De toepassing van nucleaire beeldvorming voor de detectie en karakterisatie van primair prostaatcarcinoom bij patiënten met behulp van 99mTc-Tricine/TPPTS/HYNIC-Aca-Bombesine(7-14) SPECT/CT

Gepubliceerd: 22-10-2010 Laatst bijgewerkt: 30-04-2024

Primary Objectives: a. Optimization of the 99MTc-HABN SPECT/CT scanning protocol in the first 5 patients (Phase 0). b. Detection and characterization of primary prostate cancer (tumor uptake and tumor-to-background ratio) in patients with 99MTc-HABN...

Ethische beoordeling	Goedgekeurd WMO
Status	Werving gestopt
Type aandoening	Voortplantingsorgaan- en urogenitale neoplasmata, geslacht niet-gespecificeerd NEG
Onderzoekstype	Interventie onderzoek

Samenvatting

ID

NL-OMON35521

Bron
ToetsingOnline

Verkorte titel
99mTc-HYNIC-BN(7-14) SPECT/CT en primair prostaatcarcinoom

Aandoening

- Voortplantingsorgaan- en urogenitale neoplasmata, geslacht niet-gespecificeerd NEG

Synoniemen aandoening
prostaatkanker

Betreft onderzoek met

Mensen

Ondersteuning

Primaire sponsor: Universitair Medisch Centrum Groningen
Overige ondersteuning: Ministerie van OC&W,verstrekte subsidies

Onderzoeksproduct en/of interventie

Trefwoord: bombesine, kanker, prostaat, SPECT

Uitkomstmaten

Primaire uitkomstmaten

- An interim analysis of the first 5 scans will be made to determine the optimal scanning procedure (see study procedure paragraph 3 of this chapter). After this interim analysis, all scans will be performed in the same way for the remaining patients. In the first 5 patients also the pharmacokinetic properties of the tumour in the first 20 minutes will be determined. The interim analysis will also show if the CT is able to correctly discriminate between prostatic uptake and excretion of activity via the bladder. Prior studies with SPECT/CT have shown that bladder drainage is not necessary. But, if needed we will apply continues bladder drainage via an urinary catheter that is inserted prior to the scan.
- Pharmacokinetics of the radiopharmaceutical will be determined in serum that is obtained via an arterial canula at several intervals (canula placed prior to tracer injection).
- Detection of prostate cancer, number, position, size and intensity of hotspots (tumour-to-background ratio, subjective scoring by 2 nuclear physicians) with the use of 99MTc-HABN SPECT/CT, comparison with clinical

parameters (clinical tumour stage, overall Gleason score, serum PSA) and comparison to histologic results of the prostate specimen after radical prostatectomy (number, position, size, Gleason score of prostate cancer lesions, proliferation score of each lesion (Ki-67 staining), staining for GRPR of each lesion).

Secundaire uitkomstmaten

- As this is a *first in men* study, the heart-rate and blood-pressure of all patients will be monitored during the first hour after injection with pulsoxymeter and blood pressure-monitor.
- Significant changes (>15% change in heart-rate, >15 mmHg change in systolic and/or diastolic blood pressure) and other reported side-effects will be documented for all patients.

Toelichting onderzoek

Achtergrond van het onderzoek

Prostate cancer is one of the most common causes of cancer in men and a common cause of morbidity and death in the world. In order to determine the most optimal treatment of prostate cancer, the disease stage at primary diagnosis has to be established. On the basis of clinical parameters it is decided if 99mTc-methylene diphosphonate bone scintigraphy and/or a pelvic lymph node dissection have to be performed in order to detect prostate cancer metastases in the most likely places, i.e. pelvic lymph nodes and bone.
In non-metasized patients a calculation is made on the basis of their serum PSA, histology and clinical tumour if organ-confined disease or capsular-extension/seminal-vesicle-invasion can be expected. For the latter it is more likely to benefit from radiotherapy to the prostatic region than from a surgical radical prostatectomy. For the patients with organ-confined disease, both treatment modalities are equally effective. The sensitivity of CT and MRI is insufficient for routine application in staging of the primary tumour.
Nuclear imaging techniques like positron emission tomography (PET) or single photon emission computed tomography (SPECT) could improve detection of

