Ga-68-DOTA-RGD2 PET/CT in patients with head and neck cancer: a potential tracer to image angiogenesis in tumors.

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

Summary

ID

NL-OMON43594

Source
ToetsingOnline

Brief title
PET/CT imaging with Ga-68-DOTA-RGD2 in HNSCC

Condition

- Miscellaneous and site unspecified neoplasms benign

Synonym
Head and neck cancer, HNSCC

Research involving
Human

Sponsors and support

Primary sponsor: Department of Radiology and Nuclear Medicine
Source(s) of monetary or material Support: ZonMw-Grant no. 95104005

Intervention

Keyword: Angiogenesis, Feasibility study, Head and neck cancer, PET imaging

Outcome measures

Primary outcome

The main study parameter is the uptake of Ga-68-DOTA-RGD2 in the tumor lesions as quantified by PET/CT. Therefore, tracer uptake in tumor tissue, liver, muscle and blood will be determined quantitatively (Standardized Uptake Values, SUVs). With the SUVs, tumor-to-blood and tumor-to-background ratios are calculated. SUVs are obtained by drawing regions of interest, drawn by an investigator, blinded for the immunohistochemical data. Positive ratios are defined as a ratio higher or equal to 2.

Secondary outcome

Additional study parameters are the pharmacokinetics, pharmacodynamics, biodistribution and in vivo stability of Ga-68-DOTA-RGD2, and integrin *v*3 expression of the tumor lesion as determined immunohistochemically.

Study description

Background summary

Head and neck cancer includes malignancies arising in the oral cavity, oro- and hypopharynx and larynx. 90% of all head and neck cancer are squamous cell carcinomas (HNSCC). With an incidence of 2955 in 2014, HNSCC is the 8th and 9th most common cancers in the Netherlands for men and women, respectively. The choice of treatment of HNSCC depends on size and site of the tumor, stage of the disease, and expected oncological and functional outcomes. Whereas early- and locally advanced tumors are treated with surgery or radiotherapy, treatment of advanced HNSCC tumors often includes combinations of surgery, radiotherapy and chemotherapy.

When treating patients with HNSCC, quality of life is an important factor to consider. Early non-invasive monitoring of treatment response would allow clinicians to determine whether the treatment should be adjusted. This could consequently improve patient outcome in the future as well as enhance patients* quality of life by avoiding further side effects of treatments that are ineffective. Monitoring treatment response may also avoid unnecessary health care costs. There is currently an unmet need to identify biomarkers or imaging tools that can steer treatment decisions.

Angiogenesis is a crucial process for tumor growth and metastasis in head and neck cancers and other types of solid tumors. Non-invasive methods to monitor angiogenesis in the tumor can be of great value for treatment selection and response monitoring to steer treatment decisions.

Preclinical studies carried out by us and other research groups have focused on using RGD-based imaging peptides. RGD-peptides bind integrin *v*3, which is expressed on newly-formed blood vessels. Radiolabeled RGD-peptides can image expression of integrin *v*3, which is overexpressed on newly formed tumor endothelial cells. Tumor uptake of radiolabeled RGD-peptides may act as a biomarker for tumor growth.

Our preclinical experiments with human tumor xenografts proved that radiolabeled DOTA-RGD2 can be used as an angiogenesis-specific tracer. We showed that in HNSCC integrin *v*3 is only expressed on the neovasculature of tumors, rather than on the tumor cells themselves and thus the tracer accumulates in tumors with newly formed blood vessels only. Furthermore, in one of our preclinical experiments we showed that DOTA-RGD2 could serve as a clinical tool to monitor angiogenic responses after radiotherapy. The FaDu xenograft models showed a decreased uptake of DOTA-RGD2 after tumor irradiation. Using Ga-68-DOTA-RGD2 as an imaging biomarker of angiogenesis may act as an early biomarker of response to therapy for HNSCC patients. Furthermore, guiding treatment decisions in an early stage can improve patient outcome, it can minimize the side effects, and it may also avoid unnecessary health care costs.

In this study we aim to determine whether this novel imaging tracer (Ga-68-DOTA-RGD2) can monitor responses early after initiation of therapy. First, we will determine whether it is feasible to image tumor angiogenesis in tumors with Ga-68-DOTA-RGD2 and this uptake correlates with the expression of the integrin *v*3. Secondly, the uptake of Ga-68-DOTA-RGD2 as a non-invasive clinical imaging tool during (chemo)radiotherapy will be determined.

