PRISMA-PET – Primary Staging of Prostate Cancer: A Randomized Controlled Trial Comparing 18F-PSMA-1007 PET/CT to Conventional Imaging

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Department of Urology, Hospital Sønderjylland, Kresten philipsens vej 15, 6200 Aabenraa.

The project will be performed according to this protocol, relevant legislation and ICH-GCP guidelines.

Time plan:

We expect to start recruiting for the project in summer 2021. Recruiting and scanning procedures are expected to be finished in summer 2024, hence the medical part of the project will end by then. The patients will be followed for 20 years after inclusion in the patient record and with questionnaires.

Problem, aim, and hypothesis

Molecular targeting treatments and diagnostics in Prostate cancer (PCa) have evolved in recent years, while mortality from PCa has remained unchanged in Denmark (1). One molecular target is the prostate specific membrane antigen (PSMA), which is overexpressed in prostate cancer cells and can therefore serve as target for diagnosis, staging, and treatment. Positron Emission Tomography (PET) / Computed Tomography (CT) with radiolabelled PSMA (PSMA-PET/CT) has recently been implemented in the Danish Prostate Cancer guidelines (DAPROCA) as a potential tool for detecting relapsing local and metastatic disease. This decision is based on convincing studies showing a superior diagnostic accuracy of PSMA-PET/CT compared to conventional imaging in this patient setting (1).

When it comes to initial staging in primary PCa, however, there are only small diagnostic studies available performed retrospectively in heterogeneous study designs (2), and accordingly guidelines still recommend conventional imaging with contrast enhanced CT (CE-CT) and bone scintigraphy (BS) for staging in this setting(1). We believe that there is a need for larger prospective trials analyzing effects in terms of benefit for patients and society of implementing radiolabelled PSMA-PET/CT compared to conventional imaging for N-staging (lymph node metastases in the pelvic region) and M-staging (lymph node metastases outside the pelvic region, bone metastases and metastases in other organs).

The overall aim of this project is in a randomized design to compare ^{18}F-PSMA-PET/CT to conventional imaging for initial staging in intermediate and high risk PCa with regard to accuracy, impact on treatment strategy and progression free survival. In a subgroup analysis we aim to analyze the added value of ^{18}F-PSMA-PET/Magnetic Resonance (MR) for local staging.

We hypothesize that

- *Staging intermediate and high risk PCa with ^{18}F-PSMA PET/CT and PET/MRI is more accurate at local-, N- and M-staging compared to conventional staging and therefore will lead to a change in treatment strategy with improved progression free survival.*

Background

PCa is the most frequent cancer form in men in developed countries (3) with approximately 4,500 new cases reported annually in Denmark, 980 of which are based in the Region of Southern Denmark (RSD). The relative 5-year survival is 87% (4). The course of disease ranges from well differentiated tumors localized to the prostate gland itself, being potentially curable, to aggressive, rapidly disseminating variants with poor prognosis despite intensive treatment.

Choice of treatment regimen at primary diagnosis is based on risk stratification, staging of the disease, and general health condition of the patient (1, 5). In intermediate and high risk PCa, further staging procedures besides T-staging (6) is warranted. CE-CT or magnetic resonance (MR) is used for N-staging in cases when pelvic lymph node dissection is avoided during radical prostatectomy or when surgery is refrained from (7), although either modality has a reported sensitivity of approximately 40% (8). M-staging is traditionally obtained from BS, which reflects bone metabolism and has a reported sensitivity as well as specificity of

80% (9). An alternative modality reflecting bone metabolism is the ^{18}F-sodium fluoride PET/CT (NaF-PET) which has a superior accuracy compared to BS (10, 11). BS has been substituted with NaF-PET in clinical routine at our department, and will as well in this study. Multiparametric MRI (mpMRI) of the pelvis may be performed in high-risk patients for accurate T-staging and thereby planning of resection level (R-staging) before radical prostatectomy.

The treatment regimens for different stages of PCa ranges from observation, radiation therapy, radical prostatectomy and androgen deprivation to intensive chemotherapy and experimental therapeutic regimens (1, 5). The treatment regimens are associated with a specific risk of potential adverse effects, so correct staging is paramount in order to avoid unnecessary treatment complications. Curatively intended surgery or radiation treatment followed by a surveillance program is the initial intervention for patients with localized disease.

