18F-FDHT PET/CT for re-staging patients with recurrent of prostate cancer after radiotherapy; a pilot study

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Primary Objective: To assess the detection rate of 18 F-FDHT PET/CT in men with recurrent prostate cancer after radiotherapy who are candidates for local salvage treatment.Secondary Objective(s): To assess the detection rate and accuracy of 18 F-...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Reproductive neoplasms male malignant and unspecified
Study type	Observational invasive

Summary

ID

NL-OMON43219

Source
ToetsingOnline

Brief title
FDHT PET/CT for restaging recurrent prostate cancer

Condition

- Reproductive neoplasms male malignant and unspecified
- Prostatic disorders (excl infections and inflammations)

Synonym
prostate cancer, recurrent

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: FDHT PET/CT, prostate cancer, PSMA PET/CT, recurrence

Outcome measures

Primary outcome

- Visual assessment of number of lesions en conclusion of re-staging (localized disease, systemic disease or a combination of the two) according to 18 F-FDHT PET/CT on patient-by-patient basis.

- Semi-quantitative lesion by lesion assessment measuring and evaluating the maximum and mean standardized uptake value (SUVmax , SUVmean)

Secondary outcome

Lesion-based analysis by comparing the number of detected lesions in different sites of recurrence/metastases with FDHT PET/CT to PSMA PET/CT and with lesions detected by mMRI and information from follow-up (PSA response to salvage therapy, confirmative biopsy or lymph node dissection and other imaging studies (X-ray, bone scans)). To assess the overall accuracy, sensitivity, specificity, PPV (positive predictive value) and NPV (negative predictive value) of 18 F-FDHT PET/CT.

Study description

Background summary

Prostate cancer is the most common type of cancer among men worldwide 1. In the Netherlands, incidence and estimated deaths of prostate cancer in 2014 were respectively 9926 and 2535 per 100.000 Dutch men (www.cijfersoverkanker.nl). According to the Dutch guidelines of prostate cancer, patients with localized prostate cancer (cT1-2 Nx-0 Mx-0V TNM classification 2009) can be divided in three groups by local extent of the tumor (T stage), prostate specific antigen

(PSA) and histological profile described by Gleason score. These cancer specifics classify the primary prostate tumor as either low, medium or high-risk. Together with patient characteristics (i.e. wish of patient, expected side effects, life expectancy and co morbidities), the risk classification determines the definitive choice for either active treatment or active surveillance. The current active treatment options are radical prostatectomy (RP), external beam radiotherapy (EBRT) or brachytherapy2. Alternative and emerging treatment options for patients with clinically localized prostate cancer who are not suitable for RP, are cryosurgical ablation of the prostate (CSAP) and high-intensity focused ultrasound (HIFU) 3-5.

Rising PSA levels after radiotherapy do not distinguish between local, regional or distant recurrence (lymph nodes or bone metastasis). CT sensitivity for detecting local recurrences or lymph node metastasis is low. Bone scan and CT is only recommended in patients with BCR after radical prostatectomy when the baseline PSA is high (>10) or PSA kinetics is high or a patient has symptoms of bone metastasis. Bone scintegraphy has low specificity compared to newer tracer assisted positron emission tomography (PET)/CT6. In addition, BS cannot measure tumor activity and is not a suitable for follow-up of therapy response7. TRUS is not reliable after radiation therapy to show local recurrence8-10. The current new European guideline advices to re-stage patients with BCR, who are potential candidates for local salvage therapy, either PET/CT or with multiparameter MRI (mpMRI) of the prostate. mpMRI can also be used to guide local salvage treatment and for biopsy targeting. Various studies showed that sensitivity of prostate biopsies to proof local recurrence of prostate cancer after radiotherapy is considered low11,12. In the concept guideline by the Dutch Urology Organization about prostate cancer (version 2.1), is written that PSMA PET/CT is proven to be just as good and maybe better than choline PET/CT, and can therefore be used instead of choline in the clinical setting. This is already in use since this year in many academic centers in the Netherlands, where PSMA has completely replaced choline as PET/CT tracer. Link to new concept guideline:
https://www.radiologen.nl/files/File/kwaliteit/Protocollen%20en%20richtlijnen/Abdominale%20Radiologie/2016%2002%2022%20MODULE%20PET-CT%20Richtlijn%20prostaatcarcinoom.pdf.

