**FULL STUDY TITLE**

Salvage 177Lu PSMA for PSA Biochemical Failure After Radical Prostatectomy for High-Risk Prostate Cancer

**SHORT STUDY TITLE**

SLAP

**CONFIDENTIAL**

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# STATEMENT OF COMPLIANCE

This document is a protocol for a clinical research study. The study will be conducted in compliance with all stipulations of this protocol, the conditions of ethics committee approval, the NHMRC National Statement on Ethical Conduct in Human Research (2007, update 2018) and the Note for Guidance on Good Clinical Practice (CPMP/ICH-135/95) as adopted in Australia.

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PROTOCOL SYNOPSIS

|  |  |
| --- | --- |
| Title | **Salvage 177Lu PSMA for PSA Biochemical Failure After Radical Prostatectomy for High-Risk Prostate Cancer** |
| Short Title | **SLAP** |
| Objectives | Primary: To determine the PSA response following a single cycle of 177Lu-PSMA therapy following PSA biochemical failure after radical prostatectomy for high-risk prostate cancer  Secondary: To report on morbidity associated with a single cycle of 177Lu-PSMA therapy following PSA biochemical failure after radical prostatectomy for high-risk prostate cancer |
| Study Design | Pilot case series, single-center, prospective |
| Planned Sample Size | Up to 10 male participants |
| Selection Criteria | Men ≥ 50yo who have undergone radical prostatectomy for NCCN defined high risk prostate cancer who have a PSA level greater than or equal to 0.20ng/mL. Final pathology will have negative surgical margins. No detectable local, nodal or metastases observed on 18F-DCFPyL PSMA PET/CT and mpMRI at study entry. |
| Study Procedures | Single cycle of 177Lu PSMA therapy. PSA monitored 3 monthly. |
| Statistical Procedures  Sample Size Calculation:  Analysis Plan: | Exploratory study of up to 10 subjects |
| Duration of the study | 12 months |

# GLOSSARY OF ABBREVIATIONS

|  |  |
| --- | --- |
| **ABBREVIATION** | **TERM** |
|  |  |
|  |  |
|  |  |

# 

# STUDY MANAGEMENT

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# INTRODUCTION AND BACKGROUND

* 1. **Background Information**

Prostate cancer (PCa) is the second most common cause of male related cancer death in Australia.  More men succumb to prostate cancer than the numbers of women who succumb to breast cancer (1). It is well understood that many men diagnosed with prostate cancer will die of unrelated causes and for this reason many cases will be clinically insignificant.  Changes in clinical practice have seen increasing uptake of conservative management approaches for low grade and low volume prostate cancer in the form of Active Surveillance (AS).  At the same time, changes in clinical practice have seen an increasingly aggressive approach to higher grade cancers that were previously treated conservatively. Data shows that the higher-grade cancers benefit most from definitive intervention (2). Approximately 50% of men with high-risk prostate cancer will develop prostate-specific antigen (PSA) biochemical recurrence (BCR) by 5-years (3). Usually, the disease is ‘microscopic’ (ie. undetectable on conventional or novel imaging). Most men who undergo radical prostatectomy for high-risk disease have good performance status, many will survive long enough to experience morbidity or mortality from progressive disease. 

* 1. **Research Question**

How does a single cycle of PSMA-targeted 177Lu affect PSA in undetectable biochemical failure? What are its associated morbidities? Will it defer or avoid the need for androgen deprivation therapy?

