PROTOCOL TITLE '^{68}Ga-PSMA-PET/CT imaging for locally advanced, recurrent and metastatic adenoid cystic carcinoma or salivary duct carcinoma'

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Laboratory sites	Not applicable
Pharmacy	Pharmacy Department / Department of Radiology and Nuclear Medicine Radboudumc Geert Grooteplein 10 6525 GA Nijmegen Licence number: 4095 F

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

11C	Carbon-11
18F	Fluoride-18
68Ga	Gallium-68
177Lu	Lutetium-177
ABR	ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)
ACC	Adenoid cystic carcinoma
ACCRF	Adenoid Cystic Carcinoma Research Foundation
AE	Adverse Event
ALT	Alanine transaminase
AR	Adverse Reaction
AST	Aspartate transaminase
CCMO	Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek
CT	Computed Tomography
CV	Curriculum Vitae
DSMB	Data Safety Monitoring Board
EU	European Union
FDG	Fluorodeoxyglucose
GCP	Good Clinical Practice
IB	Investigator's Brochure
IC	Informed Consent
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
KWF	Koningin Wilhelmina Fonds (Dutch Cancer Society)
MBq	Megabecquerel
METC	Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)
MRI	Magnetic resonance imaging
PD	Progressive disease
PET	Positron emission tomography
PIF	Patient information form
PR	Partial response

PSA	Prostate specific antigen
PSMA	Prostate specific membrane antigen
(S)AE	(Serious) Adverse Event
SD	Stable disease
SDC	Salivary duct carcinoma
SPC	Summary of Product Characteristics (in Dutch: officiële productinfomatie IB1-tekst)
Sponsor	The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.
SPSS	Statistical package for the social sciences
SUSAR	Suspected Unexpected Serious Adverse Reaction
SUV	Standardized uptake value
ULN	Upper limit of normal
Wbp	Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)
WMO	Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen

SUMMARY

Rationale: PSMA is a transmembrane protein, which is expressed on prostate cancers cells, ACC and other malignancies. In prostate cancer, distant metastases can be visualized sensitively and non-invasively with ^{68}Ga-PSMA-PET/CT scans and if the uptake of ^{68}Ga is high enough, patients can be treated with the β-emitting radionuclide ^{177}Lu-PSMA. In the current study, we will evaluate the uptake of ^{68}Ga-PSMA by performing ^{68}Ga-PSMA-PET/CT scans in advanced ACC and SDC patients. If the uptake is high enough, this will form the rationale for a therapeutic study with ^{177}Lu-PSMA in ACC and SDC.

Objective: The primary objective is to evaluate the uptake of ^{68}Ga-PSMA in locally advanced, recurrent and metastatic ACC/SDC by performing ^{68}Ga-PSMA-PET/CT scans. The secondary objectives are to calculate the SUV tumor-to-background ratio and tumor-to-'healthy salivary gland tissue' ratio. To correlate the SUV to the degree of immunohistochemical PSMA expression of the primary tumor on archival tissue, and to establish whether new metastatic lesions are found by ^{68}GA-PSMA-PET/CT imaging.

Study design: Diagnostic study which evaluates the level of PSMA expression in ACC/SDC patients with ^{68}Ga-PSMA-PET/CT imaging in order to establish whether these patients are eligible for ^{177}Lu-PSMA therapy.

Study population: Patients with locally advanced, recurrent or metastatic ACC/SDC of ≥18 years old.

Main study parameters/endpoints: the main study endpoints are the tumor SUV, the SUV tumor-to-background ratio, the SUV tumor-to-'healthy salivary gland tissue' ratio, and the correlation between the SUV and the degree of immunohistochemical PSMA expression of the primary tumor on archival tissue.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Participants will undergo ^{68}Ga-PSMA-PET/CT imaging and a venapuncture. These are standard diagnostic procedures with a known minimal safety risk. The participant will be asked to make 2 study related visits, which will take 3 hours in total. A participant will not benefit from participating in this study. The study does not involve minor or incapacitated subjects.

