Radio guided lymph node dissection in oligo metastatic prostate cancer patients

Published: 02-12-2019
Last updated: 10-04-2024

The primary aim of this study is to evaluate the feasibility and safety of In-111-PSMA I&T radio guided surgery in patients diagnosed with prostate cancer who are highly suspected of having pelvic lymph node metastasis based on pre-operative...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Renal and urinary tract neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON50037

Source
ToetsingOnline

Brief title
DETECT

Condition

- Renal and urinary tract neoplasms malignant and unspecified
- Renal and urinary tract therapeutic procedures

Synonym
Lymph node metastases in prostate cancer, lymphogenic prostate cancer spread

Research involving
Human

Sponsors and support

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

Intervention

Keyword: diagnostics, prostate cancer, PSMA, radio guided surgery

Outcome measures

Primary outcome

The primary aim of this study is to evaluate the feasibility of 111In-PSMA-I&T radio guided surgery in patients diagnosed with prostate cancer who are highly suspected of having one or more pelvic lymph node metastasis/metastases based on pre-operative imaging. Feasibility will be defined as the ability to intra-operatively detect the lymph nodes (using a gamma probe) which were pre-operatively identified on PSMA-PET/CT.

Secondary outcome

Secondary objectives comprise:

* To assess accuracy of 111In-PSMA-I&T radio guided surgery as compared to histopathological findings (gold standard).

* To assess safety of 111In-PSMA-I&T by monitoring (S)AE*s according to the common terminology criteria for adverse events (CTCAE).

* To determine the pharmacokinetics of 111In-PSMA-I&T.

* To assess the correlation between the gamma-counts as detected by gamma probe (ex-vivo) and tumour/lymph node size.

* To assess the correlation between the gamma-counts as detected by gamma probe (ex-vivo) and PSMA-staining on histopathology.

* To assess the correlation between the gamma-counts as detected by gamma probe (ex vivo) and SUV as determined on PSMA-PET/CT.

* To validate both nano-MRI images and SPECT/CT images of resected samples

using histopathologic findings.

* To assess the correlation between pre-operative imaging (nano-MRI and

PSMA-PET/CT), intra operative imaging and postoperative imaging (ex vivo).

Study description

Background summary

Patients diagnosed with prostate cancer do not die from the primary tumour, but from (extended) metastatic disease. One of the first steps towards extended metastatic disease is the presence of lymph node metastases, which is an important factor in determining therapy and prognosis. Although historically all patients with lymph node metastases are considered incurable, research has shown that patients with only small (<8mm) nodal metastases have a better prognosis as compared to patients with more extensive involvement . In patients with only small nodal metastases, therapy with curative intent might be pursued, e.g. by surgical resection or loco-regional radiotherapy. With continuously improving opportunities to very selectively treat small numbers of metastatic sites it is of utmost importance to accurately diagnose the first signs of oligo-metastatic disease and to define its extent.
Conventional imaging techniques such as CT and MRI are limited in detecting small lymph node metastases. Consequently, nodal involvement is detected only through lymph node dissection and research demonstrated that even standard pelvic lymph node dissection (PLND) may miss lymph node involvement outside the standard boundaries of the surgical template. Within the Radboudumc ferumoxtran-10-enhanced MRI (nano-MRI) as well as68Ga/18F-PSMA PET/CT are innovative techniques which are promising for presurgical diagnosis of limited nodal disease, especially when used complementary.
However, the biggest challenge we currently face is the surgical removal of these (small) lymph nodes, to histopathologically validate the presurgical imaging findings and to treat oligometastatic disease with curative intent (resection of all identified lymph node metastases). Small suspicious lymph nodes, deeply embedded in highly vascularised abdominal lipid tissue, may be difficult to detect during surgery.
When radiolabelled, PSMA ligands can be used as a tracer to identify prostate cancer metastases. Therefore, we propose a clinical trial to investigate the feasibility of radio-guided surgery, using a radiolabelled tumour-targeting tracer (111In-PSMA-I&T) which can be detected by a gamma-probe during PLND. This technique could potentially aid the surgeon in detecting (small) lymph node metastasis intra-operatively.

Study objective

The primary aim of this study is to evaluate the feasibility and safety of In-111-PSMA I&T radio guided surgery in patients diagnosed with prostate cancer who are highly suspected of having pelvic lymph node metastasis based on pre-operative imaging.