Currently most centers shift from anatomic imaging techniques to metabolic/molecular imaging for the detection of recurrent prostate cancer. PET/CT with a radiolabelled choline can be used after radical prostatectomy for restaging, but sensitivity and specificity depend on PSA value and is only recommended in patients with PSA >1 ng/mL. After radiotherapy, the PSA cutoff after which choline PET/CT is useful is unclear because of lack of data but PSA kinetics seems to be a better predictor than PSA value alone, for detection rate13.

Although choline PET/CT shows the potential of single step whole body imaging, its accuracy will be limited as non-cancer specific tracer. Although choline PET/CT is and was a good first tracer for single step whole body imaging, its

accuracy will be limited as non-cancer specific tracer. Crucial for targeted imaging is the use of tracers that are specifically over expressed in prostate cancer but low in normal cells. Prostate specific membrane antigen (PSMA) is over expressed in most prostate cancers; thereby labeled PSMA proves to be more accurate for restaging of localized prostate cancer after radiotherapy14. The first prostate specific membrane antigen antibody 111In-capromab pendetide (ProstaScint, Cytogen, Princeton,USA), which binds to an intracellular part of the antigen showed disappointing results on detection of local recurrence in patients with BCR after radiotherapy15,16. First studies on newly developed PSMA tracers binding to the extracellular domain of the receptor showed that 68Gallium-PSMA PET/CT is highly specific in imaging prostate cancer. Hybrid 68Gallium PSMA-ligand PET/CT has a higher detection rate in recurrent prostate cancer after radical prostatectomy (>90% at PSA levels >1ng/mL) than hybrid PET/CT with other tracers. Tumor detection was positively associated with PSA value and higher Gleason score17. Another study was published on detection rates in patients with recurrent prostate cancer after different primary treatment. In this study tumor detection was positively associated with androgen deprivation therapy (ADT)18. However, these studies were retrospective and used a heterogeneous patient population (mixing stages and recurrences after different kinds of primary treatment) which makes the outcomes hard to interpret18-20.

In our center, there are currently two studies who assess 18F-FDHT PET/CT for predicting outcomes of treatments in different stages of prostate cancer. 18F-FDHT images the androgen receptor with high binding affinity and selectivity21. Dehdashti et al demonstrated that metastatic and recurrent prostate cancer lesions can be detected by 18F-FDHT PET22. The sensitivity on a patient basis was 63% (12 out of 19 patients) and the sensitivity on a lesion basis was 86% (24 out of 28 lesions identified by two conventional imaging modalities)22. Larson et al found corresponding results. 18F-FDHT PET was able to detect 78% (46 out of 59) of lesions identified by conventional imaging23. Moreover, 18F-FDHT PET disclosed 17 additional, previously unknown foci of tracer uptake most consistent with metastatic disease23.

The imaging technique that is advised for restaging patients with prostate cancer by the European Association of Urology(EAU) guidelines is multi-parameter magnetic resonance imaging (mpMRI). Parallel imaging techniques combined give more information about different tissues en therefore can be used for different diagnostic purposes. Diffusion weighted MRI (DWI) does not require intravenous contrast and derives his imaging from differences of motions between intra and extracellular protons24. The apparent diffusion coefficient (ADC) is the quantitative parameter describing microscopic water diffuse ability. Pilot data suggest that the ADC value could be a biomarker, when compared to SUV in 11C-choline PET/CT 25. Dynamic contrast-enhanced MRI (DCI-MRI) uses differences in time of contrast enhancement between benign tissue and tumor, following intravenous administration of contrast26. DCE MRI is a promising tool to detect local recurrence of prostate cancer after radiotherapy. The enhancement of post-radiation fibrosis is slow, whereas recurrent cancer is usually hyper vascular. When compared to T2 weighted