* 1. **Rationale for Current Study**

Radical prostatectomy is an effective treatment for local disease control in men with high-risk prostate cancer (2). A proportion of these men will develop PSA biochemical failure (defined as serum PSA ≥0.2ng/mL) despite negative surgical margins on histopathology and an undetectable post-operative PSA (3). Biochemical failure (BCF) is associated with clinically significant risk of disease progression and regarded as an indication of prostate cancer persistence or recurrence. Representing either detectable or undetectable local, nodal, or metastatic disease. The Timing of Androgen Deprivation (TOAD) study demonstrated that early commencement of androgen deprivation therapy (ADT) at PSA BCF is beneficial with improved long-term survival compared to a delayed commencement (4). A minority of men will benefit from salvage radiotherapy to the prostate bed with or without additional radiotherapy to the pelvis. However, the majority will experience systemic relapse and ultimately require androgen deprivation therapy.  ADT is not curative and associated with significant adverse effects. Grade 3-5 toxicities are potentiated when ADT is used concurrently in a multimodal approach (5). According to the CHAARTED trial, the range of grade 3/4 adverse events among patients who received the docetaxel-containing regimen was from 0.3% in thrombocytopenia to 12.1% in neutropenia (6). The STAMPEDE trial showed that grade 3–5 adverse events were reported among 32% of patients who received standard of care therapy, 32% of those who received standard of care therapy plus zoledronic acid, and 52% among those who received standard of care therapy plus docetaxel (7). Accordingly, there is a need to explore alternative treatment that might provide opportunity for cure as well as avoiding or deferring the requirement to commence ADT and its associated adverse effects.

Theranostic PSMA-labelled Lutetium177 is an emerging treatment option that has demonstrated profound clinical benefit in men with high-volume castrate resistant metastatic prostate cancer (mCRPC) (8). Its role is currently being evaluated in hormone sensitive metastatic disease and as neoadjuvant therapy prior to radical prostatectomy. In a recent systematic review and meta-analysis of 24 studies (n= 1192) assessing 177Lu-PSMA efficacy and toxicities, the aggregate data showed that approximately 46% of CRPC patients being treated with one or more cycles have PSA reductions of ≥ 50% indicating that these agents are objectively effective for this patient population (8). Standard treatment protocols for advanced disease comprises of intravenous administration of 177Lu-PSMA every 6 weeks for up to 6-cycles. High-grade toxicity remains low but can be observed with as little as 2-3 cycles. The total pooled estimated proportion of grade 3 or 4 adverse events was <10% (8).

Considering its successful application in advanced stages of prostate cancer and low rate of toxicity, we believe there is potential for its use in men with undetectable BCF. This state represents a particularly low cancer burden, so the theoretical basis for a single dose of 177Lu with curative intent would satisfy an exploratory study. Permitting a reasonable balance between efficacy, toxicity, and cost. The SLAP study aims to evaluate the effect of a single cycle of 177Lutetium-PSMA-targeted on PSA in undetectable BCF with the hope that this novel treatment will defer or avoid the need for ADT.

* 1. **Rationale for clinical protocol publication prior to completion of case series**

We request permission to publish this clinical protocol in the British Journal of Urology International (BJUI) prior to recruitment, follow-up and completion of this pilot case series in order to spearhead a new standard of care ahead of competitors. 177Lutetium-PSMA will be applied as an off-label used under a TGA authorized prescriber scheme (approval number pending). This treatment is currently utilized as an off label in the LUTECTOMY study conducted by Prof Declan G. Murphy at Peter MacCallum Cancer Centre, Melbourne, VIC, Australia.

# STUDY OBJECTIVES

* 1. **Primary Objective**
* To determine the proportion of participants in whom PSA levels become undetectable (at 3 months)
  1. **Secondary Objectives**
* To determine the proportion of subjects in whom PSA levels fall below pre-treatment levels.
* To report on adverse events following a single cycle of 177Lu-PSMA therapy
* To determine if androgen deprivation therapy was avoided or delayed
* Health Related Quality of Life using the Extended Prostate Cancer Index Survey (EPIC-26)

# STUDY DESIGN

* 1. **Type of Study**

Pilot case series

* 1. **Describe the Study Design**

Pilot case series, single-center, prospective

* Not randomized or blinded,
  1. **Standard of Care procedures**

Standard of care for PSA biochemical failure is to consider commencing androgen deprivation therapy with or without radiation to the pelvis. Patients with biochemical failure are re-staged with a PSMA PET/CT and discussed at an MDT to obtain consensus on suitable future treatment.

Detection of local recurrence with standard of care PSMA PET/CT is occasionally limited due to the urinary excretion of the radioligand. To mitigate this limitation and ensure our study remains robust, participants will undergo an additional re- mpMRI of the prostate bed to exclude local recurrence.