Study design

The study is a prospective, single arm open label phase I/II study. Patients with prostate cancer who have a high risk of lymph node metastases based on PSMA PET/CT and scheduled for PLND (with or without prostatectomy) will be recruited. Eligible patients will receive an additional nano-MRI to complement pre-operative imaging. Twenty-four hours before surgery, patients will receive 111In- labelled PSMA-I&T. According standard of care, PLND*s are performed at the Canisius Wilhelmina Hospital (CWZ) in Nijmegen, through existing collaboration of the urology departments. During surgery, the surgeon will be provided with a gamma-probe to detect PSMA expressing lymph nodes in vivo. Dissected samples will be systematically assessed on tracer accumulation using the gamma probe in vivo as well as ex vivo. After surgery, the samples will be scanned in the small animal SPECT/CT and 7T-MRI. After scanning, samples will be presented to pathologists for pathological analysis according to standard of care including staining for PSMA expression. At 3 months after surgery, patients will undergo a PSMA-PET/CT. Up until one year after surgery patients will be followed according to standard of care-guidelines by 3-monthly serum-PSA measurements.

Intervention

Not applicable.

Study burden and risks

The main burdens and risks for participating patients are summarized below.

Exposure to contrast agents
Investigational product
Radio guided surgery will be performed using the radiolabelled PSMA agent 111In-PSMA-I&T. This product is a composition of the radio-isotope Indium-111 and the ligand PSMA-I&T. The composed product it is a relatively new, non-registered pharmaceutical, which was first synthesized in 2015 at the Technical University München (1). No specific toxicity data on the combination of PSMA-I&T and Indium-111 is available in literature, however clinical studies in over 30 patients reported no adverse events or complications related to the administration of the tracer (2, 3). Furthermore, more extensive safety data on the PSMA-I&T ligand is available. These studies investigated the toxicity and safety of this ligand when labelled with Gallium-68 and Lutetium-177 in both tumour baring mice and humans (4, 5). In those studies no clinically

significant adverse effects were found related to the administration of the ligand.
Considering this data and the fact that the administered activity of 177Lu-PSMA-I&T is significantly higher than the radiation dosage of Indium in this study-protocol, we do not expect clinically significant adverse effects of 111In-PSMA-I&T. However, we will assess the safety of the tracer in this study by closely monitoring adverse events, laboratory and vital parameters. Based on biodistribution and dosimetry studies, the main potential organs at risk are the kidneys. Low tracer uptake in normal bone marrow and salivary glands may also be of particular interest, especially in therapeutic applications (higher activity dosages)(5). Based on these findings, we will assess the potential bone-marrow toxicity and nephrotoxicity by laboratory tests before and after administration. For more detailed information on this subject also refer to the Investigator Brochure on 111In-PSMA-I&T (D1).
The extra radiation dosage which patients receive from the administration of 150 MBq of this agent is calculated to be an effective radiation dosage of 8.1mSv. When considering patient category and age, the relative radiation dosage however will be 1.62mSv (see also the Radiation Ethics Form, K6). This falls within the scope of other commonly used imaging modalities in nuclear medicine practice and is considered to be an acceptable dose according to the International Commission on Radiological Protection (ICRP).

Non-investigational products: ferumoxtran-10 enhanced MRI
All study participants will undergo a nano-MRI scan prior to their surgery (PLND). For this nano-MRI scan, patients will receive ferumoxtran-10 contrast 24 hours prior to scanning. Within the Radboudumc there is much experience with this agent and scanning method, which is carried out on a daily basis. The burdens of this imaging modality to participants consist of the intravenous injection of the contrast agents, which will be administered over the course of 60-75 minutes, and the duration of the MRI-scan, for which the patient has to lie still for approximately 1.5 hours.
Risks related to the contrast agent ferumoxtran-10 are discussed more extensively in the Investigators Brochure of ferumoxtran-10 (D1). Safety data is based on 1663 treated patients or healthy volunteers. Forty-four of those patients (2.6%) experienced SAE*s, from those patients only 7 were considered related to the contrast agent (an estimated risk of 0.2-0.9%). Serious potentially allergic reactions have been uncommonly (0.4%) observed during clinical studies of Ferumoxtran-10. These types of reactions, which included anaphylactic shock, may very rarely be life- threatening or fatal. They can occur irrespectively of the dose of Ferumoxtran-10 administered. In the unlikely event an allergic reaction occurs, anti-anaphylactic medication will be present in the room where the infusion takes place. Mild adverse events are implied to be related to infusion speed. Most reported side effects were back pain (3%), headache (2.5%) and hypersensitivity symptoms (up to 2.5%). These symptoms were mild to moderate, short (less than one hour after infusion) and had a favourable outcome. By lowering the infusion speed the risk of adverse

events is limited.