The transmembrane protein, PSMA, is expressed in abundance on the surface of prostate cancer cells. Radiolabelled ligands targeting PSMA has been developed for use in PET/CT-scanners. The ligand PSMA-1007 can be labelled with the positron emitting isotope ^{18}F (12) and is only slowly excreted through the urine as opposed to the more widely used ^{68}Ga-PSMA-11 (13). The slow urinary excretion of ^{18}F-PSMA-1007 poses the advantage of avoiding difficulties discriminating between excreted tracer in the urinary bladder from pathological uptake in adjacent lymph nodes. Another advantage of ^{18}F labelled ligands is that they can be produced in large amounts on sites with a cyclotron whereas ^{68}Ga is produced in a ^{68}Ge/^{68}Ga generator with limited capacity resulting in only a limited number of scans per generator per day. Of further interest is that the molecular structure, biodistribution, and tumor uptake of ^{18}F-PSMA-1007 is very similar to that of ^{177}Lu-PSMA-617(12), which is a radiotherapeutic agent (14). This could provide invaluable information on dosimetry calculations as well as predictive information in a potential future theranostic approach.

The ^{18}F labeled PSMA-PET/CT has so far shown detection rates of up to 94% in patients with biochemical recurrence of PCa after radical prostatectomy with curative intend (15). Several studies of the feasibility of the ^{68}Ga labelled PSMA-PET/CT in various settings of PCa patients and with various endpoints have been reported (2, 16-19). These all show promising results for ^{68}Ga-PSMA PET/CT but also remark upon the heterogeneous nature of the somewhat sparse data available and call for randomized controlled trials. The literature regarding ^{18}F-PSMA-PET/CT for staging of primary PCa comprises only two retrospective studies with 10 and 8 patients, respectively (20, 21), both of them also focusing on the added value of combining ^{18}F-PSMA-PET with mpMRI for a combined T- and N-staging.

Indeed, randomized controlled studies in well powered designs addressing patient relevant outcomes of staging primary in PCa with ^{18}F-PSMA-PET/CT compared to conventional imaging are considered highly relevant. This is also highlighted in a recent international consensus report on molecular imaging and theranostics in PCa (22).

The research medicine

The research medicine, ^{18}F-PSMA, is a PET-tracer produced and applied clinically every week in the Departments of Nuclear Medicine, RSD, for the detection of relapse of PCa after curative intended therapy, hence ^{18}F-PSMA is medicine we know very well. We have the license to use ^{18}F-PSMA intravenously for a PET/CT scan for all cancer types expressing PSMA on the surface, as prostate cancer does. The difference in this proposed protocolled use of the drug from the current clinical use is the time point for application in the disease course. Today it is used when the patients are suspected for relaps after curatively intended therapy. In the PCa patient setting, we will use ^{18}F-PSMA when the patients are newly diagnosed with PCa and not yet treated. Research shows promising results for accuracy of ^{18}F-PSMA-PET/CT in this patient setting (23), but the patient benefit from being staged with PSMA-PET/CT is not yet evaluated.

The risks for the patients scanned with this drug are very discrete. We are not aware of any patients reacting allergically or with any other side effects, presumably because ^{18}F-PSMA is administrated in extremely small doses, and it is not considered having any pharmacological or pharmaco-dynamic effect. We consider the risks of this medicine no larger than the medicine for conventional imaging.There will be no difference in the dose administered in our study compared with the use in clinical practice, 2 MBq pr kg. bodyweight, between 150 and 300 MBq; max. 1,8 mg PSMA and in many cases much less. The drug will be administered only once, 60 min before the scan, intravenously and in the coorporating departments by authorized personel as in the clinical setting. Paravenous injection can rarely happen with following local irritation shortly, but the medicine has a short half life in the body (< 2 hours).

Labelling, storage, compliance and destruction of the medicine is not considered a problem, as the patients are injection in the involved departments as in clnical routine. As the patients are all men, anticonception for fertile women is not relevant. As the medicine is used in very small doses, excretion in seemen is in a level where anticonception is not considered relevant for this reason.