* 1. **Number of Participants at each study site**

Study site: Sydney Adventist Hospital

Sample size: n = 10

* 1. **Expected Duration of Study**

Ethics and governance approval by September 2022. Participant enrolment, imaging, interventions thereafter.

Study duration: 12months - December 2022 – September 2023

* 1. **Primary and Secondary Outcome Measures**

**Primary outcome**

* To determine the proportion of participants in whom PSA levels become undetectable (at 3months)

**Secondary outcomes**

* To determine the proportion of subjects in whom PSA levels fall below pre-treatment levels.
* To report on adverse events following a single cycle of 177Lu-PSMA therapy
* Time to commencing androgen deprivation
* Time to radiologic progression

# STUDY TREATMENTS

* 1. **Treatment Arms**
     1. **Description**

177Lu-PSMA-I&T is supplied as a clear, sterile and pyrogen free solution for intravenous injection.

* + 1. **Dosage and Route of Administration**

7.5GBq of 177Lu-PSMA-I&T (+/- 5%) is dispensed using aseptic technique by a qualified nuclear medicine technologist under the supervision of a nuclear medicine physician into a 10ml syringe. Total radioactivity is measured in an appropriately calibrated and serviced dose calibrator prior to injection. The 177Lu-PSMA-I&T is administered via an intravenous cannula.

* + 1. **Dose modification**

This will depend on weight and renal function

* 1. **Preparation and administration of study drug**

Patient-specific doses of 177Lu-PSMA-I&T are supplied to the department as a ready to inject radiopharmaceutical prepared from a centralised radiopharmacy. The 177Lu-PSMA-I&T supplied will contain, at a minimum, the quantity of radioactivity requested for the individual patients’ treatment. As is routine with all radiopharmaceuticals, due to the nature of radioactive decay it will be necessary for the department to dispense the exact dose of 177Lu-PSMA-I&T from the supplied product in the hot-laboratory within the nuclear medicine department.  The product has undergone quality testing prior to release and is accompanied by a quality release form from the centralised radiopharmacy (*Radiopharmaceutical Release Form)*.

The dose is supplied to San Radiology and Nuclear Medicine in an appropriately labelled and shielded container as per radiation safety regulations for the transport and delivery of radioactive materials.

The 177Lu-PSMA-I&T is administered via an intravenous cannula that was recently inserted and confirmed to be patent, over a 10-minute period through an infusion pump behind Perspex and lead glass shields. At the conclusion of the infusion the lines are flushed with 10 ml of normal saline. A further 1L of normal saline is administered over 60 minutes through the cannula.

Upon completion of the administration of 177Lu-PSMA-I&T including flushing of lines, the residual radioactivity is measured and documented in the patients notes and a total amount of radioactivity administered is calculated and recorded.

* 1. **Dispensing and Product Accountability**

The 177Lu-PSMA-I&T radiopharmaceutical is supplied as a single-use individual dose. The supplied 177Lu-PSMA-I&T is received in the hot-laboratory as per radiation safety regulations. It is recorded in an electronic hot-laboratory management system including details of the supplier and is stored in a lead lined cupboard as per radiation safety guidelines until the dose is ready to be dispensed.

In the hot-laboratory, the patient dose is aseptically withdrawn from the 177Lu-PSMA-I&T vial into a 10mL syringe and diluted with normal saline by a qualified nuclear medicine technologist. The dispensed dose is measured in an appropriately calibrated and serviced dose calibrator to ensure the correct amount of radioactivity is dispensed for the patient. The dispensed dose is verified by another nuclear medicine technologist and a nuclear medicine physician. The syringe containing the prescribed dose is labelled with identifying features including Patient Name; Patient Hospital Identification Number; Patient Date of Birth; Examination/Treatment; Radiopharmaceutical Name; Prescribed Radioactivity (in MBq); Quantity of Radioactivity dispensed (in MBq); Date and Time of radioactivity measurement; and staff dispensing initials. These details are also recorded in an electronic hot-laboratory management system.

The patient dose of 177Lu-PSMA-I&T is diluted to a maximum volume of 10ml with normal saline and then placed into the infusion pump behind Perspex and lead glass shields.