imaging (T2WI) DCE MRI showed higher specificity and sensitivity (ranges between 64-93% and 60-97%) than T2WI (54-88% and 39-85%) for imaging recurrent prostate cancer after EBRT10,27.
Accurate localization of recurrence prostate cancer is needed for appropriate treatment selection (local salvage therapy or systemic therapy) Toxicity of salvage treatments was observed in 30% of patients in all three treatments in a study of Peters et al.(2010)28. Possible complications vary from mild lower urinary tract symptoms to recto-anal fistula. These high toxicity rates make the need for careful selection of patients for salvage treatment even more essential. In a study performed in this center (not yet submitted) we found that choline PET/CT for restaging scan in patients with biochemical recurrence after radiotherapy, could not locate assess advanced disease in 617% of patients, since this patientsey showed no biochemical response to salvage cryoablation. In studies by Afshar-Oromieh et al. and Eiber et al 17,29 , PSMA PET/CT was superior to radio labeled choline PET/CT. Together with our retrospective findings, that choline is not able to identify the patients who are eligible candidates for cryoablation, We want to perform a pilot head-to-head study to determine accuracy and detection rate of in which we compare 68-PSMA-PET/CT to 18F-FDHT PET/CT and determine accuracy of both scans compare finding of FDHT PET/CT to the imaging modalities made in the contect of standard care: d to standard from European guidelines; multiple parameter MRI and 68 Ga-PSMA-11 PET/CT. The result of this pilot can hopefully lead to a larger study, if 18 F-FDHT PET/CT shows promising results.

Study objective

Primary Objective: To assess the detection rate of 18 F-FDHT PET/CT in men with recurrent prostate cancer after radiotherapy who are candidates for local salvage treatment.

Secondary Objective(s): To assess the detection rate and accuracy of 18 F-FDHT PET/CT to imaging made in the context of standard care (mpMRI and 68 Ga-PMSA PET/CT) in men with recurrent prostate cancer after radiotherapy who are candidates for local salvage treatment.

Study design

n this study, a 18 F-FDHT PET/CT will be made. A multi-parameter MRI and 68 Ga-PSMA PET/CT will be made in the context of standard care and to be used as reference standards, so accuracy of 18 F-FDHT PET/CT scan can be determined. After the scan is made, the study ends for the subject. All scans will be made in the University Medical Centre Groningen (UMCG).
Since this is a pilot study, we aim to include 20 men who suffer from biochemical recurrence prostate cancer after primary radiotherapy. Biochemical recurrence is defined as PSA of nadir + 2 ng/mL(Phoenix definition)30.

The result of PET/CT scan will not be communicated to the patient. FDHT report will not be published in the patient file, and only be send and stored anonymously by the study team. Therefore, any result of the scan will not lead to further diagnostics and/or treatment changes.

To obtain written informed consent, patients will receive a brochure containing necessary information about the study, procedures, risks and possible side effects. Also logistics and an explanation about what patients normally experience during each scan will be described in the brochure.

Study burden and risks

Subjects have to an additional PET scan combined with low-dose CT for anatomical context.
For 18 F-FDHT PET/CT:
- Patients will be given an intravenous catheter (I.V.) for administration of the tracer. The I.V. will be removed after administration and will therefore give minimal discomfort and risk.
- Patients will have to lie still on their backs for approximately 20-30 minutes (depending on weight).
-18 F-FDHT PET/CT is a tracer with no documented risks when administered to humans. Like all tracers, there is risk for an allergic reaction, for which a medical doctor of Nuclear Medicine department is nearby during all PET/CT scans in the UMCG. Possible risks of I.V.placement are hematoma, infection and extravasation of fluid or tracer.
- The radiation burden for 18F-FDHT is 0.018 mSv/MBq. For the injected dose of 200 MBq the total radiation burden is approximately 3.6 mSv. The low dose CT, which will be used for attenuation correction and anatomical co-registration, has a radiation burden of approximately 1.9 mSv. Total burden is 5.1 mSv.

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

- Histologically proven prostate cancer for which the subject has undergone radiotherapy with curative intent
- Biochemical recurrence according to Phoenix criteria (PSA nadir +2 ng/mL)
- PSA <10 ng/mL
- Written informed consent
- No androgen deprivation therapy in the past 12 months
- Planned for restaging or patients who have recently have been restaged with a mpMRI and 68 Ga-PSMA PET/CT (last scan not more than 28 days ago)

Exclusion criteria

- Active cancer besides prostate cancer
- Suspected metastases
- PSA > 10 ng/mL
- Androgen deprivation therapy in the past 12 months
- A contra-indication for undergoing MRI. (namely implants containing metal or metal schrapnels in the eyes or body and claustrophobia)

Study design

Design

Study type: Observational invasive
Masking: Open (masking not used)

Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	19-01-2018
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	18-F-FDHT
Generic name:	16beta-[18F]fluoro-5alfa-dihydrotestosterone

Ethics review

Approved WMO Date:	14-11-2016
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	20-12-2016
Application type:	First submission
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
EudraCT	EUCTR2016-000533-52-NL
CCMO	NL56762.042.16