Correlation of tumor size/status and ctDNA release in colorectal cancer

Summary

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Supervisor:	Prof. Dr. Ellen Heitzer
Availability:	This position is available.
Offered by:	Medical University of Graz
Application deadline:	Applications are accepted between July 15, 2019 00:00 and September 15, 2019 23:59 (Europe/Zurich)

Description

Background:

The analysis of ctDNA (cell-free circulating tumor DNA) is a very promising tool and might revolutionize cancer care with respect to early detection, identification of minimal residual disease, assessment of treatment response, and monitoring tumor evolution. The utility of ctDNA as a reliable biomarker to early detect cancer recurrence, to predict tumor burden and treatment response, as well as to identify resistance mechanisms and the emergence of novel actionable targets has been proven in numerous studies (summarized in (1-5)). Moreover, the assessment of ctDNA levels can be used as prognostic marker. It has been shown that patients having higher ctDNA levels at certain time points, i.e. prior to therapy initiation, prior or after tumor resection had significantly shorter PFS (progression-free survival) and/or OS (6-9). In contrast to the above-mentioned clinical applications with bearing on established and late stage disease, there is a paucity of valid studies published that prove the applicability of ctDNA as a diagnostic biomarker enabling early detection of cancer. The early detection of cancer is a desirable objective as it allows the initiation of effective therapies against tumor cells which have accumulated fewer oncogenic events. The major challenges in the analysis of plasma DNA is the differentiation of circulating DNA derived from the tumor from non-tumor circulating DNA (cfDNA). In principle, attempts to use cfDNA/ctDNA as a cancer biomarker focus on two classes of alterations, i.e. quantitative and qualitative abnormalities. These approaches appeared powerful and achieved a good sensitivity, however prior knowledge about the tumor associated alterations is necessary. For early cancer screening no information about the tumor is available and therefore independent qualitative and quantitative parameters are needed to identify a tumor. Even though the detection of cancer-specific mutations offers a genotypic means to distinguish tumoral from non-tumoral plasma DNA, a major problem is that every cancer has a unique fingerprint and therefore there is no universal marker that can be used for cancer screening. Exact knowledge about the biology of cfDNA/ctDNA might reveal other useful parameters, which can be used in the early detection setting and might dramatically increase sensitivity/specificity for detecting early stage disease. However, compared to the number of studies addressing the clinical applicability of ctDNA, data regarding the actual origin, the kinetics, and the mechanisms of release and clearance are limited and often contradictory. The aim of the proposed thesis is to close this gap.

Hypothesis and Objectives:

Although a linear relationship between tumor volume and ctDNA plasma variant allele frequency (VAF) was reported in NSCLC and high- grade serous ovarian cancer (HGSOC) (10-12) there are hardly any data on correlation of ctDNA release and tumor size/properties and most reports rely on *in silico* extrapolation. Therefore, the main aim of the study is the correlation of tumor size and its molecular properties with the presence of detectable amounts of ctDNA in localized colorectal cancer patients. We hypothesize that the rate of shedding of ctDNA into the circulation is dependent upon the location, size, and vascularity of the tumor and therefore leads to a high variability in levels across patients. A sharper picture of the biology and kinetics of ctDNA release and turnover should expand the utility of circulating nucleic acids as tumor markers.

Methodology:

We will recruit stage I and II patients with colorectal cancer, whose tumors will be resected with curative intent. In early stage cancer minute amounts of ctDNA are present in the circulation, which requires a high analytical sensitivity

of methodological approaches. To date, only targeted approaches are able to achieve the necessary resolution and to this end knowledge about the genetic landscape of the primary tumor is required. We will perform molecular characterization of resected tumor material after the surgery. After next generation (NGS) sequencing of primary tumor tissue, identified mutations will be tracked in plasma DNA. To this end, we will design patient-specific assays, which allow a detection of tumor -specific mutation down to 0.1% tumor fraction. Data from plasma DNA analyses will be correlated with available clinical and histological tumor data including stage, size, proliferation status of the tumor (Ki-67), the immune status etc.

The PhD candidate will employ a variety of NGS based methodologies in order to characterize the molecular landscape of the tumor. Moreover, the candidate will make use of sophisticated bioinformatics and statistics approaches.

References:

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