prostate cancer, but current non prostate cancer specific radiotracers like 11C/18F-choline, 11C-acetate, 18F-fluorodeoxyglucose or the prostate cancer specific 111In-capromab-pendetide are lacking in accuracy, hereby limiting clinical application.
Antigens (over)expressed in prostate cancer, but sparse in normal tissue, can be used for antigen-targeted diagnostic applications. Preclinical and clinical studies where new antibody-based or peptide-based substances are tested for antigen targeted imaging of prostate cancer have shown promising results. One such interesting peptide receptor that is overexpressed in primary and metastatic prostate cancer is the gastrin-releasing peptide receptor (GRPR) or bombesin (BN) receptor. GRPR is normally found in non-neuroendocrine tissues of the breast and pancreas and in neuroendocrine cells of the brain, gastrointestinal tract, lung and to a small extent in prostate. Upon binding with the gastrin-releasing peptide or a bombesin-like peptide, the receptor effects a wide range of biological responses[20, 21]. in addition to overexpression in prostate cancer, GRPR is also overexpressed in several other types of cancer, like breast, lung, ovarian, renal and gastrointestinal cancer. Besides the preclinical and clinical use and evaluation of radiolabelled BN-like peptides for nuclear imaging of various types of cancer, several BN analogues have also been used as antagonists or carriers to deliver drugs, radionuclides and toxins specifically to GRPR positive cancers in order to inhibit tumour growth, induce tumour regression or cause cell death.
In our center we have developed 99mTc-Tricine/TPPTS/HYNIC-Aca-Bombesin(7-14) (from here on: 99MTc-HABN) in a cooperation project on bombesin imaging between the Medical Isotopes Research Center, Peking University, Peking, China and the Department of Nuclear Medicine and Molecular Imaging (NMMI) at the University Medical Center Groningen. Shi et al. (Peking University) has already published on a comparable radiopharmaceutical for its preclinical evaluation in human colon cancer xenograft models [49]. One of the radiochemists that worked on 99MTc-HABN in Peking is now working here at the department of NMMI as part of the cooperation project. In vitro experiments have shown excellent uptake of the tracer in human prostate cancer cells. In vivo experiments in human prostate cancer bearing nude mice have shown high uptake in the tumour. Results will be published in 2010.
Clinical evaluation is the logical next step to be taken to implement GRPR targeted nuclear imaging in clinical practice for tumour staging and evaluation of response to therapy. Different patient groups will be studied in different phases. First, we propose on the application of nuclear imaging for detection and characterization of primary prostate cancer in patients with 99MTc-HABN SPECT combined with computed tomography (CT) for anatomical co-registration (SPECT/CT). As this is a *first in men* study, the heart-rate and blood-pressure of the first five patients will be monitored during the first hour after injection. If no significant changes (>15% change in heart-rate, >15 mmHg change in systolic and/or diastolic blood pressure) are seen in blood-pressure or heart-rate, the monitoring can be left out of the protocol for the other patients.

If 99MTc-HABN SPECT/CT proves useful for detection and characterization of primary prostate cancer, it could have other diagnostic implications like SPECT-guided biopsies of hot-spots after repeated negative prostate biopsies in patients with an elevated serum PSA (common problem). Other possible uses of 99MTc-HABN SPECT/CT could be therapeutic; e.g. planning for nerve-sparing radical prostatectomy in prostates with limited uptake of the tracer, more accurate planning for brachytherapy or guidance of intensity modulated radiotherapy, with a higher radiation dose to areas with elevated uptake of the tracer. Also, 99mTc-HABN SPECT/CT might be a useful technique for detection of lymph node or bone metastases of prostate cancer. Intra-operative near-infrared imaging using the same target could be useful for real-time determination of radical tumor resection.
.

Doel van het onderzoek

Primary Objectives:
a. Optimization of the 99MTc-HABN SPECT/CT scanning protocol in the first 5 patients (Phase 0).
b. Detection and characterization of primary prostate cancer (tumor uptake and tumor-to-background ratio) in patients with 99MTc-HABN prior to a radical prostatectomy, Comparison with histology and clinical parameters (Phase 1). Phase 0 patients (5) and Phase 1 patients (15), a total of 20 patients.
c. Pharmacokinetics of the radiopharmaceutical will be determined in serum that is obtained via an arterial canula at several intervals (first 5 patients).