The patients will be treated clinically following the national clinical guidelines for PCa at any time.

The project will be monitored by the local GCP-unit at OUH, part of OPEN, J.B. Winsløws Vej 9, 3. sal, 5000 Odense C.

Safety

We will register side effects from the ^{18}F-PSMA during the 2 hours the patients are in our department after the injection. As the drug is non-detectable the next day, we expect potential side effects to show in this period – according to “the summary of product characteristics, 4.8” no adverse reactions to the medicine are reported. We will encourage the patients to contact the principal investigator if anything unusual happens during 24 hours after injection. Any suspected side effect will be registered in the REDCap database.

In case of a Serious Adverse Event they will be reported to the sponser within 24 hours from knowledge of it. The sponsor will report Suspected Unexpected Seriuos Adverse Reactions within 2 days to The Ethics Comite and the Danish Medicines Agency, as well as all principal investigators. Yearly reporting of safety and adverse events to The Ethics Comite and the Danish Medicines Agency will be performed by the sponsor.

As the medicine has the short half life in the body, the patients should be followed a maximum of 24 hours after injection. We will register the dose given in the electronic patient file as usually done in clinical practice, and it will be registered in the projects REDCap database along with the other project registrations. The medicine is well known to have no adverse effects and is only used for diagnoses. In case of reported "Serious Adverse Events" or "Suspected Unexpected Seriuos Adverse Reactions" related to the medicine, termination of the project will be considered.

Research plan

The study is planned in a prospective randomized controlled design as illustrated in appendix 1 and 2 and will be carried out in close collaboration with the Department of Urology. The patients will be included and randomized as a part of one of the initial doctors appointments in a consultation room, and they will be encouraged to bring a relative to this consultation. Patients are identified when they have an appointment at Department of Urology, and the researchers will be given information from the clinicians, which means that they will not access the patient journals before enrolling. The patients will be informed about the project from the PhD-student, a physician from the Nuclear Medicine Departments, an Urologist from the coorporating departments or a nurse involved in the project, all with expertise in prostate cancer. They will be offered time to consider enrolment in the trial. The patients will be offered further information and answering of upcoming questions over the telephone after the initial talk. At this time or one of the following days, when they have accepted to be enrolled in the project and signed the written consent, they will be randomized in REDCap, where the randomisation code is kept. The randomization will be stratified according to the patients clinical risk status and pathology of biopsies. The written consents will be collected at the Nuclear Medicine Department, when they meet for their scan and at the earliest the day after the information in Department of Urology. Our study population will comprise men with a newly diagnosed intermediate or high risk (including locally advanced) PCa (1) or with a clinical suspicion of metastases based on other findings. Included patients will be randomized into a control group (A) and an interventional group (B). Group A will be staged by conventional imaging, i.e. CE-CT for N-staging and NaF-PET for M-staging. Group B will be staged by ^{18}F-PSMA PET/CT for both N- and M-staging. A subset of patients with risk of extracapsular extension considered for radical prostatectomy in group B will also have an ^{18}F-PSMA-PET/mpMRI-scan for T-staging (evaluation of the tumor). This scan will be performed in continuation of the ^{18}F-PSMA-PET/CT, i.e. on the same administered dose of ^{18}F-PSMA. Furthermore, a subgroup of patients in group B will have a blinded NaF-PET-scan for the purpose of performing comparative accuracy analyses.

Biopsy of suspected metastatic lesions in N- and M-positive patients (suspicion of metastases) as well as lymph node specimen in N- and M-negative patients will be intended as reference standard in both groups as well as a nadir unmeasurably low post-surgery prostate specific antigen blood sample to indicate no residual disease where applicable. Reference standard in the accuracy analysis of ^{18}F-PSMA PET/mpMRI with regard to T- staging is histopathology on surgical specimen. As the risk of distant metastases increases with increasing PSA-levels, analyses will be performed on both population level as a whole as well as in two PSA-strata with cut-off being PSA=100 ng/ml.

Treatment and subsequent follow-up will be planned on the basis of the results of the scans and according to current guidelines (1, 5).