The patient dose will not be administered to a patient if the quality release form (*Radiopharmaceutical Release Form)* for 177Lu-PSMA-I&T accompanying the radiopharmaceutical does not indicate the product is acceptable for use.Radiochemical purity is determined by several tests conducted at the centralised radiopharmacy as detailed below.

|  |  |
| --- | --- |
| **Test** | **Limit Value/s** |
| HPLC | Not less than 90% |
| ITLC | Not less than 98% |
| pH | 4-8 |
| Visual Inspection | Particle free, clear, colourless to slightly yellow solution |

* 1. **Measurement of participant compliance**

Not applicable. Only a single dose of 177Lu-PSMA is administered and no compliance beyond this is required. Follow-up will be arranged with the principal investigator

* 1. **Excluded medications and treatments**

- Nil known contraindicated medications

* 1. **Pre and Post 177Lu-PSMA therapy** 
     1. **On the day of treatment**
* Oral pre-hydration ~2-3 glasses of water before arriving to hospital.
* On arrival to Radiology Reception 1, Tulloch Building Level 3. The participant will be greeted by the front desk staff who will enter your personal and Medicare details into the computer software.
* The participant will then proceed to treatment room. The doctor will explain the procedure again and answer any questions they may still have and they will be asked to sign a standard Sydney Adventist Hospital treatment consent for the administration of 177Lu-PSMA.
* The participants vital signs will be monitored
* An intravenous cannula (small plastic tube) will be inserted into your vein at the elbow crease to administer the 177Lu-PSMA.
* The 177Lu-PSMA will be administered via a special pump over 10-15 minutes by the doctor
  + 1. **After treatment**
* Following the 177Lu-PSMA injection the patient will be given some more intravenous fluids through the cannula
* The participants wellbeing, and vitals will be assessed again
* The participants will be encouraged to sit on the toilet to empty bladder regularly while in the department
* Radiation levels will be monitored, and you will be allowed to leave the facility when radiation levels are considered safe as per local radiation protection regulation and this is usually after 2-4 hours
* Upon leaving a small amount of radiation will persist and precautions will need to be taken to minimise radiation exposure to others and these will be in provided in writing in our Radiation Safety Instructions information sheet (appendix 1).
* The following morning images will be taken on the nuclear medicine SPECT-CT scanner to check the distribution of the dose in Nuclear Medicine, Suite 306, San Clinic

# PARTICIPANT ENROLLMENT AND RANDOMISATION

* 1. **Recruitment**

All men considered appropriate for this study will already be undergoing routine follow up with their urologist following robotic assisted radical prostatectomy for NCCN high or very high-risk prostate cancer (table 3). This study will be discussed with men undergoing PSA biochemical failure (defined as PSA ≥0.2ng/ml) satisfying all inclusion criteria and none of the exclusion criteria.

The eligible participant will be provided with a patient information and consent form to complete. Each case will be discussed at the Prostate Cancer Multidisciplinary Team Meeting at Sydney Adventist Hospital for confirmation of suitability for study participation. If, study participation will be finalized, and the participant will be provided an enrolment number and subsequently undergo a repeat mpMRI and 18F-DCFPyL PSMA PET/CT to exclude detectable local, nodal, or distal recurrence prior to receiving 177Lu-PSMA theranostic therapy.

* 1. **Eligibility Criteria**
     1. **Inclusion Criteria**

|  |
| --- |
| Inclusion |
| Men who have undergone a radical prostatectomy for NCCN high or very high-risk prostate cancer. |
| Negative surgical margins on radical prostatectomy histopathology |
| PSA initially undetectable following radical prostatectomy. |
| PSA biochemical failure – defined as greater than or equal to 0.20ng/mL |
| PSMA expressing prostate cancer on pre-operative 18F-DCFPyL PSMA PET/CT |
| 18F-DCFPyL PSMA PET/CT demonstrating no evidence of uptake to suggest detectable residual or metastatic disease |
| No local recurrence on post-operative mpMRI |
| No artifact disrupting interpretation of initial prostate cancer imaging |
| Significant PSMA expressing tumour on initial staging |
| Ability to give written informed consent, participate in and comply with study |

