Liquid biopsies for CNS tumors

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Liquid biopsies may bypass the need for surgery but its use in brain tumor patients has historically been challenging. Recent data has demonstrated that circulating tumor DNA (ctDNA) can reliably be detected in plasma of brain tumor patients using...

Ethical review	Approved WMO
Status	Pending
Health condition type	Nervous system neoplasms malignant and unspecified NEC
Study type	Observational invasive

Summary

ID

NL-OMON53668

Source
ToetsingOnline

Brief title
Liquid biopsies for CNS tumors

Condition

- Nervous system neoplasms malignant and unspecified NEC

Synonym
brain tumor

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Ministerie van OC&W,Off Road grant ZonMW

Intervention

Keyword: Brain tumor, Glioma, Liquid biospy

Outcome measures

Primary outcome

The ability to detect ctDNA in patients with brain tumors while using the

Med-Seq technique

Determine whether T cell phenotype changes during the course of the disease of

glioma

Secondary outcome

NA

Study description

Background summary

Brain tumors are a heterogeneous group of tumors that constantly evolve, generally recur and often progress to more malignant subtypes. Patients often have a short life expectancy. Current diagnostic criteria an clinical management rely on the tissue profiling obtained by invasive neuro-surgical procedures.
Gross total tumor resection is associated with a better survival and better quality of life in patients with brain tumors. However, in many patients gross total resection is not safely possible. In these patients, a biopsy of the tumor has to be taken with the sole reason to obtain tissue for diagnosis. No patient benefit is to be expected from the biopsy. A biopsy comes with a significant risk of neurological deterioration (even death).

Following the initial diagnosis, patients are currently monitored by magnetic resonance imaging (MRI) to determine residual tumor mass, examine growth speed and screen for signs of malignant dedifferentiation (i.e. presence of regions with contrast enhancement). A major limitation of MRI is the limited ability to distinguish therapy-induced necrosis (*pseudo-progression*) from genuine tumoral burden or to identify minimal tumoral burden. New advanced MRI techniques and nuclear imaging techniques cannot distinguish pseudo-progression form genuine tumoral burden with a sufficient diagnostic accuracy.

Study objective

Liquid biopsies may bypass the need for surgery but its use in brain tumor patients has historically been challenging. Recent data has demonstrated that circulating tumor DNA (ctDNA) can reliably be detected in plasma of brain tumor patients using high throughput methylation profiling. Clinical implementation however requires an additional increase in detection sensitivity. Med-Seq is a novel methylation technique that we hypothesize to be more sensitive than currently employed techniques to detect ctDNA for brain tumor diagnostics. This project will explore the use of this technique and its suitability for tumor diagnosis and monitoring.

The overall goal of this project is to bring the promising non-invasive *liquid biopsy* technique from the lab to clinical practice in brain tumor patients. We therefore aim to identify and characterize ctDNA in blood from brain tumor patients using Med-Seq, and assess its diagnostic value. Our research question is: *Can we identify ctDNA from brain tumor patients using Med-Seq and use it for tumor diagnosis and disease monitoring?*.

As the concept of liquid biopsies in glioblastoma has exclusively focused on the detection of tumor cells or tumor DNA in the peripheral blood with limited results, we here also assess a new angles to solve this problem. Interestingly, the value of immunophenotyping of lymphocytes in the peripheral blood to monitor glioblastoma disease progression has never been assessed. In previous work, we identified a significant increase in T cells in recurrent glioma compared to their initial counterpart. Remarkably, these T cells are in majority CD3+ but not CD8+, probably suggesting an immunosuppressive phenotype. These T cells are recruited from the peripheral blood. We hypothesize that upon glioblastoma progression, peripheral blood T cell counts decrease and T cell phenotype becomes more tumorsuppressive as compared to the stable disease status.

The overall aim of this project is to improve glioblastoma disease monitoring with T cells as peripheral blood biomarker.

Study design

Med-Seq will be used to identify ctDNA in plasma of patients with a brain tumor. Genome-wide DNA methylation profiling will be done by sequencing fragments generated by a methylation sensitive restriction enzyme. All data will be combined with data from other tumor types and normal tissues, and bio-informatical analysis (principle component analysis/tSNE/UMAP, logistic regression, Random Forest) will be used to predict tumor presence and type.

To assess the phenotype of T cells in the tumor in comparison to peripheral blood, we will use spectral flow cytometry. A pre-existing 38 marker-panel

dedicated to T cells in the brain will be applied towards 12 fresh glioblastoma samples that will be transferred from the operating room directly to the lab, and on peripheral blood mononuclear cells (PBMCs) derived on the day of surgery from the same patient. We will isolate tumor DNA and RNA, perform multiplex immunofluorescence stainings on the tumor to inform on spatial distribution of immune effector cells, and annotate clinical data including age, sex and ethnicity.
T cells in tumor and peripheral blood will be compared. We anticipate to find major differences, but hypothesize to also find intriguing similarities, like T cells in the peripheral blood with a brain residency associated phenotype.
Prospective analysis of peripheral blood T cells and relation with tumor progression
To find a change in peripheral T cell count and phenotype in the course of the disease, we will apply a 13-panel flow cytometry on PBMCs on prespecified time points during the course of the disease, until tumor progression is confirmed on MRI. Thirty glioblastoma patients (first 12 included in previous step) will be included. Patients will be treated and followed-up as per clinical protocol. Clinical and imaging data will be collected.

This is a pilot study to test the technique. We will draw 30ml of blood from 30 brain tumor patients. Their data will be compared to the already available data of healthy controls.

Study burden and risks

Blood will be drawn at timepoints where blood drawing is already indicated for medical reasons, except for one moment (day of surgery), when an extra blood drawn will be scheduled. 30ml extra blood will not cause burden or risk for the patient

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Radiological suspected brain tumor

Exclusion criteria

None

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-10-2023
Enrollment:	20
Type:	Anticipated

Ethics review

Approved WMO Date:	23-02-2023
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-05-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-03-2024
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL80486.078.22