Follow-up data will be collected from patient journals by the researcher/principal investigator or a delegate, and will consist of clinical information, examination reports, blood test results, information about treatments and pathology reports, all performed in a clinical setup as determined by the clinician. No extra visists, scans or blood test are required except for questionnairesThe patients will be asked to fill in questionnaires (EQ-5D-5L, FACT-P and EPIC 26) concerning quality of life during at baseline and 3, 6, 12, 24, 60, 120 og 236 months after recruitment. The questionnaires will be delivered to the patients e-boks from REDCap automatically at the specific time points. All collected information will be used in this project for analysis of treatment decision, relapse detection, overall survival and quality of life in the two patient groups.

Primary endpoints (Group A vs. B)

1. Treatment strategies and progression-free survival
2. Quality of life measures

Secondary endpoints

1. Overall survival (Group A vs. B)
2. ^{18}F-PSMA-PET/MR for evaluation of extension of tumor in the prostate gland and surrounding structures compared to histopathology on surgical specimen.
3. Accuracy of ^{18}F-PSMA-PET/CT compared to NaF-PET/CT for evaluation of bone metastases

Four publications are planned, cf. section “Planned publications” below. Studies 1 and 4 will address the presumed patient benefit from staging with ^{18}F-PSMA PET/CT in a randomized design, and outcome measures will consequently be impact on stage migration, treatment decision, progression free survival, and time to relapse in group A vs. group B. As studies 2 and 3 are comparative studies, outcome measures in this setting will be accuracy measures regarding N- and M-staging in study 2, and T- and R-staging as well as change in treatment intend in study 3.

Beyond the scope of this PhD-project we plan a follow-up time period of up to 20 years for analysis of disease free period, overall survival and quality of life.

Admittance to documents and data including patients journals are given to the relevant GCP-units and the Danish Medicines Agency for monitoring, audition and inspection of the project.

Sample size and statistical analyses

Assuming that staging intermediate and high risk PCa with 18F-PSMA PET/CT leads to upstaging in 20%, 398 patients, i.e. 199 patients in each arm, will be necessary to estimate the proportion of upstaged patients with 18F-PSMA PET/CT with sufficient precision as the expected length of the Wilson-score 95% CI for this proportion will be 11% (simulation study with N=2000 trials). These numbers are sufficient to indicate that the proportion of upstaged patients with 18F-PSMA PET/CT is statistically significantly larger than 12.9%

under above assumptions (power: 80%; two-sided testing; Type I error: 5%). A total of 448 patients (224 in each arm) are sufficient to indicate a statistically significant difference in progression free survival with assumed hazard rates of 0.35 and 0.5 for 18F-PSMA PET/CT and conventional staging respectively, implying a hazard ratio of 0.7. Estimates are based on a study duration of 4 years, consisting of 3 years accrual time and minimum follow-up period of 1 year before the first data collection, and a loss-to-follow-up of 10% (two-sample comparison of survivor functions; Exponential test; Type I error: 5%). Therefore, **448 patients (224 in each arm**) will be included in the study. For sample size calculation for the accuracy analyses planned in Group B only, we assumed a prevalence of metastases of 30%, sensitivity and specificity of 0.38 and 0.91 for conventional imaging, and 0.85 and 0.98 for PSMA-PET/CT. Then, a sample size of **128 patients** is sufficient to indicate a superior sensitivity for PSMA-PET/CT and a non-inferior specificity for PSMA-PET/CT, with a non-inferiority margin of 0.052, at a significance level of 5% (two-sided) with a power of 80%. We expect 224 patients from OUH, 80 patients from Hospital of Little Belt, 72 patients from Hospital of South West Jutland and 72 patients from Hospital Sønderjylland. Patients from Hospital Sønderjylland will have their scans performed in either Hospital of Little Belt or OUH Odense.

Primary analyses will be done as indicated in the sample size rationale above. Cox proportional hazard regressions will be adjusted for available demographic and clinical baseline variables, and graphical displays will comprise Kaplan-Meier plots including risk tables (i.e. patients at risk in each group).

Descriptive statistics will be done according to data type (mean±SD or median (range) for symmetrically and unsymmetrically distributed continuous variables, respectively, as judged visually with histograms including approximating Normal curves; frequencies and percentages for categorical variables). Exploratory, bivariate testing will be done with unpaired t-tests or, alternatively, Wilcoxon's rank sum test on continuous and Chi-squared test, alternatively, Fisher's exact test for categorical variables. Level of significance will be 5%. All analyses will be done with STATA/IC 15 (StataCorp, College Station, Texas 77845 USA). If exceptions for this statistical plan is needed, it will be reported when published.