1. INTRODUCTION AND RATIONALE

PSMA is a transmembrane protein. PSMA expression can be visualized and quantified by immunohistochemical staining of tissue biopsies with anti-PSMA monoclonal antibodies.[1] This has been done for numerous healthy and malignant tissues. PSMA expression appears to be restricted to a few healthy tissues, such as the prostate, duodenum, proximal renal tubules, breast and skeletal muscle.[2] Results on PSMA expression of healthy salivary gland tissue are conflicting.[1-4] In malignant tissue, PSMA expression was found in prostate cancer cells and the neovasculature of many other solid malignancies, including renal cell carcinoma, bladder cancer, colon cancer, neuroendocrine carcinoma, melanoma, pancreatic cancer, non-small cell lung cancer, breast cancer and others.[2] In ACC, a study in 54 patients showed PSMA expression in 85% of patients, and in 70% of patients with recurrent ACC.[5] The level of PSMA expression in SDC is currently under investigation, and the first results show PSMA expression in >80% of patients.

PSMA expression is of increasing importance, as it is a target for cancer diagnostics. After labelling PSMA ligands with ^{68}Ga, PSMA expression can be visualized non-invasively with a ^{68}Ga-PSMA-PET/CT scan. In a study in 248 patients with a history of prostate cancer who presented with a rising PSA level, it was found that ^{68}Ga-PSMA-PET/CT scans visualized substantially more tumor lesions than reported for other imaging modalities, such as CT, ^{18}F-FDG-PET (figure 1), ^{11}C-choline-PET and MRI.[6] This demonstrates that radiolabeled PSMA ligands very effectively target prostate cancer lesions in vivo, allowing specific and sensitive detection of prostate cancer lesions with PET.

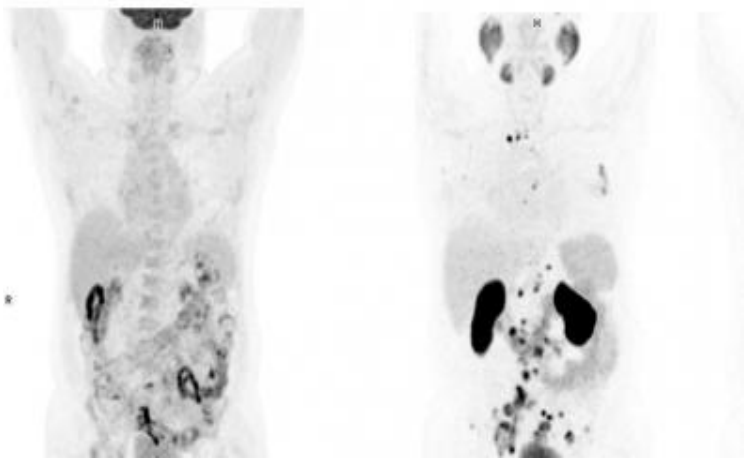

Figure 1. ^{18}F-FDG-PET scan (left) and ^{68}Ga-PSMA-PET scan (right) in a patient with metastatic prostate cancer. The black dots in the abdomen on the right scan represent prostate cancer metastases that could not be visualized by ^{18}F-FDG-PET.

Next to its diagnostic importance, the efficient and specific targeting of PSMA paved the road to exploring the therapeutic potential of PSMA ligands labeled with β-emitting radionuclides, such as ^{177}Lu. We recently showed that ^{177}Lu-PSMA effectively inhibited the growth of PSMA expressing tumors in a mouse model for prostate cancer.[7] The first results of radionuclide therapy studies with ^{177}Lu-PSMA in prostate cancer patients who failed conventional therapeutic options have been published recently.[8-10] The group in Bad Berka in Germany reported the results of the first 56 patients with castration resistant prostate cancer treated with 1-4 cycles of 6,000 MBq ^{177}Lu-PSMA. ^{177}Lu-PSMA showed high, specific and rapid uptake in prostate cancer metastases, with almost complete retention during 1-2 weeks after injection. In these advanced stage patients remarkable therapeutic responses were seen: of 56 patients, 45 (80.4 %) demonstrated a reduction in PSA levels and 31 patients (56%) had a partial response according to EORTC criteria[11] (figure 2).