Study objective

The primary objective of the study is to ascertain the feasibility and safety to image tumor angiogenesis in head- and neck cancer patients using Ga-68-DOTA-RGD2 PET/CT. Secondary objectives are to determine the

pharmacokinetics and biodistribution of Ga-68-DOTA-RGD2 and to validate Ga-68-DOTA-RGD2 as an imaging biomarker of angiogenesis.

Study design

This is a prospective, observational non-randomized feasibility study. The patients will undergo a Ga-68-DOTA-RGD2 PET/CT scan 1-7 days before their planned surgery. Ga-68-DOTA-RGD2 (200 MBq, 70 µg) will be injected intravenously. In the first cohort of five patients three static PET/CT scans will be acquired at 30, 60 and 90 minutes post injection (p.i.) (study A). The five patients in the second cohort will undergo a dynamic PET/CT scan during 60 minutes (study B). In the remaining 15 patients a 30-minute static Ga-68-DOTA-RGD2 PET/CT scan will be acquired starting at the optimal scan time as determined in study B (study C).

Study burden and risks

In this study, the feasibility and safety of the radiotracer Ga-68-DOTA-RGD2 will be determined. There is a small chance of damage because of study participation. This risk consists of unknown side effects of Ga-68-DOTA-RGD2 administration. The chance of damage is small considering the preclinical toxicity studies. Furthermore, extensive clinical experience using radiopharmaceutical compounds in experimental studies is present at the nuclear department.
The risk of adverse events is limited and serious side effects are not expected. Because this is the first time this tracer is used in clinical practice, vital signs, pharmacokinetics and liver- and kidney functions will be monitored during this study. An adverse event that may occur during the procedure of this study is bruising after venous puncture. The surgery will not be an extra risk or burden to the patient as surgery will be performed conform standard of care.
The radiation dose to the patient is based on the combination of the radiation dose from Ga-68-DOTA-RGD2 injection and from the CT portion of the study. The estimated effective dose of administration of Ga-68-DOTA-RGD2 is 4.5 mSv. This effective dose is in the range of commonly applied oncologic tracers, such as 18F-FDG (7.4 mSv for an adult). The effective dose from the CT portion range from 1-4.5 mSv.

- Patients in study A will receive three low-dose whole-body static CT scans, which will give a radiation dose of approximately 4.5 mSv. The combination of Ga-68-DOTA-RGD2 PET and low-dose CT will expose these patients to a dose equivalent of maximally 9 mSv.
- Patients in study B will receive one low-dose CT scan of the head and neck region, which will give a radiation dose of maximally 1 mSv. The combination of Ga-68-DOTA-RGD2 PET and low-dose CT will expose these patients to a dose equivalent of maximally 5.5 mSv.

- Patients in study C will receive one low-dose CT scan of the head and neck region, which will give a radiation dose of maximally 1 mSv. The combination of Ga-68-DOTA-RGD2 PET and low-dose CT will expose these patients to a dose equivalent of maximally 5.5 mSv.

The combination of Ga-68-DOTA-RGD2 PET and low-dose CT is the only test these patients will receive in addition to their normal work-up. This study corresponds to the risk category IIb as defined by the International Commission on Radiation Protection (minor to intermediate level of risk).

Because the surgery will take place at least one day after administration of Ga-68-DOTA-RGD2 the surgeon and other medical staff will not be exposed to radiation burden, since Ga-68 has a half-life of 68 minutes.

The subjects who are included will not directly benefit from participating in this study. However, imaging angiogenesis shows the potential to monitor and steer treatment decisions in patients with head and neck cancer. Therefore, this study is justified.

According to the NFU risk classification it is assumed that the added risk of study participation within this study is negligible.

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

- Proven HNSSC of the oral cavity, oro- and hypopharynx, or larynx
- At least one lesion with a diameter of at least 1.5 cm
- A diagnostic CT or MRI scan is obtained within 4 weeks prior to screenings visit
- Planned surgery as primary treatment
- * 18 years
- Ability to provide written informed consent

Exclusion criteria

- Contra-indications for PET: pregnancy, breast-feeding, or severe claustrophobia
- Abnormal renal function
* creatinine clearance * 60 mL/min according to the formula of Cockroft and Gault
- Abnormal liver function
* ALAT or ASAT level more than 3 times the upper limit of normal range
* Bilirubin more than 2 times the upper limit of normal range
- Other serious illness

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	03-02-2016

Enrollment:	25
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	nvt
Generic name:	Ga-68-DOTA-RGD2

Ethics review

Approved WMO Date:	03-07-2015
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	28-07-2015
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	21-03-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	16-08-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	02-03-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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
EudraCT	EUCTR2015-000917-31-NL
CCMO	NL52649.091.15