Effect of PROtons versus photons on IMMUNOlogical function in head and neck cancer (PRO-IMMUNO): a pilot study.

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

Summary

ID

NL-OMON51957

Source
ToetsingOnline

Brief title
PRO-IMMUNO

Condition

- Miscellaneous and site unspecified neoplasms benign

Synonym
head and neck cancer

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: head and neck cancer, immunological function, proton therapy

Outcome measures

Primary outcome

The primary study endpoint is antigen-specific immunity. Antigen-specific immunity will be assessed in peripheral blood during and after (chemo)radiation, by monitoring T-cell responses to viral peptides, such as SARS-CoV-2, CEF (CMV, EBV and Influenza) and E6 and E7 antigens of HPV16.

Secondary outcome

1) Composition and function of circulating immune cells during and shortly after (chemo)radiation, including e.g. T- and B-lymphocytes and different myeloid cells.

2) Infiltration of immune cells within the primary tumor tissue during (chemo)radiation, including e.g. PD-1 positive T cells (optional part of the study).

Study description

Background summary

Head and neck squamous cell carcinoma (HNSCC) is the sixth most common cancer worldwide (1,2). Traditional factors associated with these cancers include tobacco use and alcohol consumption (1,3). Prognosis of locally advanced HNSCC is in general poor, with a 5-year overall survival of only 40% (53). Another risk factor associated with HNSCC is human papillomavirus (HPV) leading to oropharyngeal cancer (OPC) (2,3). These HPV-positive (HPV+) OPCs behave clinically distinct from HPV-negative (HPV-) OPCs, and have a substantially better prognosis. .

Standard treatment for locally advanced HNSCC of the oropharynx, hypopharynx

and larynx, and irresectable squamous cell carcinoma of the oral cavity is radiotherapy with or without chemotherapy. For patients with recurrent/metastatic (R/M) HNSCC who have progressive disease after (chemo)radiation, immunotherapy with a programmed death 1 (PD-1) antibody improves overall survival and has become the standard of care in this palliative setting (6,7). Because of the poor prognosis of locally advanced head and neck cancer, strategies to escalate the treatment are examined in the curative setting, for example by immunotherapy. The phase 3 JAVELIN Head & Neck 100 study (8) compared concurrent chemoradiation (photons) plus placebo with concurrent chemoradiation (photons) plus avelumab (programmed death ligand 1 (PD-L1) inhibitor) followed by avelumab maintenance in both HPV+ and HPV- locally advanced HNSCC. The interim analysis did not show an improvement in progression-free survival and overall survival. However, high PD-L1 status at baseline (i.e. >=25%) showed a trend towards a better progression-free survival upon treatment with avelumab and chemoradiation. In addition, pembrolizumab (PD-1 inhibitor) concurrent with radiotherapy (photons) did not improve progression-free and overall survival in locally advanced HNSCC compared to cetuximab concurrent with radiotherapy (photons). Lack of selection of patients based on PD-L1 status could be a reason for the negative result. Other potential reasons for the disappointing result could be the ddestruction of activated T-cells during photon radiotherapy or changes in the tumour immune microenvironment caused by photon radiotherapy. Recent advances in radiotherapy for the treatment of HNSCC include the use of proton therapy instead of photon radiation, aimed at sparing healthy tissues surrounding the target volume including lymphocytes, while providing equal tumour control.

Currently, there is some preclinical and clinical evidence that protons are more effective than photons to maintain immunological function (9-11). The consensus view is that fractionated photon radiation can hinder immunological function, in part due to exposure of lymphocytes in the *off-target* low dose radiation field, resulting in lymphopenia (9,12). A randomized phase II study in esophageal cancer showed reduced treatment-related lymphopenia after concurrent chemoradiotherapy with protons compared to photons, which was related to much lower *off target* dose obtained with protons (11). In addition, the immunogenicity of radiation increases with high-linear energy transfer (LET) radiation like protons compared to low LET X-rays, like photons (9,10).

If proton therapy is less detrimental for immunological function or if proton therapy is able to maintain immunological functioning during (chemo)radiation, proton therapy might be beneficial in the response to immunotherapy. Then, proton therapy could be an attractive field for further research examining proton (chemo)radio-immunotherapy next to other treatments. So, clinical data on systemic immunological function and dynamic changes in the tumour immune microenvironment during photon versus proton (chemo)radiation for locally advanced HNSCC are needed to get more insight in the radiation-induced immunogenicity of proton versus photon radiation. Better understanding of

systemic immunological function and dynamic changes in the tumour immune microenvironment could guide the development and design of future studies. An essential question that first needs to be addressed is whether proton therapy is able to maintain immunological function in locally advanced HNSCC patients compared to photons.