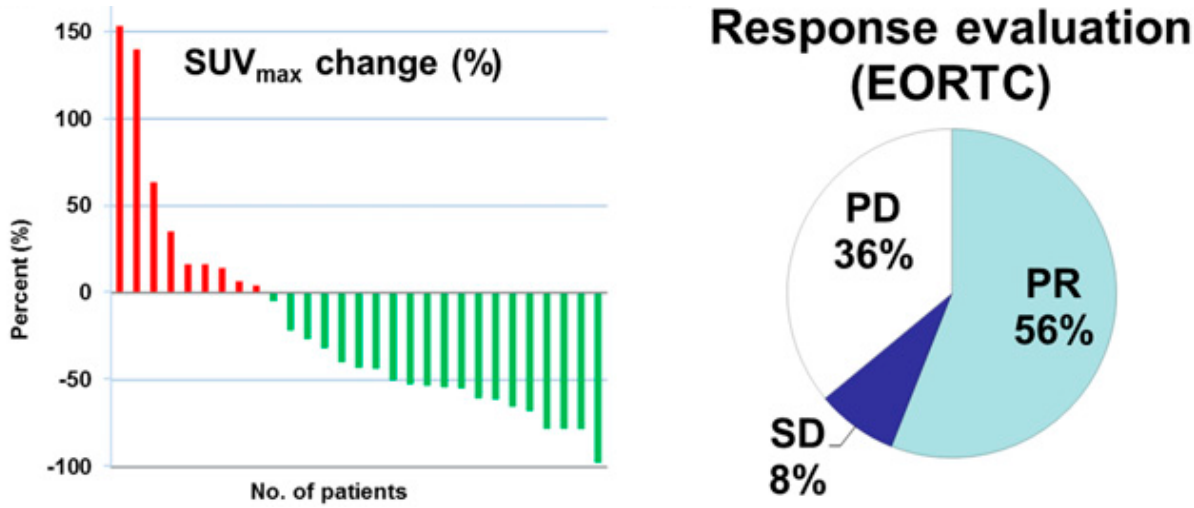

Figure 2. Response in castration resistant prostate cancer patients treated with ^{177}Lu-PSMA.[8]

The group in Munich treated 19 patients with metastatic castration resistant prostate cancer with a total of 40 cycles of 7400 MBq of ^{177}Lu-PSMA (1-4 cycles per patient). Only mild side effects were seen in part of the patients: dry mouth (37%), anemia (32%) and thrombocytopenia (25%). Most importantly, marked PSA responses were seen in most patients (44% of patients showed a reduction of ≥50%). Assessment of bone and soft tissue metastases showed complete remission in 5% of patients (figure 3), stable disease in 63% and progressive disease in 32%.

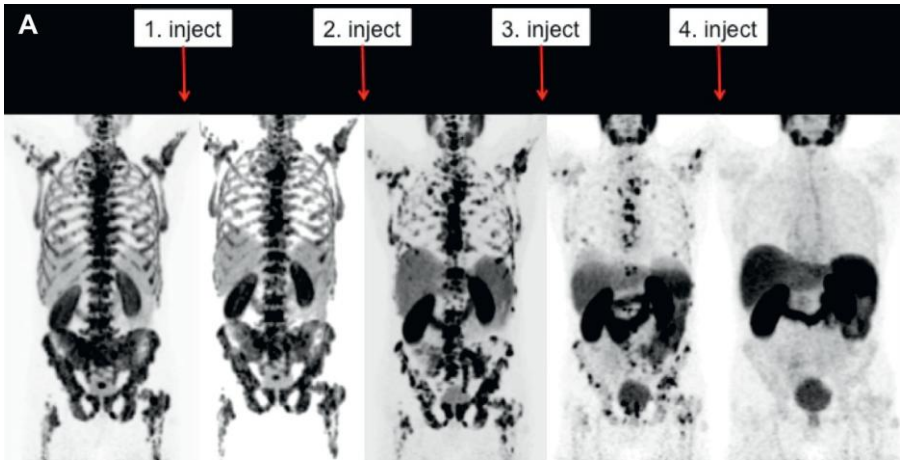

Figure 3. Complete remission in a 71-year-old patient after 4 cycles of ^{177}Lu-PSMA.[9]

In summary, prostate cancer lesions can be targeted efficiently with radiolabeled PSMA ligands. Labeled with ^{68}Ga, PSMA ligands can be used to sensitively detect these tumors noninvasively with PET. Labeled with β-emitting radionuclides such as ^{177}Lu, PSMA ligands are a new class of powerful therapeutics for targeted radionuclide therapy.

