# Early detection of head and neck cancer relapse by expression profiling of blood platelets and ctDNA detection in plasma and oral rinses

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| **Ethische beoordeling** | Positief advies |
| **Status** | Werving nog niet gestart |
| **Type aandoening** | - |
| **Onderzoekstype** | Observationeel onderzoek, zonder invasieve metingen |

## Samenvatting

### ID

NL-OMON29189

**Bron**
Nationaal Trial Register

**Verkorte titel**
HN-DETECT

**Aandoening**

Head and neck squamous cell carcinomas

### Ondersteuning

**Primaire sponsor:** not applicable
**Overige ondersteuning:** KWF

### Onderzoeksproduct en/of interventie

## Uitkomstmaten

### Primaire uitkomstmaten

Accuracy of early detection of recurrent/metastatic disease in HNSCC patients treated for cure, and the presence of ctDNA in plasma and oral rinses as well as TEPs. In addition, the median and range of time intervals between liquid biopsy findings and relapse will be determined.

# Toelichting onderzoek

### Achtergrond van het onderzoek

Rationale: Head and neck squamous cell carcinomas (HNSCC) arise in the mucosal lining of the upper aerodigestive tract and are caused by smoking and alcohol consumption or human papillomavirus (HPV) infection. Most HNSCC patients present with advanced stage of disease. Tumors are treated by radiotherapy, chemoradiotherapy, the combination of cisplatin with concomitant radiotherapy, or surgery with or without postoperative (chemo)radiotherapy. Locoregional recurrences occur in 30-40% of advanced stage patients and are difficult to manage as these are mostly detected late. When detected early, re-irradiation and particularly salvage surgery are curative treatment options, but at present only a minority of patients qualify for salvage surgery. Most reliable methods for diagnosing recurrent disease are FDG-PET and examination under general anesthesia with biopsy, but both are unsuited for screening in routine. Other imaging modalities are too insensitive. Biomarkers for early detection in body fluids as a screening assay for early diagnosis of relapse would be a major improvement in the early detection and management of recurrent disease. Liquid biopsy may guide FDG-PET imaging and/or examination under general anesthesia, and lead to earlier detection of recurrent disease and consequently improved clinical management survival of patients. In this study we focus on detection of circulating tumor DNA (ctDNA) in plasma and oral rinses as well as tumor-educated platelets (TEPs).
Tumor DNA circulates in the bloodstream and can be detected in plasma by DNA sequencing. Both copy number alteration (CNA) profiling as well as ultradeep target enrichment sequencing for mutations have been employed in preliminary studies. We have combined low coverage whole genome sequencing for copy number changes and HPV presence, with high coverage target-enrichment sequencing for mutations in a single assay. We have analyzed ctDNA of 40 HNSCC patients and 20 controls, and ctDNA was found in 78% of patients irrespective of HPV status, and not in controls.
A second potential screenings assay is the detection of tumor-educated platelets (TEPs). Blood platelets circulate through the body including the tumor and take up exosomes from the tumor, which educates them to TEPs. It has been shown that the RNA profiles of these TEPs can be used to detect the presence of a tumor. In a small pilot study we have shown that this is also the case for head and neck squamous cell carcinoma (HNSCC). In this pre-study, analyses of 45 samples from HNSCC patients showed that HNSCC could be detected with an accuracy of 91%, and in more recent analyses this improved to 98%.

Objective: The aim of the study is early detection of recurrent head and neck cancer by 1) plasma DNA sequencing for both copy number analysis and target enrichment ultradeep sequencing for somatic mutations using a selected head and neck cancer gene panel, and 2) RNA analysis of TEPs. We expect to develop a test that allows screening for recurrent disease at an early presymptomatic phase. This will allow early diagnosis and better salvage treatment outcome with currently available methods, and will further allow selection of patients for experimental treatments such as immunotherapy with checkpoint inhibitors.