* + 1. **Exclusion Criteria**

|  |
| --- |
| Exclusion |
| Positive surgical margin on radical prostatectomy specimen pathology |
| Undetectable serum testosterone |
| Non-PSMA expressing prostate cancer (e.g. ductal or neuroendocrine) |
| Artifact disrupting interpretation of initial prostate cancer imaging (e.g. THR) |
| Presence of suspected metastatic disease on pre-operative and post-operative 18F-DCFPyL PSMA PET/CT scan or mpMRI |
| Contraindication to Gadolinium |
| Contraindication to 177Lu-PSMA therapy |

* 1. **Informed Consent Process**

Eligible patients who have expressed interest in participating in this study will be provided a patient information sheet along with a consent form. The clinician will thoroughly explain the rationale, novelty, risks to the patients wishing to enroll. The investigators will inform the patient that the use of 177Lu-PSMA in this study is off label

The participants will be provided with an opportunity to ask questions and the contact details of for the corresponding investigator to ask questions at any point. The participants will be educated on their rights and explicitly told they can withdraw from this study at any point without compromising their care or relationship with any healthcare provider

Written consent forms will be uploaded into the SAN electronic medical record. The hard copies will be stored securely in a locked cabinet at the Prostate Centre of Excellence (Level 2, Clark building, Sydney Adventist Hospital).

* 1. **Enrolment and Randomisation Procedures**

The participant will be enrolled into the study after the informed consent process has been completed and the participant has met all inclusion criteria and none of the exclusion criteria. The participants details will be de-identified and provided with a study enrolment number. This will be documented in the participant’s medical record and on all study documents. Participants will not undergo randomization.

* 1. **Blinding Arrangements**

Not applicable

* 1. **Participant Withdrawal**
     1. **Reasons for withdrawal**

Possible circumstances for early termination of the study:

1. If one of the researchers ceases to be engaged at their participating organisation before the completion of the project, the principal investigator will retain ownership and responsibility of the deidentified data. The HREC office/committee would be notified in writing in the event of this occurrence.
2. Major conclusive evidence became available that made the study redundant: this is unlikely as multiple studies across different PSMA techniques, different patient groups and different geographic regions are required to provide quality evidence.
3. A major serious adverse event with PSMA: highly unlikely as 18F-DCFPyL PSMA PET/CThas been in active clinical use for several years without major adverse events reported in the literature, and fluorinated PET agents such as 18F-FDG have also been in long term use without major adverse events (but if occurred then may warrant a change in protocol or closure of the study).

In the extremely unlikely case of early termination, the principal investigators are jointly responsible for the process of terminating the study (informing participants, correspondence to HREC, compiling a final study report).

* + 1. **Handling of withdrawals and losses to follow-up**

Participants may elect to withdraw at any point up until their 6-month follow up post-treatment with 177Lu-PSMA. We will reinforce that withdrawing will never affect their quality and standard of care

* + 1. **Replacements**

Following a withdrawal of a participant, a replacement sought to ensure that the case series will include a maximum of 10 participants.

* 1. **Trial Closure**

For the purposes of this study the follow-up frequency will be 3-monthly for a total 12-months. Thereafter, participants will continue to regularly follow-up with their healthcare practitioners as part of the standard of care. The frequency following study completion will depend on if the participant has sustained a persistent/permanent adverse event, the clinical evolution of their cancer, their clinical symptoms, serum biochemistry and healthcare provider preference.

A Letter will be issued 1-month after study completion to assess for any late adverse effects. This will be followed up by a phone call should there be no response to the dispatched letter.