In the current study, we will evaluate the uptake of ^{68}Ga-PSMA by performing ^{68}Ga-PSMA-PET/CT scans in locally advanced, recurrent and metastatic ACC/SDC patients. Tumor uptake will be measured quantitatively. The tumor-to-background ratio and tumor-to-'healthy salivary gland tissue' ratio will be calculated. Tumor uptake will also be correlated to the degree of immunohistochemical PSMA expression of the primary tumor on archival tissue.

This study is of relevance for patients with locally advanced, recurrent or metastatic ACC/SDC because treatment options are very limited and ^{177}Lu-PSMA could be a promising new treatment option. In prostate cancer, ^{177}Lu-PSMA therapy has proven its value as stated above. In ACC/SDC this therapy may also be effective because PSMA expression in ACC/SDC is observed immunohistochemically and in a case report on ^{68}Ga-PSMA-PET/CT imaging in ACC.[12] In order to establish whether ACC/SDC patients are eligible for ^{177}Lu-PSMA therapy, the level of PSMA expression has to be established with ^{68}Ga-PSMA-PET/CT scans. This is the goal of this study. If this study indeed shows sufficient PSMA expression, a therapeutic study with ^{177}Lu-PSMA will be started in next future.

2. OBJECTIVES

Primary Objective: To evaluate the uptake of ^{68}Ga-PSMA in locally advanced, recurrent and metastatic ACC/SDC by performing ^{68}Ga-PSMA-PET/CT scans.

Secondary Objective(s):

- To calculate the SUV tumor-to-background ratio and tumor-to-'healthy salivary gland tissue' ratio.
- Correlate the tumor uptake (SUV) to the degree of immunohistochemical PSMA expression of the primary tumor on archival tissue.
- To establish whether new metastatic lesions are found by ^{68}GA-PSMA-PET/CT imaging

3. STUDY DESIGN

Design: diagnostic study which evaluates the level of PSMA expression in ACC/SDC patients with ^{68}Ga-PSMA-PET/CT imaging in order to establish whether these patients are eligible for ^{177}Lu-PSMA therapy.c

Duration: each patients has to make 2 additional visits (apart from normal patient care) when he or she participates in this study. These 2 visits will take approximately 3 hours in total.

Setting: single center study (Radboud university medical center, Nijmegen, the Netherlands)

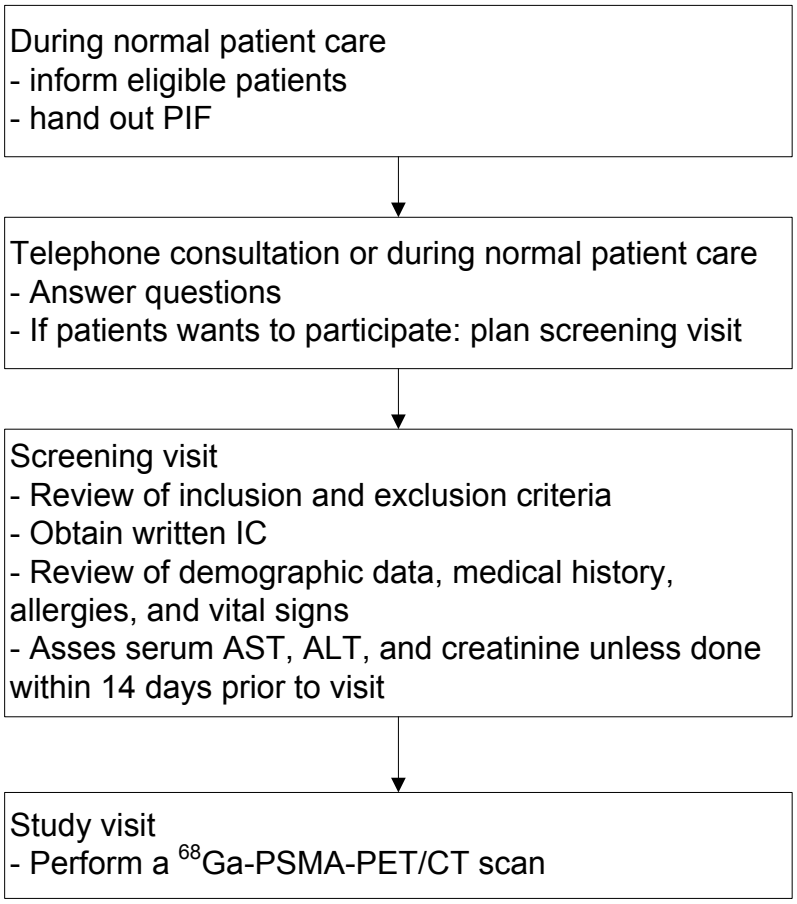

Figure 4. Flow chart of study procedures.