Study design: This is a prospective observational cohort study. At baseline and during each follow-up visit 4 tubes with 7 ml of blood will be drawn as well as an oral rinse collected. In general patients visit the outpatient center for regular control 10x. At baseline also a tumor biopsy and 4 ml blood sample for mutation analyses will be obtained in addition. In surgically treated patients also the post-surgery rinse fluid will be collected. In case of relapse an extra biopsy of the relapse will also be obtained for DNA sequencing. DNA and TEPs will be isolated from the blood according to standard methods. DNA of plasma will be analyzed by DNAseq for mutations and copy number alterations, while RNA of the platelets will be profiled by RNAseq. Presence of ctDNA and TEP profiles will be associated with the occurrence of relapse and survival.

Study population: Patients >18 yrs with HNSCC and able to understand the information and study procedures will be included.

Main study parameters/endpoints: Endpoints of the study are the accuracy of early detection of relapse by ctDNA or TEP analyses in relapsed and relapse-free cases, the time frame of relapse detection before the diagnosis of relapse, and the accuracy of early diagnosis in relation to clinical parameters.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Under general anesthesia 1-3 extra biopsies next to the standard biopsy will be taken of primary tumor and relapse, and blood and an oral rinse will be collected. For surgically treated patients we will also collect the post-surgical rinse fluid in addition. Risk and discomfort will be minimal. At all scheduled follow-up visits (on average 10x) additional blood samples and oral rinses will be collected, which is of low risk and limited burden. Adverse events from extra biopsies or blood withdrawal are not expected. The tests are still experimental, and positive findings have formally no scientific meaning. However, the mutations in the tumor are known and when mutations disappear and reappear in the blood, we will report this to the treating physician and discuss it in the multidisciplinary team that might decide on subsequent imaging. This will not influence the main endpoint of the study: early detection of relapse. We will record changes in clinical management.

## Doel van het onderzoek

We expect to develop a test that allows screening for recurrent disease at an early presymptomatic phase. This will allow early diagnosis and better salvage treatment outcome with currently available methods, and will further allow selection of patients for experimental treatments such as immunotherapy with checkpoint inhibitors.

**Onderzoeksopzet**

Tumor material, plasma and oral rinses will be collected at baseline and during follow-up plasma and oral rinses will be collected of enrolled patients. Follow up visits will be every 6-8 weeks in the first year and every 2-3 months in the second year, gradually increasing to 5 years.

# Contactpersonen

## Publiek

Amsterdam UMC
Annouk Pierik

0612971904

## Wetenschappelijk

Amsterdam UMC
Annouk Pierik

0612971904

# Deelname eisen

## Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

• HNSCC stage II, III and IV
• Sufficient knowledge of the Dutch language to understand the aim of the study and the procedures as described in the patient information.
• Signed the informed consent for the study.
• (+)18 years of age

## Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

• Patients scheduled for palliative treatment will be excluded from participation in this study.

# Onderzoeksopzet

## Opzet

| | |
|---|---|
| Type: | Observationeel onderzoek, zonder invasieve metingen |
| Onderzoeksmodel: | Anders |
| Toewijzing: | N.v.t. / één studie arm |
| Blindering: | Open / niet geblindeerd |
| Controle: | N.v.t. / onbekend |

## Deelname

Nederland

| | |
|---|---|
| Status: | Werving nog niet gestart |
| (Verwachte) startdatum: | 01-05-2021 |
| Aantal proefpersonen: | 100 |
| Type: | Verwachte startdatum |

## Voornemen beschikbaar stellen Individuele Patiënten Data (IPD)

**Wordt de data na het onderzoek gedeeld:** Nog niet bepaald

# Ethische beoordeling

Positief advies

| | |
|---|---|
| Datum: | 14-04-2021 |
| Soort: | Eerste indiening |

# Registraties

## Opgevolgd door onderstaande (mogelijk meer actuele) registratie

ID: 49182
Bron: ToetsingOnline
Titel:

## Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

## In overige registers

| Register | ID |
|---|---|
| NTR-new | NL9400 |
| CCMO | NL72940.029.20 |
| OMON | NL-OMON49182 |

# Resultaten