Secondary Objective(s):
Monitoring of heart-rate (with puls-oxy-meter) and blood-pressure after injection of 99MTc-HABN. Documentation of reported side-effects.

Onderzoeksopzet

The current study is an imaging study in which the 99MTc-HABN SPECT/CT is studied for its ability to detect and characterize primary prostate cancer in patients scheduled for a radical prostatectomy. Results of the SPECT/CT are compared to clinical parameters and histology. All patients (20) have been scheduled for a radical prostatectomy (main inclusion criterium) which is part of normal prostate cancer treatment. The patients will undergo a combined SPECT/CT. The scans are the only procedures patients will be submitted to as part of the study. In the first 5 patients an extended SPECT scan will be made to determine the optimal scanning protocol. When this has been determined, the remaining 15 patients will be submitted to the optimal SPECT scan protocol. In the first 5 patients pharmacokinetics of the radiopharmaceutical will be determined in serum that is obtained via an arterial canula at several intervals.

As this is a *first in men* study, the heart-rate and blood-pressure of all patients will be monitored during the first hour after injection. Significant changes (>15% change in heart-rate, >15 mmHg change in systolic and/or diastolic blood pressure) and other reported side-effects will be documented for all patients.

After the SPECT/CT scan, the study has ended for the patient. After the scan the patient will undergo the radical prostatectomy, which will not be postponed for study purposes. Normal waiting time for such a treatment is 4 to 6 weeks. This should be enough time for inclusion, for patients to decide on their participation and for performing the scan(s).

Also, the results of the first 5 patients will be reported to the local ethics committee before proceeding to scan the remaining 15 patients.

Histologic examination of prostate cancer tissue after prostatectomy is part of normal tissue analysis; number, position, size and Gleason score of each cancer lesion will be documented. Analysis will however be extended by introducing Ki-67 staining (proliferation marker) and GRPR staining (bombesin receptor). This will have no clinical implications and can be done with the prostatectomy specimen that was resected as part of normal clinical practice.

The results of the SPECT/CT will be compared with histology results and clinical parameters (serum-PSA, Gleason-score and clinical tumour stage).

Onderzoeksproduct en/of interventie

--

Inschatting van belasting en risico

Justification: Currently, there are no imaging techniques available for detection/staging of primary prostate cancer. Prostate cancer is diagnosed on the basis of elevated serum levels of PSA, rectal examination and random biopsies of the prostate. Octant biopsies of the prostate are false-negative in 30% of cases and will have to be repeated when prostate cancer is expected. 99MTc-HABN SPECT/CT might be a technique that is both able to detect intra-prostatic hot-spots, thereby guiding prostate biopsies. 99MTc-HABN SPECT/CT might also be able to stage prostate cancer and, based on its findings, therapy can be amended (e.g. planning for nerve-sparing radical prostatectomy in prostates with limited uptake of the tracer, more accurate planning for brachytherapy or guidance of intensity modulated radiotherapy, with a higher radiation dose to areas with elevated uptake of the tracer). Also, 99mTc-HABN SPECT/CT might be a useful technique for detection of lymph node or bone metastases of prostate cancer. Intra-operative near-infrared imaging using the same target could be useful for real-time determination of