4. STUDY POPULATION

4.1 Population (base)

Study population: Patients with locally advanced, recurrent or metastatic ACC/SDC.

Source population:

- Patients with locally advanced, recurrent or metastatic ACC/SDC who are treated at the Department of Medical Oncology of the Radboudumc.
- Patients with locally advanced, recurrent or metastatic ACC/SDC who heard or read about this study and contact the investigators to ask whether they can take part in the study. Potential participants will not be actively recruited. However, there will be a message on the website of Dutch Salivary Gland Cancer Patient Platform: http://speekselklierkanker.org/. This message is added to this submission (see 'E3 Wervingsmateriaal').

As the Radboudumc is the largest clinic and research center for locally advanced, recurrent and metastatic ACC/SDC in the Netherlands, we do not expect problems to recruit 15 ACC and 10 SDC patients.

Feasibility analysis

The Radboud University Medical Center is a tertiary referral center for head and neck cancer and salivary gland cancer in particular, receiving referrals from the other academic medical centers in the Netherlands. In 2016 40 new advanced SGC patients were seen at our outpatient department. In addition, patients who have been under control for longer at our OPD may be included directly from the start of the study. Therefore we believe it is feasible to enroll 15 ACC patients en 10 SDC patients within the relatively short time period of 12 months.

4.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- locally advanced, recurrent or metastatic ACC/SDC
- Age ≥ 18 years old
- Ability to provide written informed consent

4.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Contra-indication for PET imaging
    - Pregnancy
    - Breast feeding
    - Severe claustrophobia
- Impaired renal function: MDRD <30 ml/min/1,73 m^2
- Impaired liver function: AST and ALT ≥ 2.5 x ULN (≥5 x ULN for patients with liver metastases)

4.4 Sample size calculation

The main purpose of this study is to establish the feasibility and value of ^{68}Ga-PSMA-PET/CT scans as a non-invasive method to assess PSMA expression in ACC/SDC patients. An exact sample size calculation is not applicable, because baseline information concerning the uptake of ^{68}Ga-PSMA in ACC/SDC patients is not available. Therefore we will establish ^{68}Ga-PSMA-PET/CT scanning in 15 ACC and 10 SDC patients. If the technique does not prove its value in these patients, we will conclude that it is not a valuable imaging technique for ACC/SDC patients.

5. TREATMENT OF SUBJECTS

Not applicable (no intervention study)

6. INVESTIGATIONAL PRODUCT

6.1 Name and description of investigational product(s)

PSMA-HBED –CC consists of a PSMA binding sequence glutamate-urea-lysine coupled to the chelator HBED-CC which allows labelling with Ga-68. More information about the investigational product can be found in the IB (chapter 4: Physical, Chemical and Pharmaceutical Properties and Formulation, page 8) and the IMPD (chapter 2.1.S: drug substance, page 6)

6.2 Summary of findings from non-clinical studies

See the IB, chapter 5: nonclinical studies, page 11

6.3 Summary of findings from clinical studies

See the IB, chapter 6: clinical studies, page 13

6.4 Summary of known and potential risks and benefits

See the IB, chapter 6.2: safety and efficacy, page 15

6.5 Description and justification of route of administration and dosage

The final formulation of the product is 68Ga- PSMA-HBED-CC in ethanol 7% in PBS (14 ml), 2MBq / kg / body weight 68Ga, 10 µg PSMA-HBED-CC, which is administered intravenously in a single injection. This is in line with previous studies on the investigational product for prostate cancers patients.

6.6 Dosages, dosage modifications and method of administration

Dosage and method of administration are mentioned above. Dosage modifications are not applicable as participants get only one dose.

6.7 Preparation and labelling of Investigational Medicinal Product

Information about the preparation of the investigational product can be found in the IMPD (chapter 2.1.S.2: Manufacture, page 8). Information about labelling can also be found in the IMPD (chapter 2.1.P.7: ContainerClosureSystem, page 28).

