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How mouth bacteria affect radiation treatment for head and neck cancer

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Registration date 13/02/2026	**Overall study status** Ongoing	[ ] Statistical analysis plan [ ] Results
Last Edited 13/02/2026	**Condition category** Cancer	[ ] Individual participant data [X] Record updated in last year

Plain English summary of protocol

Background and study aims

Head and neck cancer is the sixth most common type of cancer worldwide. People diagnosed with head and neck cancer often experience poor outcomes, with only about half of patients surviving beyond five years. Besides, patients receiving radiotherapy (radiation treatment) frequently suffer from painful mouth sores called oral mucositis. These mouth sores make it very difficult to eat, drink, and speak, and can prevent doctors from giving patients the full doses of radiation they need. Recent research has shown that the tiny living organisms (bacteria, viruses, and fungi) that live in our mouths, collectively called the oral microbiota or mouth microbiota, may influence how well radiotherapy works and how severe side effects become. However, scientists have not yet proven whether changing the mouth microbiota could actually improve cancer treatment outcomes and reduce mouth sores.

This study aims to discover whether there is a direct link between the bacteria and viruses in patients' mouths before and during radiotherapy and how well their cancer is treated and how severe their side effects are. We hope to use this information in the future to personalize radiotherapy treatments based on each patient's unique mouth microbiota, potentially reducing side effects and improving treatment success.

Who can participate?

Patients aged 18 years and older with head and neck squamous cell cancer (cancer starting in the flat cells lining the mouth, throat, or voice box) can participate. Patients must be suitable candidates for radiotherapy treatment as their primary treatment or as additional treatment after surgery. Patients with previous radiotherapy to the head and neck region will not be able to participate, nor will patients with connective tissue disorders such as lupus or scleroderma.

What does the study involve?

This is an observation study where patients do not receive any new or experimental treatments. All patients receive standard radiotherapy according to current medical guidelines. The study will follow 96 new patients being treated at the National Cancer Institute Foundation in Milan, combined with data from 180 patients already studied in a previous research project, for a total of 276 participants.

Patients will provide saliva samples (spit samples) at three timepoints: before radiotherapy starts, at two weeks into their radiotherapy, and at the end of radiotherapy. These saliva

samples will be analyzed using advanced genetic technology to identify all the bacteria, viruses, and other organisms present in the mouth. Patients will also undergo routine clinical evaluations including medical scans (MRI and PET-CT), blood tests, and questionnaires about their quality of life and any side effects they experience. These assessments are performed during the standard treatment process and will be recorded and analyzed. Patients will be followed up for three years after their treatment ends to check for cancer recurrence and any long-term side effects.

What are the possible benefits and risks of participating?
By participating, patients will help researchers understand whether mouth bacteria influence radiotherapy outcomes. This information could lead to new personalized treatment strategies in the future that might reduce mouth sores and improve cancer control for patients treated later. Additionally, participating patients will receive careful monitoring and comprehensive health assessments throughout the study.
The study involves only observation of patients receiving standard treatment and does not test any new drugs or procedures. The only additional procedures beyond routine care are the collection of three saliva samples. There are no known significant risks from saliva collection. All patient information will be kept confidential and anonymous during analysis.

Where is the study run from?
The study is conducted at the Fondazione IRCCS Istituto Nazionale dei Tumori, located in Milan, Italy. This is a major cancer research and treatment center in Italy. All patient recruitment, treatment, sample collection, and follow-up will take place at this institution.

When is the study starting and how long is it expected to run for?
Patient recruitment is scheduled to begin in June 2025 and will continue for 3 years. The entire study, including the 3-year follow-up period for all enrolled patients, is expected to last approximately 6 years, with completion expected around 2031.

Who is funding the study?
The study is funded by the Italian Association for Cancer Research (AIRC).

Who is the main contact?
The principal investigator of the study is Dr. Jacopo Iacovacci based at the Data Science Unit of Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy.