Missing data will be reported in the publications. Illegitimate data will be excluded. Reason for un-used data will be reported.

The primary analysis of QoL and morbidity will be based on the changes in the FACT-P questionnaire at the timepoints: inclusion and 12 months. An 8-point decline in the global FACT-P score will be considered clinically relevant. The secondary analyses include the group difference in a repeated measurement analysis, making use of data collected at the several time points of FACT-P. Secondary analyses will likewise be conducted using the EQ-5D-5 and EPIC-26. The time from baseline to decline of 8 points in global FACT-P score will be visualized by Kaplan-Meier plots and explored with a two-sided log-rank test. The level of significance will be 5%. All analyses will be done with STATA/IC 15 (StataCorp, College Station, Texas 77845 USA).

Organization and collaboration

PRISMA-PET is intended to be a part time PhD-project spanning 4 years. It is planned to be one of several projects in a larger research program established in a collaborative research center, entitled: Personalized

Assessment of Prostate Cancer: A Research Centre in Clinical and Translational Molecular Medicine (PASSPORT). PASSPORT represents a multidisciplinary collaborative team.

The overall purpose of PASSPORT is research, development and implementation of novel molecular imaging modalities and theranostic methods in PCa. The PRISMA-PET project focuses on the performance of ^{18}F-PSMA PET/CT and PET/mpMRI in primary staging of intermediate and high risk PCa.

Other parallel PASSPORT projects in the clinical work package intend to investigate ^{18}F-PSMA in recurrent and metastatic PCa, impact on clinical decision making and response monitoring, and treatment of progressive metastatic PCa with ^{177}Lu-PSMA. Other work packages in PASSPORT aim at developing new therapeutic radiopharmaceuticals and at profiling PCa with biomarkers and genomic profiling. Several medical specialties and departments from OUH and intentionally from departments of other hospitals in RSD will be participating in PASSPORT center. Already participating specialties from OUH include nuclear medicine, urology, oncology, pathology, clinical biochemistry and clinical genetics, thus representing a truly multidisciplinary approach.

Patient involvement

We have included two patient representatives in our study group to:

- Contribute in the development of information material for study participants.
- Contribute with valuable input in relevant project meetings when discussing patient related issues as well as ethical considerations.
- Aid in communicating study results to citizens, e.g. via the Danish prostate cancer patient organization “Prostatakræftforeningen” - PROPA.

International collaboration

Collaboration, including study visits, with the “Munich-group” and/or the “Heidelberg-group” with regards to PSMA-expertise is considered relevant, but not yet formalized.

Feasibility

Patient recruitment will be performed in collaboration with relevant departments of urology in RSD. One or more parallel PhD-projects on the same study population, but nested in the Department of Urology, OUH, is planned, thereby enabling patient recruitment on either of the two departments in close cooperation. It is considered achievable to include the required 448 patients in this setting.

The Department of Nuclear Medicine, OUH, received approval to produce ^{18}F-PSMA-1007 from the Danish Medicines Agency in 2019. ^{18}F will routinely be produced on our two cyclotrons, and our well-equipped radiochemistry is trained in the production and labelling of a wide variety of PET-tracers complying with Good Manufacturing Practice (GMP). The tracers will be shipped to the cooperating departments. We currently have five state-of-the-art PET/CT-scanners and a PET/MRI-scanner, and will as such have all the

prerequisites for tracer production and performing the planned scans together with the cooperating Nuclear Medicine Departments.

The PSMA-PET scans performed in OUH will be evaluated and documented as in clinical practice by the applicant and three supervisors as well as a PhD student from another PhD-project - all being Nuclear Medicine specialists along with specialists in radiology, and the same set-up is planned in the cooperating departments. Conventional scans will be evaluated as part of the daily routine at the Departments of Nuclear Medicine (NaF-PET) and Radiology (CE-CT, mpMRI). The SharePoint and RedCap systems will be used for data collection and management in line with the European data protection regulation (GDPR) implemented by May 25 2018. Sharepoint will be used for safe storage of permissions and registrations, and REDCap for patient data.