6.8 Drug accountability

The investigational product will be produced on site (Department of Radiology and Nuclear Medicine, Radboudumc).The investigational product is dispensed in a closed 20ml sterile glass type 1 vial with a sterile bromobutyl stopper (sealed with an aluminium cap), and labeled as depicted on page 28 of the IMPD. These labels of the bulk vial are only to be used for internal use in the cleanroom in which the product is dispensed and in which aseptic compounding is performed (“Hotlab”). Labeling of the patient dose in the syringe complies to annex 13 and is also shown on the same page. After aseptic compounding of the patient dose, the remaining solution is stored as retention sample.

7. NON-INVESTIGATIONAL PRODUCT

Not applicable

8. METHODS

8.1 Study parameters/endpoints

8.1.1 Main study parameter/endpoint

The SUV of ^{68}Ga-PSMA estimated with ^{68}GA-PSMA-PET scanning. If the SUV of tumor tissue is higher than the SUV of healthy salivary gland tissue and/or comparable to the SUV in prostate cancer, the level of PSMA expression is deemed high enough to pursue a therapeutic study with ^{177}Lu-PSMA.

8.1.2 Secondary study parameters/endpoints

- the SUV tumor-to-background ratio
- the SUV tumor-to-'healthy salivary gland tissue' ratio.
- The correlation between the SUV and the degree of immunohistochemical PSMA expression of the primary tumor on archival tissue.
- The establishment of new metastatic lesions.

8.1.3 Other study parameters

- Birth date
- Gender
- General medical history
- Medication use
- Allergies
- ACC/SDC history: diagnosis date, location primary tumor, TNM stage at diagnosis, ex-PA?, AR-status, HER2-status, type of surgery, date of surgery, postoperative radiotherapy, date of radiotherapy, adjuvant systemic therapy, location of recurrence, date of recurrence, palliative treatments
- Laboratory tests: MDRD, AST, ALT
- Pathology: immunohistochemical PSMA expression on archival tissue

8.2 Randomisation, blinding and treatment allocation

Not applicable

8.3 Study procedures

- Interview to collect background data

  - During the screening visit the participants will be asked questions to obtain background data, such as birth data, past medical history, current medication use and allergies.
- Review of electronic patient file
  - Participants will be asked their consent for review of their patient file in order to obtain specific background data, such as type of surgery performed and date of surgery.
- Laboratory tests
  - If not performed within the last 14 days, AST, ALT and creatinine levels will be tested. All test will be done by the Clinical Chemical Laboratory of the Radboudumc. For this, blood will be taken with a 3 ml lithium-heparin tube (light-green cap). The remaining blood will be destroyed after the laboratory tests were performed.
- ^{68}Ga-PSMA-PET/CT imaging
  - The patients will be injected with ^{68}Ga-PSMA with a dose of 2MBq/kg body weight and PET/CT scanning (from groin to skull top, 3 minutes per bed position, 4-5 bed positions) will be performed 45-60 minutes post injection.
- Pathology: PSMA staining
  - On archival tissue, PSMA expression will be evaluated immunohistochemically in order to correlate immunhistochemical PSMA expression to the SUV.

8.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

8.5 Replacement of individual subjects after withdrawal

If a subject decides to withdraw, another patient will be recruited until 15 ACC and 10 SDC patients have completed the study protocol.

8.6 Follow-up of subjects withdrawn from treatment

Subjects who decide to withdraw, will not get study related follow-up.

8.7 Premature termination of the study

As ^{68}Ga-PSMA-PET/CT imaging is a imaging modality often used in prostate cancer, we do not except unforeseen side effect of this imaging modality. If unexpected side effect do appear in this patient group, termination of the study will be considered, depending on the seriousness and frequency.

9. SAFETY REPORTING

9.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

9.2 AEs, SAEs and SUSARs

9.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the trial procedure. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

9.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission will not be considered as a serious adverse event.

The investigator will report all SAEs to the sponsor without undue delay after obtaining knowledge of the events. .

The sponsor will report the SAEs through the web portal ToetsingOnline to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8

days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

9.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Adverse reactions are all untoward and unintended responses to an investigational product related to any dose administered.

Unexpected adverse reactions are SUSARs if the following three conditions are met:

1. the event must be serious (see chapter 9.2.2);
2. there must be a certain degree of probability that the event is a harmful and an undesirable reaction to the medicinal product under investigation, regardless of the administered dose;
3. the adverse reaction must be unexpected, that is to say, the nature and severity of the adverse reaction are not in agreement with the product information as recorded in the Investigator's Brochure.