Study objective

We aim to establish the difference in immunological function of HNSCC patients undergoing (chemo)radiation with protons versus photons. These preliminary data are required to follow-up with larger studies to compare the effect of proton (chemo)radio-immunotherapy next to other approaches.

Study design

This is a pilot prospective observational study, comprising patients with stage III-IV HNSCC treated with standard of care chemoradiation either with photons (n=10) or protons (n=10), or with standard of care radiation alone with photons (n=10) or protons (n=10). Patients will be assigned for protons or photons based on the guidelines of the National Indication Protocol for Proton therapy. There is only a preference for proton therapy in case the risk of long-term toxicity (i.e. xerostomia and/or dysphagia) can be reduced with proton therapy. The risk of toxicity can be examined in a radiation treatment plan comparison (photons versus protons) before the start of (chemo)radiation. The probability of being selected for protons mainly depends on the location of the primary tumour site in relation to the most important organs at risk and not by tumour extension (TN-stage), which is the main driver of outcome in terms of local control and survival.

Immunological function will be evaluated by peripheral blood samples. Blood samples will be collected at baseline, during (chemo)radiation (end of week 3 and/or before delivery of cycle 4 of chemotherapy) and after completion of (chemo)radiation (week 9, week 12, week 20, week 34 and week 60, respectively 1 week, 5 weeks, 3 months, 6 months and 12 months after completion of (chemo)radiation). To quantify immunological function, PBMCs collected during (chemo)radiation and after (chemo)radiation will be compared with that before (chemo)radiation (week 0), using IFN-γ-ELISPOT to screen for the presence of T-cell responses to viral peptides, such as sars-cov-2, CEF (CMV, EBV, Influenza) and E6 and E7 of HPV-16. Furthermore, flow cytometry panels will be used to determine global changes in immune cell proficiency.

Histological evaluation will take place at baseline and week 3 to examine changes in immune infiltration within tumour tissue during proton versus photon (chemo)radiation. This biopsy part of the study is optional for the patient. Archival tissue from the biopsy that was taken at diagnosis will be used for the baseline assessments. An extra biopsy at baseline will only be taken in

case of insufficient or unavailable tumour tissue of the diagnostic biopsy. Biopsy at week 3 week will be taken for all patients who agree to participate in this optional part of the study.

Study related visits will be (as much as possible) combined with regular hospital visits.

Study burden and risks

(Chemo)radiation either with protons or photons is standard-of-care in HNSCC. The study procedures require seven visits to the hospital, which will be mostly combined with the standard-of-care visits. During these visits blood will be drawn (100 mL) for the collection of PBMC. We will try to combine these venapunctures with routine blood tests as part of the standard of care and standard of care follow up. We will minimize the number of extra vena punctures.
In case the patient has given additional written informed consent, maximum two additional tumor biopsies will be obtained.

We expect that the burden and risks associated with participation will be minimal. Minimal risks are associated with a biopsy, like minimal risk of (radiation-)ulcer, bleeding and/or infection.

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

1) Newly diagnosed stage III-IV HNSCC of the oral cavity, oropharynx, hypopharynx or larynx.
2) Treatment with definitive (chemo)radiation (70 Gy with or without weekly cisplatin) with photons or protons
3) Age of 18 years and older
4) Elective or therapeutic bilateral neck irradiation indicated
5) Written informed consent according to local guidelines

Exclusion criteria

1) Unilateral radiation therapy of the neck.
2) (Diagnostic) resection of the primary tumour.
3) Chemoradiation with carboplatin and 5-FU or radiation with cetuximab.
4) Has a history of an autoimmune disease or other systemic intercurrent disease that might affect the immunocompetence of the patient, or current or prior use (4 weeks before start of the trial) of high dose immunosuppressive therapy.
5) Has a known additional malignancy that is progressing or has required active treatment within the past 3 years. Note: participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ (e.g. breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded.
6) Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior enrolment in this trial. Note: participants who have entered the follow-up phase of an investigational study may participate as long as it has been 4 weeks after the last dose of the previous investigational agent.
7) Has received a live vaccine within 30 days prior to enrolment in this trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette-Guérin (BCG), and typhoid vaccine. Seasonal influenza

vaccines for injection are generally killed virus vaccines and are allowed. In addition, Covid vaccines are allowed.
8) Has an active infection requiring systemic therapy.
9) Has a history or current evidence of any condition, therapy or laboratory abnormality that might confound the results of this trial, interfere with the subject*s participation for the full duration of this trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.
10) Current pregnancy.

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	23-09-2021
Enrollment:	40
Type:	Actual

Ethics review

Approved WMO Date:	07-01-2021
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	30-06-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO	

Date:	12-01-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	11-05-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	NL75013.042.20