Contact information

Type(s)
Public, Scientific, Principal investigator

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Study information

Scientific Title
MIcrobiota-Guided RAdiotherapy for Head and Neck cancer (MIGRHAN)

Acronym
MIGRHAN

Study objectives
Head and neck cancer (HNC) is the sixth most common cancer worldwide. Therapeutic outcomes for HNC remain unsatisfactory and heterogeneous, with 5-year survival rates ranging from 28% to 67% overall. Moreover, HNC patients experience side effects during treatment, including inflammation and ulceration of the oral mucosa caused by radiation or cytotoxic agents (oral mucositis), which represents a limiting factor for both the escalation of radiotherapy dosage and the duration of treatment.
Several observational studies have highlighted statistical associations between the oral microbiota and numerous factors related to HNC and its therapeutic course. The working hypothesis of this study is that it is possible to establish causal relationships between the functional traits of the human oral microbiota and the effectiveness of radiotherapy in HNC treatment, directly from the analysis of data collected in observational cohorts, by leveraging the statistical framework of causal inference.
The oral microbiota of HNC patients enrolled in the study will be characterised through metagenomic sequencing of saliva samples collected from each patient, at radiotherapy-baseline, at 2 weeks from radiotherapy start and at radiotherapy end.

Main Objectives of the Study:
1. Creation of a dataset of the oral microbiota in HNC patients, including both bacterial and viral components, as well as data linked to treatment effectiveness and side effects.
2. Estimation of the causal effect of the functional traits of the oral microbiota on the modulation of radiotherapy in HNC.
3. Development of predictive models for local tumour control and for oral mucositis, based on the oral microbiota of HNC patients.

Clinical Relevance:
The causal relationships inferred between the functional/metabolic traits of the microbiota and radiotherapy effectiveness will help build interpretable predictive models and reveal strategies to reprogram the microbiota functionality of patients with head and neck cancer. This will increase the likelihood of tumour eradication or control while reducing the risk of radiation-induced side effects.

Ethics approval required
Ethics approval required

Ethics approval(s)

Approved 07/10/2025, Comitato Etico Territoriale Lombardia 4 (Via G. Venezian 1, Milan, 20133, Italy; +39 (0)22390; comitato.etico@istitutotumori.mi.it), ref: INT 84/25

Primary study design
Observational

Study design
Singlecentre prospective observational cohort study

Study type(s)
Efficacy

Health condition(s) or problem(s) studied
Head and neck cancer

Interventions
The research question addressed by this study is the need to bridge the current gap in understanding the role of the microbiota, as well as potential microbiotatargeted therapies such as antibiotic use, in the treatment of head and neck cancer (HNC). The working hypothesis is that causal relationships can be established between the functional traits of the human oral microbiota and the effectiveness of radiotherapy for HNC, using the statistical framework of causal inference. Identifying this causal knowledge is essential to design and implement microbiotaguided radiotherapy, where the patient's oral microbiota is profiled prior to treatment and evaluated against the risk of developing oral mucositis and/or experiencing unfavorable outcomes. From a microbiotabased perspective, assessing whether different radiotherapy plans may result in tolerable or intolerable side effects would be crucial for developing personalized radiotherapy programs that could enhance tumor control. Furthermore, since this study involves functional metagenomic analysis of the microbiota, it will be possible to infer the mechanisms through which the microbiota modulates radiotherapy and to exploit these insights for the design of new microbiotabased clinical strategies. Such strategies may include administration of specific nutritional supplements, antibiotics, or probiotics to optimise therapy tolerance and improve treatment outcomes.

Study design and setting:
MIGRHAN is a singleinstitution, prospective observational cohort study with an expected total duration of approximately 6 years. At least 96 consecutive patients with head and neck cancer referred for curative radiotherapy will be enrolled over a 36month period. Their treatment, toxicity monitoring, and followup (3 years) will follow routine clinical practice in accordance with national and international guidelines. Recruitment will take place exclusively at Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, with patient enrollment starting in September 2025 and planned completion by October 2031.

Study workflow:
Before enrolment, patients will provide written informed consent. Baseline assessments (from 28 days to treatment start) will include demographic data, medical history, dental evaluation, clinical examination, laboratory tests (blood tests, urinalysis, thyroid function, coagulation), radiological imaging (CT scan, multiparametric MRI, whole body FDGPET/CT or bone scan), and collection of a saliva sample for microbiota profiling. During radiotherapy, weekly clinical evaluations, toxicity assessments following CTCAE v5.0, and patient questionnaires will be conducted, alongside repeated laboratory analyses and collection of

dosimetric treatment data (DICOMRT). At the end of radiotherapy and during followup visits (3, 6, and 12 months), patients will undergo repeat clinical evaluations, imaging (MRI, CT, PET/CT or bone scan as indicated), laboratory tests, and additional saliva collections. Longterm followup will include survival assessment up to three years posttreatment.