Ethical aspects

All study procedures will be performed after having obtained informed consent from each patient. The project will be performed according to this protocol, comply with the Declaration of Helsinki and ICH-Good Clinical Practice guideline and relevant legislation (GDPR, the Health Act and the Data Protection Act) and as well as follow procedures for control of quality. If the protocol is not strictly followed, the sponsor will be informed by the principal investigators by mail or telephone. Approval is obtained by the local Ethical Committee (S-20190161 11-12-2019 and 31-03-2020) and the study protocol has been registered at the Danish Data Protection Agency (20/20086, 01-05-2020) . The study will be registered at the international clinical trial-registries (clinicaltrials.gov) before it is initiated. The patients are insured as a part of the clinical set up. No extra insurance is taken.

The critical data of the project will be the time point for progression, determined by the second of two following PSA blood tests with rising values. Time of death will be registered, possibly from our personal register. QoL questionairres will be evaluated statistically.

Radiation dose for each element of the different scan types are estimated to:

- NaF-PET: 4.8 mSv from NaF and 3-6 mSv from low-dose CT, i.e. 7.8-10.8 mSv.
- ^{18}F-PSMA PET/CT: 3.1-4.6 mSv from PSMA and 10 mSv from CE-CT, i.e. 13.1-14.6 mSv
- mpMRI gives no radiation dose

Radiation dose from staging by conventional imaging in group A will add up to 17.8-20.8 mSv. Patients in group B will receive a total of 20.9-25.4 mSv from ^{18}F-PSMA PET/CT and the blinded NaF-PET, i.e. an additional radiation dose of up to 7.6 mSv. As annual background radiation dose in Denmark amounts to 3-5 mSv and the patient population consists of primarily middle-aged to elderly patients, the added radiation dose in group B is considered well within limits of reason.

Planned publications

1. Clinical impact on stage migration and treatment strategy when using 18F-PSMA PET/CT compared to conventional imaging in primary staging of PCa (Group A vs B).

2. A prospective comparative accuracy study of 18F-PSMA PET/CT for N- and M-staging compared to conventional imaging in primary PCa (Group B).
3. The added value of PSMA-PET/mpMRI compared to PSMA-PET/CT on T, N, and R-staging (R = resection level) (Subgroup of B).
4. The impact on progression free survival and biochemical relapse when using 18F-PSMA PET/CT compared to conventional imaging in primary staging of PCa (Group A vs. B - planned as a joint publication with PhD student from the Department of Urology).

It is the intention to publish the results no matter if they are positive, negative or inconclusive. The results will be published inwww.clinicaltrialsregister.eu.

Authorship order will be depending on work effort and involvement according to the Vancouver Declaration (IMJCE). No clauses agreed.

Initiators of the project:

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Mie Holm Vilstrup, Nuclear Medicine Department, OUH Odense
Mads Hvid Poulsen, Department of Urology, OUH Odense
Steinbjørn Hansen, Department of Oncology, OUH Odense

Funding

Funding for one year salary for Principal Investigator (578.000 kr) and scans (600.000 kr) has been received from The Region of Southern Denmark. The researchers are all employed in The Region of Southern Denmark for clinical work.

No industrial financing.

