However, PSA screening comes with a large proportion of false-positive results as PSA is an organ-specific but not disease-specific marker [2]. Therefore, other means for PC screening are urgently needed.

The analysis of ctDNA (cell-free circulating tumor DNA) is evolving to a promising tool for early detection of cancer. The utility of ctDNA as a reliable biomarker to predict tumor burden and treatment response or to identify resistance mechanisms and novel occurring actionable targets has been proven in numerous studies (summarized in [3-7]). Our lab has extensive experience in ctDNA analyses from patients with prostate cancer (example in [8]). However, in contrast to the applications mentioned above, there is a lack of valid studies that prove the applicability of ctDNA as a diagnostic biomarker enabling early detection of PC.

Hypothesis and Objectives:

The main objective of the proposed thesis is to assess the use of ctDNA for the non-invasive detection of early PC. To this end, we will first determine the ctDNA detection rate in localized PC. Since ctDNA levels in early PC are low, we will comprehensively analyze the genetic landscape of primary tumor tissue and track the identified alterations in plasma. As a secondary aim, we will correlate shedding of ctDNA with tumor burden, grade, and vascularity to improve our knowledge about the biology and kinetics of ctDNA release in PC. In the next step, we will correlate our findings with clinical variables, morphological imaging, and other molecular markers (PCA-3, PHI, testosterone, PSA-density, mpMRI) to assess the combined use of multiple biomarkers for early detection. Our findings might enhance the diagnostic accuracy for PC detection in men and eventually reduce unnecessary prostate biopsies and associated morbidity in negative or low-risk situations.

Specific hypotheses are:

1. Genetic alterations identified in mpMRI elastic fusion prostate biopsy specimens can be detected in ctDNA.
2. The presence of ctDNA and/or abundance of mutations is associated with mpMRI morphologic tumor volumes and PC aggressiveness.
3. A combined evaluation of multiple makers (PCA-3, PHI, testosterone, PSA-density, mpMRI, or ctDNA) achieves a higher sensitivity/specificity to a single marker approach for the detection of PC.

Methodology:

This project will be performed in close collaboration with Dr. Johannes Mischinger, Department of Urology of the Medical University of Graz, who recruited >200 men with a clinical suspicion of PC based on elevated PSA and/or digital rectal exam. Clinical records, biological (PSA/PHI), and morphologic MRI images are already available.

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The PhD candidate will employ a variety of NGS-based methodologies to characterize the primary tumor's molecular landscape and subsequently will analyze corresponding plasma samples. Moreover, the candidate will make use of sophisticated bioinformatics and statistical approaches. Therefore, experience with Linux-based NGS data analysis is favored but not mandatory; basic experience with lab work is desirable.

References:

1. Bray F, Ferlay J, Soerjomataram I et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018; 68: 394-424.

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3. Heitzer E, Ulz P, Geigl JB. Circulating tumor DNA as a liquid biopsy for cancer. Clin Chem 2015; 61: 112-123.

4. Siravegna G, Bardelli A. Blood circulating tumor DNA for non-invasive genotyping of colon cancer patients. Mol Oncol 2016; 10: 475-480.

5. Diaz LA, Jr., Bardelli A. Liquid biopsies: genotyping circulating tumor DNA. J Clin Oncol 2014; 32: 579-586.

6. Crowley E, Di Nicolantonio F, Loupakis F, Bardelli A. Liquid biopsy: monitoring cancer-genetics in the blood. Nat Rev Clin Oncol 2013; 10: 472-484.

7. Heitzer E, Haque IS, Roberts CES, Speicher MR. Current and future perspectives of liquid biopsies in genomics-driven oncology. Nat Rev Genet 2019; 20: 71-88.

8. Ulz P, Perakis S, Zhou Q et al. Inference of transcription factor binding from cell-free DNA enables tumor subtype prediction and early detection. Nat Commun 2019; 10: 4666.

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