radical tumor resection.
Benefits: Since this is a new technique and it has not proven to be of benefit for local staging of prostate cancer, there is no direct benefit for this group of patients. Results of this study will not be used for treatment decision.
Risk Assessment:
Risks due to placement of arterial and venous canula: the formation of a haematoma is minimal. The placement of the canula is painful, however minimal.
Risk due to injection of 99MTc-HABN: please refer to the IMPD pages 1 to 10 for a detailed description of the substance, toxicology and human exposure of radiolabelled bombesin-like peptides. In short, no adverse effects have been reported in prior studies with similar compounds, so no adverse effects are expected.
Risks due to exposure to radiation: the use of CT and gamma-photon emitting isotopes means the exposure to radiation. Because of the potential hazards of radiation, guidelines for the exposure of volunteers are specified in *Besluit Stralingsbescherming Kernenergiewet (BSK2000)*, according to the guidelines of the International Commission of Radiological Protection (ICRP 62, 1992).
A CT of the prostatic region (pelvis) will be performed from the upper iliac crest to the pubic bone. A SPECT scan of the prostatic region will be performed after injection of 500-700 MBq of 99MTc-HABN. The first 5 patients will undergo multiple SPECT scans, this won*t give extra radiation, except for a second CT at the 20 hour time-point.
Calculation of radiation: 99MTc-HABN is expected to deliver a radiation dose of 4.5E-3 mSv/MBq, at a maximum dosage of 700 MBq this will come down to 3.2 mSv. CT of the prostatic region will be 1.5 mSv. Leading to a total of 3.2 + 1.5 = 4.7 mSv per person. (the first 5 patients will have 2 CT scans and therefor 3.2 + 1.5 + 1.5 = 6.2 mSv per person)
The amount of radiation falls into category II-B (1-10 mSv) of the ICRP-62 guidelines (Normal background radiation per person per year is 2-2.5 mSv). This guideline states that medical research with category II-B exposure should be aimed directly to improvements in the diagnosis, cure or prevention of disease. In the first subparagraph of this paragraph and throughout the protocol the necessity of this study is pointed out. The benefit of a good diagnostic tool suitable for detection of prostate cancer is more than substantial. Formation of a second primary malignancy due to radiation because of SPECT/CT procedure is possible, but unlikely. Moreover, since most patients in this group are elderly people, the latency of secondary malignancies (15-30 years) will make it very unlikely to cause any problems.
Burden:
For group 1: 5 patients in which an extended SPECT protocol is applied: To minimize patient burden, all patients will be submitted to the urology ward on a Tuesday. The scanning protocol can be started on Tuesday, and 20 hours later on Wednesday the last scan can be performed. After the last scan the patients will return to the urology ward and being prepared for surgery (radical prostatectomy), which is always performed on Wednesday.
For group 2: 15 patients with the definitive SPECT protocol: one visit to the department of NMMI or depending on the planning patients can be submitted to

the urology ward. Scanning time point is uncertain at this moment.
Another burden is the minimally painful placement of the venous canula (20 patients) or the arterial canula (5 patients) prior to the SPECT scan.
Group relatedness: the group of patients participating in this study is the same as the target-group (prostate cancer patients).

Contactpersonen

Publiek

Universitair Medisch Centrum Groningen

Hanzeplein 1
9713 GZ Groningen
NL

Wetenschappelijk

Universitair Medisch Centrum Groningen

Hanzeplein 1
9713 GZ Groningen
NL

Locaties

Landen waar het onderzoek wordt uitgevoerd

Netherlands

Deelname eisen

Leeftijd
Volwassenen (18-64 jaar)
65 jaar en ouder

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

- Histologisch bewezen prostaat kanker
- Patienten ondergaan een radicale prostatectomie (als onderdeel van normale behandeling)
- Vrijwillige deelname aan de studie; informed consent getekend
- >60 jaar

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

- Enig teken van neurologische of psychiatrische aandoening die de patiënt verhindert zijn vrije wil uit te spreken
- Enig teken van ziekte of aandoening die het de patiënt verhindert gedurende een uur in dezelfde positie te liggen
- Andere medische studie waarin patiënt is blootgesteld aan straling gedurende het afgelopen jaar
- serum kreatinine >110 umol/l
- Enig teken of voorgeschiedenis van andere maligniteit in het bekken

Onderzoeksopzet

Opzet

Type: Interventie onderzoek

Blindering:	Open / niet geblindeerd
Controle:	Geen controle groep
Doel:	Diagnostiek

Deelname

Nederland

Status:	Werving gestopt
(Verwachte) startdatum:	08-06-2011
Aantal proefpersonen:	20
Type:	Werkelijke startdatum

In onderzoek gebruikte producten en hulpmiddelen

Soort:	Geneesmiddel
Merknaam:	99mTc-Tricine/TPPTS/HYNIC-Aca-Bombesine(7-14)
Generieke naam:	99mTc-Tricine/TPPTS/HYNIC-Aca-Bombesine(7-14)

Ethische beoordeling

Goedgekeurd WMO Datum:	22-10-2010
Soort:	Eerste indiening
Toetsingscommissie:	METC Universitair Medisch Centrum Groningen (Groningen)
Goedgekeurd WMO Datum:	01-06-2011
Soort:	Eerste indiening
Toetsingscommissie:	METC Universitair Medisch Centrum Groningen (Groningen)

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

Geen registraties gevonden.

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

Register	ID
EudraCT	EUCTR2008-007184-16-NL
CCMO	NL25790.042.10