Still applying for further financing,

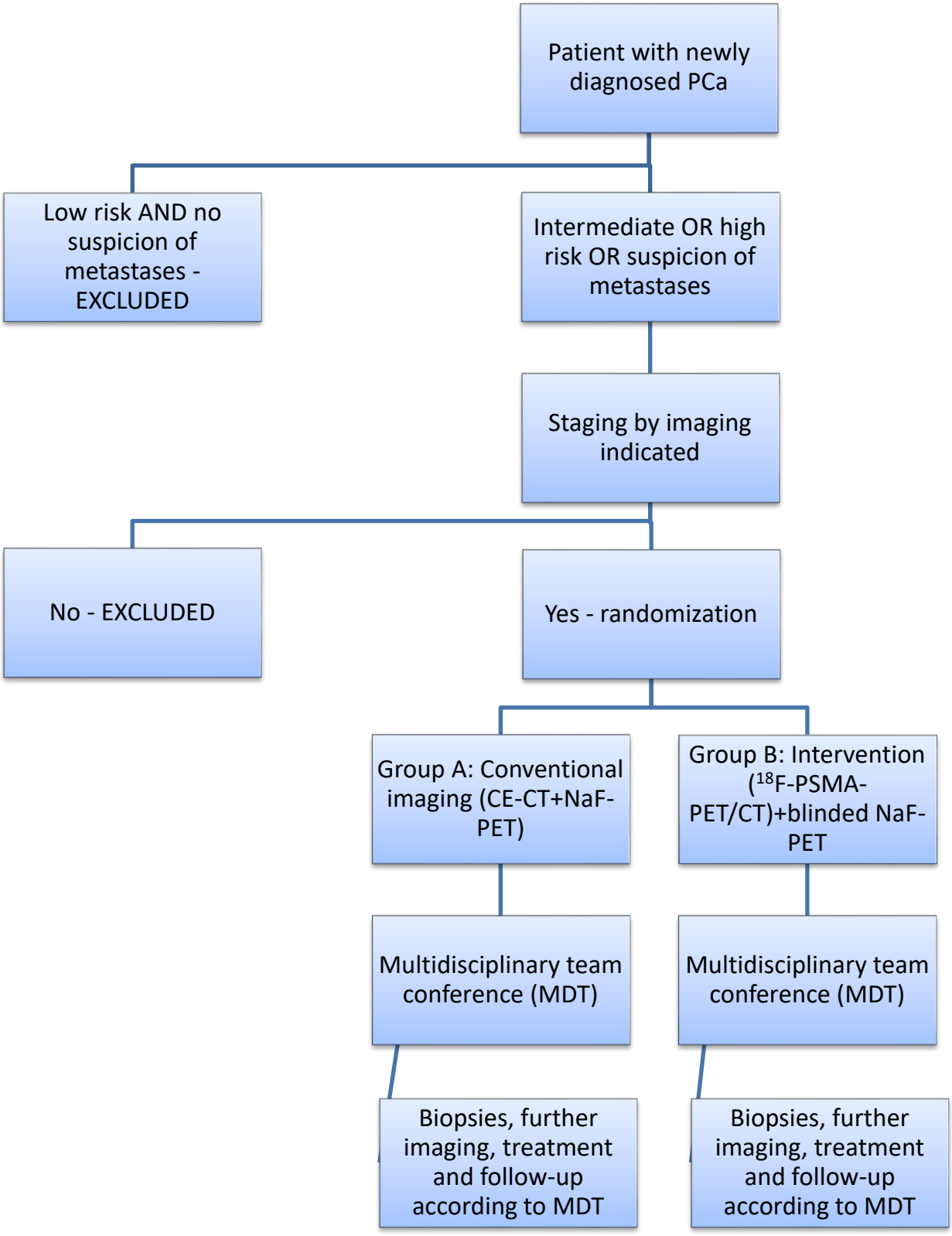
Funding will be spent at salary for PhD-student (75 % salary in 4 years), nurse for recruitment, scans that are not clinical/standard, GCP-monitoring and OPEN/REDCap.

Funding will be deposited in a bank account for research in Nuclear Medicine Department OUH Odense (Jyske Bank, 7562 0001090051; SE: 30 04 91 79, CVR: 29 19 09 09).

Appendix 1, inclusion and exclusion criteria

Inclusion critera, all must be fulfilled	Exclusion criteria, any criterion fulfilled warrants exclusion
Has given informed consent to participate	Consent not given
Can read and understand provided patient information material in Danish	Inability to read and/or understand provided patient information material in Danish
Biopsy verified, newly diagnosed and untreated PCa	Previously given consent to this study withdrawn for any reason
Any, some, or all of the following features: • PSA ≥ 20 ng/ml OR • Gleason Score ≥ 4+3 OR • Tumor stage cT2c or above as determined by digital rectal exploration and/or transrectal ultrasonography • Suspicion of metastases as judged clinically, e.g. bone pain	Staging by imaging not warranted as judged clinically
Staging by imaging is warranted	Allergy towards NaF, PSMA or other contents in the solutions

Appendix 2, patient flow



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