Non-investigational product: 18F/68Ga-PSMA-PET/CT
In patient follow up after surgery, patients will receive an extra 18F/68Ga-PSMA-PET/CT scan. Extensive experience has been gained in research as well as clinical use of this product. Risks related to the administration of this contrast agent are discussed extensively in the Investigators Brochure on 18F-PSMA-1007 (D1.3.) and 68Ga-PSMA-HBED-CC (D1.4.). The main burdens of this imaging modality are related to the extra exposure to ionizing radiation. This is discussed in the Radiation Ethics Form (K6). The total effective dose for this scan is 17mSv (18F-PSMA-PET/CT, 68Ga is lower). When considering patient category and age, the relative radiation dosage will be 3mSv. This falls within the scope of other commonly used imaging modalities in nuclear medicine practice and is considered to be an acceptable dose according to the International Commission on Radiological Protection (ICRP).

Total ionising radiation exposure
The total effective dose (including 111In-PSMA-I&T and 18F/68Ga-PSMA-PET/CT) for patients when participating in this study is calculated to be approximately 22mSv. Considering our patient population a detriment factor of 0.2 is used to correct for this category. The relative radiation dosage will be approximately 5 mSv. According to the ICRP guidelines, the risk coefficient for stochastic effects (fatal cancer) after exposure to radiation at low dose is 5.5% per 1000 mSv(6).

Increased clinic visits
Compared to standard of care, patients who are included in the study protocol will be subject to increased clinic visits. Two extra trips to the hospital are incorporated in this study protocol, comprising the injection of intravenous nano-contrast, nano-MRI scanning and injection of 111In-labelled PSMA-I&T. To limit discomfort for patients due to the extra visits, we will combine these procedures in a minimal amount of two visits. Those visits will take place at the Radboudumc for all participants, during the two days prior to the planned surgery. The visits will not cause any delay to surgery planning.
Post-operatively, all study related visits will be combined with standard visits.

Invasive measurements
For safety analysis, blood clearance analysis and the injection of contrast agents for imaging, participants will be submitted to several intravenous injections/drips. To minimize invasiveness, we will use infusion systems were possible. In total, patients will have 3 infusion systems (for both injection and blood sampling), 2 intra muscular injection (within scope of nano-MRI), 1 venepuncture and 1 intravenous injection.

Other potential burdens
During surgery, urologists will be provided with a gamma-probe to

detect tumour-positive pelvic lymph nodes. Since this is an extension to normal PLND (without the use of detection devices, standard of care), the usage of the device might prolong the duration of the surgery up to maximally 15 extra minutes. Surgeons and operation room staff will be lectured in handling the probe to minimise delay.

Potential benefits
Participants do not directly benefit from participation in the study.

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

Histological proven cancer of the prostate, based on prostate biopsy-core analysis.

At least one 68Ga/18F-PSMA-PET/CT positive metastasis in lymph nodes, located in pelvis.
Patient is scheduled and fit for robot assisted surgery (PLND or radical prostatectomy +PLND).
Patient is suitable for PLND (and radical prostatectomy) conform institutional guidelines and is not yet treated pre-operatively. (Prior prostate cancer treatment is defined as prostate and/or pelvic radiotherapy, hormonal treatments such as androgen deprivation therapy, prostate brachytherapy, prostate cryotherapy, high intensity focused ultrasound (HIFU) and/or prostate electroporation.)
Age>=50 years.
Ability to give voluntary written informed consent to participate in this study.

Exclusion criteria

No detectable lesion on the 68Ga/18F-PSMA-PET/CT with an uptake level above liver uptake level.
Patients who are not scheduled for PLND.
Prior pelvic surgery assosiated with pelvic lymphadenopathy.
Unequivocal evidence of metastases outside the pelvis.
Presence of any medical condition that in the opinion of the investigator/treating physician will affect patients* clinical status by participating in this trial.
Prior prostate cancer treatment in the form of surgery, radio-, hormonal- or chemotherapy.
Contraindication for MRI-scanning, i.e. claustrophobia, intracranial metal clips, metallic bodies in the eye, implanted electric and electronic devices not eligible for MRI (pacemakers, insulin pumps, cochlear implants, neurostimulators).
Inability to lie still for at least 60 minutes or comply with imaging.
Contraindication for iron infusion or hypersensitivity/allergy to the active substance or any of the excipients.
The patient is already enrolled in one or more concurrent studies, which would confound the results of this study, according to the investigators.

Study design

Design

Study phase: 2

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	28-08-2020
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	F-18-PSMA-1007
Generic name:	F-18-PSMA-1007
Product type:	Medicine
Brand name:	Ga-68-PSMA-HBED-CC
Generic name:	Ga-68-PSMA-HBED-CC
Product type:	Medicine
Brand name:	In-111-PSMA-I&T
Generic name:	In-111-PSMA-I&T

Ethics review

Approved WMO Date:	02-12-2019
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	13-01-2020
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	11-06-2020

Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	24-11-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	15-02-2021
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	EUCTR2019-003284-21-NL
CCMO	NL71151.091.19