Intervention Type
Other

Primary outcome(s)
Locoregional tumour control: The primary endpoint is local tumor control at 12 months of followup, considering both partial and complete responses as defined by the oncological RECIST 1.1 radiological criteria. Tumor volume analysis from MRI imaging between preRT and 3 months postRT will be used to quantify tumor volume reduction (shrinkage) in patients undergoing curative radiotherapy alone. Tumor volume analysis from MRI imaging at 3, 6, and 12 months postRT will be used to quantify tumor volume recurrence. Time Frame: 1 year following radiotherapy end

Key secondary outcome(s)
Acute toxicity: Toxicity assessment will be performed by the radiation oncologist in accordance with CTCAE v.5.0 recommendations, through the completion of questionnaires and clinical evaluation. Clinicianreported outcomes (CROs), collected weekly during radiotherapy, will be used to define longitudinal descriptors of the onset and severity of treatmentrelated side effects. Descriptors of interest will include mean mucositis grade, incidence of grade ≥3 mucositis, and maximum mucositis grade. In addition to CRObased descriptors, the feasibility of defining quantitative toxicity descriptors will be explored through the analysis of normal tissues on MRI images by extracting textural features. Time Frame: <8 weeks from radiotherapy end

Completion date
30/10/2031

Eligibility

Key inclusion criteria
1. Age ≥18 years
2. ECOG Performance Status ≤3
3. Histological diagnosis of squamous cell carcinoma, undifferentiated carcinoma, epithelial glandular and nonglandular carcinoma (including adenoid cystic carcinoma, adenocarcinoma, mucoepidermoid carcinoma, neuroendocrine carcinoma, etc.) originating from the oral cavity, oropharynx, nasopharynx, hypopharynx, larynx, salivary glands, paranasal sinuses, or from an unknown primary site.
4. Stage III–IV nonmetastatic disease for pharyngeal, laryngeal, or unknownprimary tumors, according to AJCC 7th edition. Patients with stage III–IV tumors of salivary gland or paranasal sinus origin, and patients with stage I–II pharyngeal or laryngeal tumors, will only be included if prophylactic irradiation of cervical lymph node stations is indicated and/or if the oral and oropharyngeal mucosa as well as swallowingrelated structures are included within the irradiated volume.
5. Indication for treatment in either definitive or adjuvant settings, with or without systemic therapy (concurrent systemic therapy, with or without prior neoadjuvant chemotherapy, permitted. Adjuvant systemic therapy is allowed for selected advanced stages of pharyngeal carcinoma, according to institutional guidelines).
6. Formal acceptance of study participation requirements (written informed consent).

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 Years

Upper age limit
100 Years

Sex
All

Total final enrolment
0

Key exclusion criteria
1. Prior radiotherapy to the headneck region.
2. Presence of connective tissue disorders (e.g., lupus erythematosus or scleroderma) or synchronous head and neck malignancies, except for superficial skin cancers or surgically treated carcinoma in situ not requiring radiotherapy or systemic therapy.
3. Absence of formal acceptance of study participation requirements (written informed consent).
4. Indication for treatment exclusively in the postoperative setting.

Date of first enrolment
15/10/2025

Date of final enrolment
15/10/2028

Locations

Countries of recruitment
Italy

Study participating centre
Fondazione IRCCS Istituto Nazionale dei Tumori di Milano
Via Giacomo Venezian 1
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Sponsor information

Organisation
Fondazione IRCCS Istituto Nazionale dei Tumori

ROR
https://ror.org/05dwj7825

Funder(s)

Funder type
Government

Funder Name
Fondazione AIRC per la ricerca sul cancro ETS

Alternative Name(s)
AIRC Foundation for Cancer Research in Italy, Fondazione AIRC, Associazione Italiana per la Ricerca sul Cancro, AIRC

Funding Body Type
Government organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
Italy

Results and Publications

Individual participant data (IPD) sharing plan
The ownership of data and samples generated for the study will belong to the sponsor (IRCCS National Cancer Institute Foundation of Milan). The datasets generated and/or analysed during the current study are not expected to be made fully available as there is no requirement by the funding body. However, microbiome sequencing data and associated metadata might be published as a supplement to the results publication.

IPD sharing plan summary
Other