The sponsor will report expedited the following SUSARs through the web portal ToetsingOnline to the METC:

- SUSARs that have arisen in the clinical trial that was assessed by the METC;
- SUSARs that have arisen in other clinical trials of the same sponsor and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the clinical trial that was assessed by the METC.

The remaining SUSARs are recorded in an overview list (line-listing) that will be submitted once every half year to the METC. This line-listing provides an overview of all SUSARs from the study medicine, accompanied by a brief report highlighting the main points of concern.
The expedited reporting of SUSARs through the web portal Eudravigilance or ToetsingOnline is sufficient as notification to the competent authority.

The sponsor will report expedited all SUSARs to the competent authorities in other Member States, according to the requirements of the Member States.

The expedited reporting will occur not later than 15 days after the sponsor has first knowledge of the adverse reactions. For fatal or life threatening cases the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report.

9.3 Annual safety report

In addition to the expedited reporting of SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to the accredited METC, competent authority, and competent authorities of the concerned Member States.

This safety report consists of:

- a list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions, ordered by organ system, per study;
- a report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

9.4 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. SAEs need to be reported till end of study within the Netherlands, as defined in the protocol

9.5 Data Safety Monitoring Board (DSMB)

A DSMB is deemed unnecessary because patients are exposed to a known diagnostic procedure with a low risk profile.

10. STATISTICAL ANALYSIS

10.1 Primary study parameter(s)

SUV will be calculated according to the following formula:
(measured activity concentration [MBq/mL] * body weight [g]) / injected activity [MBq]

The PET/CT images will be reconstructed in three dimensions. The PET and CT images will be fused and the SUVs will be aligned with CT to assess ^{68}Ga-PSMA uptake in tumor lesions, healthy salivary gland tissue, and the background.

10.2 Secondary study parameter(s)

Tumor-to-background ratios and tumor-to-'healthy salivary gland tissue' ratios will be calculated using the SUV. It will be presented as mean and standard deviations.

Immunohistochemical PSMA expression on a tissue sample of the primary tumor will be quantified using a four point scale for tumor PSMA expression (0 = no expression, 1 = weak expression, 2 = moderate expression, and 3 = strong expression) and the number of PSMA-positive blood vessels per mm^2 will be counted.

The correlation between the immunohistochemical PSMA expression and tumor SUV will be evaluated using linear regression analysis. A p-value of <0.05 will be considered significant. Analyses will be performed using SPSS version 22.0.

10.3 Other study parameters

Background variable will be described using simple desricptive statistics and will be presented in a table. Missing data will be mentioned in the final manuscript.

10.4 Interim analysis

Not applicable

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (version 8, 19 October 2013), in accordance with the Medical Research Involving Human Subjects Act (WMO), the personal data protection act (Wet Bescherming Persoonsgegevens), and the Medical Treatment Agreement Act (WGBO).

11.2 Recruitment and consent

Patients will be informed about the study by their treating physician during normal patient care. Detailed information about the study can be offered by the investigators during normal patient care or by phone call. If a patient decides to participate, a screening visit will be planned, which starts with signing the IC. At least 24 hours will be taken into account between informing patients about the study and signing the IC.

11.3 Objection by minors or incapacitated subjects

Not applicable

11.4 Benefits and risks assessment, group relatedness

Risk assessment: as ^{68}Ga-PSMA-PET/CT imaging is a known diagnostic procedure used for prostate cancer in normal patient care, the risks of this procedure are well known and minimal. Next to this, 30 ml blood will be drawn from the participants by a venapuncture. This risks of this procedure are also well known and minimal.
Benefit assessment: participants will not benefit directly from this study as it is a non-therapeutic trial. If the study is successful, participants may participate in a therapeutic study with ^{177}Lu-PSMA which may be beneficial.
Group relatedness: the study does not involve minors and/or incapacitated subjects

11.5 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO.

The sponsor also has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

11.6 Incentives

Travel expenses and parking costs will be paid.

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

Participants will get a unique research code to anonimize data. The identification code list will be secured with a password. The source data will be noted on a eCRF. The eCRF data will be noted in a secured database (Castor). Once the study is finished, the database will be locked. Data will be stored for 15 years after the end of the study. Handling of data is in accordance to the Dutch Personal Data Protection Act (WBP).

