The oropharyngeal microbiome and metabolome as potential novel biomarker for disease progression or treatment response in head and neck squamous cell carcinoma (HNSCC); a pilot study.

Published: 16-06-2020
Last updated: 11-06-2024

Primary objectives: • To define any alterations in the oral and gut microbiome and metabolome in patients with HNSCC compared to healthy controls;• To investigate the dynamics oral and gut microbiome and metabolome in HNSCC before, during and after...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Miscellaneous and site unspecified neoplasms malignant and unspecified
Study type	Observational invasive

Summary

ID

NL-OMON52923

Source
ToetsingOnline

Brief title
Oropharyngeal micro- and metabolome in head and neck cancer.

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
head and neck cancer, Head and neck squamous cell carcinoma

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: Oncode Institute funding

Intervention

Keyword: Biomarker, Head and neck squamous cell carcinoma, Metabolome, Microbiome

Outcome measures

Primary outcome

Microbiome assays:

To assess the oral-, oropharyngeal and fecal microbiome, which includes bacteria, Archea, viruses, parasites and fungi. RNA and DNA will be isolated from oral swabs and feces for sequencing and molecular methodologies (e.g. PCR, qPCR).

Metabolome assays:

Saliva bio-specimen will be analysed using Liquid Chromatography Tandem Mass Spectrometry (LC-MSMS).

Secondary outcome

The oral/oropharyngeal and gut microbiome and metabolome will be correlated to clinical parameters such as therapy response and survival. In addition, an intra-patient comparison will be made between the actual tumor microbiome/metabolome and adjacent normal mucosa.

Study description

Background summary

The human microbiota is defined as the collective of microorganisms that reside in the human body or its surfaces. The *microbiome* is reserved for the genomes of this collective group of microorganisms. Microbial imbalance (dysbiosis) on or inside the body may affect oncogenesis, tumor progression and response to cancer therapy1,2. First of all, risk factors for dysbiosis, such as antibiotics, smoking, diet and alcohol consumption, may also promote carcinogenesis directly. Secondly, an altered gut microbiota may affect the incidence and progression of both locoregional carcinogenesis and extra-intestinal cancers1. Of interest, microbes present at mucosal sites may exert different immune-modulatory effects. Segment-ed filamentous bacteria, which can breach the gut mucus layer and attach to intestinal epi-thelial cells (IECs) are a potent inducer of T helper 17 cells and for instance Helicobacter pylori may lead to an increase in loco-regional Tregs3,4.

During cancer therapy, radiation or drug regimens may exert toxic effects on bacteria, there-by promoting dysbiosis. On the other hand, (gut) microbiota may influence the therapeutic efficacy and side effects of cancer drugs via pharmacodynamics and immunological mecha-nisms1,2. Indeed, recent work has shown that gut microbiota interfere with tumor responses to chemotherapy and aPD1 or aCTLA4 immunotherapy3,5,6.

Omic technologies aim to comprehensively study the molecules that make up a cell, tissue or an organism. The primary aim of this holistic approach is the global detection of molecules in a biological sample, in a non-targeted and unbiased manner. Among all the *omic* tech-nologies, metabolomics is the closest link to the phenotypes of biological systems. The analysis of the metabolome of a cell, a tissue, a bio-fluid or an organism has the aim to iden-tify alterations in biochemical networks. Oral diseases are known to be closely associated with oral biofilm metabolism. The collection of saliva specimen is inexpensive and non-invasive, presents high potential of biomarkers discovery, as well as longitudinal disease monitoring7-9. Despite these opportunities, today, only few reports addressed the metabolic composition and changes of salivary samples. However, a deeper understanding of perturba-tions of the salivary metabolome in association with the microbiome composition is essential for clarifying complex pathogenic mechanisms, such as cancer or dysbiosis related disorders. At first, the detection of metabolic alterations will allow for a more comprehensive un-derstanding of disease progression, the possible evaluation of therapeutic outcomes, and simultaneously shed light on cancer metabolism, the involvement of the oral microbiome as well as their interplay. On the long term, a more complete understanding of these alterations, could very well contribute to the development of personalized diagnosis, boost the improve-ment of safety and efficacy of treatment as well

as promote personalized therapy.

In head and neck squamous cell carcinoma (HNSCC), the oral cavity harbors more than 700 bacterial species and is one of the most densely microbial populated areas of the human body. The oral cavity is the largest core of commonly shared microbes among unrelated indi-vidual and provides an ideal source for biomarker discoveries due to low inter- and intra- bio-logical variations. The oral cavity includes several distinct habitats as the tooth sur-face/gingival crevice, tongue, tonsils and oropharynx, each host a distinct microbiota10. Dif-ferences in bacterial- and viral composition have been described for oral cancers in patient series11, potentially serving as biomarker for oral cancer. The microbiome, its metabolome, and its potential effect on cancer treatment in HNSCC were never studied before. The ac-cessibility of the oral region allows spatial and temporal analyses of the connection between the micro- and metabolome in a non-invasive manner.

As previous research suggests a potential key role for microbiome and metabolome analyses in tumor response to treatment, the results of this study may have implications for the devel-opment of novel biomarkers for the prediction of treatment response and clinical outcome in head and neck cancer.

Study objective

Primary objectives:
• To define any alterations in the oral and gut microbiome and metabolome in patients with HNSCC compared to healthy controls;
• To investigate the dynamics oral and gut microbiome and metabolome in HNSCC before, during and after different treatment regimens.

Secondary Objective(s):
To investigate the correlation of the microbiome and metabolome with demographic, clinical, pathological and imaging data as well as genomic date (if available).

Study design

This is a prospective, bicenter (NKI-AVL and LUMC), observational cohort study in which 60 patients with locally HNSCC will be included. In addition, 20 healthy volunteers will serve as a control population. There will be no randomization or blinding.

Study burden and risks

When swabs are taken during a routine physical investigations or routine general anesthesia (in case of surgery), this will hardly cause any extra burden to the patient as these procedures were already planned as part of the

treatment. The risk of swabs and fecal sampling is negligible. Patients will collect stool at home using a stool collection kit and hand in the sample during their routine hospital visits. This procedure is considered simple and non-invasive.
After surgery, tissue is standard fixed in formaldehyde for pathology. A section will be nitrogen frozen for metabolome analyses by tissue mass spectrometry and the pathology section and metabolome section will be matched later. This does not provide any additional burden to the patient and will include only additional handling of the surgical specimen.
The participation of a patient in this trial will not affect the treatment that the patient will receive and will not directly have a benefit for individual patients. The data that will be acquired in this study will be of benefit to the general cancer patient population as they can help to answer complicated research questions in the field of chemical immunology and oncology.

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

For patients:
1. Age >=18 years
2. T1-4N0-3M0 squamous cell carcinoma of the head and neck.
3. With an indication for curative (C)RT or definitive surgery.
4. WHO 0-2
5. Written informed consent, For healthy volunteers:
1. Age >=18 years

Exclusion criteria

• Incurable HNSCC;
• Current antibiotic use (topical antibiotics e.g. ear drops, cream are acceptable) ;
• The presence of any medical condition that might, in the investigators* opinion, render study participation undesirable or that might obscure interpretation of results.

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	14-06-2021
Enrollment:	80

Type:	Actual

Ethics review

Approved WMO Date:	16-06-2020
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	30-11-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	16-01-2023
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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	NL68847.058.19