12.2 Monitoring and Quality Assurance

A DSMB is deemed unnecessary because patients are exposed to a known diagnostic procedure with a low risk profile. Data will be monitored for accuracy by the investigators. For this, univariate checks (empty fields, outlayers), multivariate checks (logical order of dates) and visual checks will be used.

12.3 Amendments

A 'substantial amendment' is defined as an amendment to the terms of the METC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the METC and to the competent authority.

Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

12.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

12.5 Temporary halt and (prematurely) end of study report

The sponsor will notify the accredited METC and the competent authority of the end of the study within a period of 90 days. The end of the study is defined as the last patient's last visit.

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC and the competent authority within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC and the Competent Authority.

12.6 Public disclosure and publication policy

We aim to submit the study results in a major peer-reviewed oncology journal, i.e., Annals of Oncology, Journal of Clinical Oncology within 6 months after the final study procedure.

13. STRUCTURED RISK ANALYSIS

13.1 Potential issues of concern

a. Level of knowledge about mechanism of action

68Ga-PSMA-PET imaging is a specific and sensitive method to target prostate cancer lesions in vivo.[6] In this study we will investigate its value in patients with salivary gland cancer, i.e. adenoid cystic carcinoma and salivary duct carcinoma. There are several reasons why this could be a valuable imaging modality for these patients. First of all, immunohistochemical PSMA-staining show that most ACC and SDC tumor are PSMA-positive. Second, 68Ga-PSMA-PET scans in prostate cancer patients show uptake of 68Ga-PSMA in the salivary glands. Third, a case report has proved the principle of 68Ga-PSMA-PET imaging in a patient with ACC.[12]

b. Previous exposure of human beings with the test product(s) and/or products with a similar biological mechanism

68Ga-PSMA-PET imaging is an imaging modality which is increasingly being used in recurrent prostate cancer patients.[13] Because of the wide experience with this imaging modality in prostate cancer patients, the safety is well known, and serious adverse events have never occurred (see also chapter 6.2 in the IB).

c. Can the primary or secondary mechanism be induced in animals and/or in ex-vivo human cell material?

In preclinical studies, excellent PSMA-specific tumor imaging in vivo with high tumor uptake (3.29 ± 0.77% ID/g) as well as high tumor-to-blood (22:1) and tumor-to-muscle (122:1 at 120 min p.i.) ratios at 120 min p.i. has been described for the PSMA+ tumors. Next to this, high specific uptake in PSMA+ murine tissues (among others the salivary glands) is observed. More information can be found in the IB (chapter 5: nonclinical studies, page 11).

d. Selectivity of the mechanism to target tissue in animals and/or human beings

PSMA specific imaging is found in animals (see answer to previous question) as well as in prostate cancer patients (IB, chapter 6: clinical studies, page 13).

e. Analysis of potential effect

The safety window is wide, as no serious adverse events have been reported in the literature. See the IB (chapter 6.2 and 7, page 15) for more information.

f. Pharmacokinetic considerations

See the IB, chapter 6.1: Pharmacokinetics and Product Metabolism in Humans, page 13)

g. Study population

Patients with locally advanced, recurrent or metastatic ACC or SDC.

h. Interaction with other products

Not applicable

i. Predictability of effect

In ACC and SDC, the investigational product has not been evaluated before and is therefore not yet predictable. In this study we will correlate the SUV of the primary tumor with the level of immunohistochemical PSMA staining on archival tissue to establish whether the efficacy of PSMA-PET imaging can be predicted with immunohistochemistry.

j. Can effects be managed?

No side effects which require to be managed have been reported in the literature. However, if a participants develops unexpected side-effects, the study center (Radboudumc) can deliver adequate medical support of emergencies.

13.2 Synthesis

In conclusion, 68Ga-PSMA-PET/CT imaging is a imaging modality which is well known and often used in patients with recurrent prostate cancer. In these patients, no serious side effect have been reported. There is no reason to expect otherwise in our study population of patients with incurable ACC or SDC. In case unexpected side-effect do occur, the facilities to deliver emergency medical support are available at the study center. Therefore, we conclude that the risk of injury is small and if an injury occurs, it will be minor, which means the risk classification is negligible according to the NFU-risk classification.

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