* 1. **Continuation of therapy**

# STUDY VISITS AND PROCEDURES SCHEDULE

Figure 1. Trial schema

Diagram

Description automatically generated

Table 1. Schedule of events

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| List interventions | Enrolment visit | Radiology and Nuclear Medicine | Day-only admission for Lu177 treatment | Results consultation at week 6 | 3-monthly clinic follow-up |
| Inclusion/exclusion criteria | ✔ |  |  |  |  |
| Informed consent | ✔ |  |  |  |  |
| mpMRI |  | ✔ |  |  |  |
| PSMA/CT |  | ✔ |  |  |  |
| Lu177 treatment |  |  | ✔ |  |  |
| Repeat PSA |  |  |  | ✔ | ✔ |
| Monitoring vs referral |  |  |  | ✔ | ✔ |
| Adverse events and serious adverse events assessment |  | ✔ | ✔ | ✔ | ✔ |

# CLINICAL AND LABORATORY ASSESSMENTS

Laboratory assessments

* Serum PSA
* Serum testosterone

Imaging assessments

* 18F-DCFPyL PSMA PET/CT
* mpMRI of the prostate bed

# ADVERSE EVENT REPORTING

In the case of this protocol, any adverse event reporting will be restricted to the study period within 4-weeks (based on a half-life of 6.7 days) following IV administration of 177Lu-PSMA and 2-hours following radiotracer or contrast administration associated with PSMA-PET/CT and mpMRI respectively. Any adverse event is defined as any adverse event experienced by the patient or discovered on serum biochemistry following administration of treatment and that was not present prior.

Should an adverse event occur, it will be reported to the trial investigators and documented in the participant’s medical records and discussed at our fort-nightly morbidity and mortality audit.

* 1. **Definitions**

**Adverse event**

* 1. **Assessment and Documentation of Adverse Events**

An adverse event for medicines is also referred to as an adverse experience, any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign, symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

All medical procedures involve some degree of risk of injury. In addition, there may be risks associated with this study that are presently unknown or unforeseeable. Despite all reasonable precautions, you might develop medical complications from participating in this study.

* 1. **Serious Adverse Event Reporting**
     1. **SAEs**

**Serious adverse event (SAE):**

An unforeseen medical event that occurs during clinical research that:

* results in participant death
* is life-threatening to the participant
* requires the inpatient hospitalisation or prolongation of existing hospitalisation for the participant
* results in the participant having a persistent or significant disability/incapacity.
* Results in a medically important event or reaction

SAE reporting for clinical trials involving therapeutic products will follow the National Health and Medical Research Council (NHMRC) Guidance “*Safety Monitoring and Reporting in Clinical Trials Involving Therapeutic Goods (November 2016)”(10).*

Risk of teratogenicity is not applicable given all participants are men

* 1. **Specific Safety Considerations (e.g. Radiation, Toxicity)**

**Risk Profile 177Lu-PSMA**

177Lu labelled PSMA-targeted ligands have favourable theranostic characteristics as emitted beta-particles have limited tissue penetration (less than 2mm) minimising injury to adjacent healthy tissue. In addition, 177Lutetitium emits low-energy gamma rays enabling real-time theranostic imaging (8).  Standard treatment protocols for advanced disease comprises of intravenous administration of 5-7.5GBq 177Lu-PSMA every 6 weeks for up to 6-cycles. Although high-grade toxicity remains low, this can be observed with as little as 2-3 cycles. A recent systematic review and meta-analysis of 24 studies (n= 1192) assessing 177Lu-PSMA efficacy and toxicities, the pooled estimated proportion of grade 3 or 4 adverse events was <10% (anaemia 8%, leukopaenia 4%, thrombocytopaenia 4%, transaminitis 2% and xerostomia 2%). We suspect our Lu177 related adverse event profile to be significantly lower given we will only be administering a single cycle of 177Lu-PSMA compared to the standard 2-6 cycles in the reported literature(8).

Table 2. Summary of reported drug reactions to 177Lu PSMA Table

Description automatically generatedA Systematic Review and Meta-analysis of the Effectiveness and Toxicities of Lutetium-177-labeled Prostate-specific Membrane Antigen-targeted Radioligand Therapy in Metastatic Castration-Resistant Prostate Cancer - https://doi.org/10.1016/j.eururo.2021.03.004

**Risk profile for 18F-DCFPyL PSMA PET/CT**

18F-DCFPyL PSMA, is an FDA approved small-molecule PET radioligand, extensively evaluated in clinical trials. Not dissimilar to 68Ga-PSMA, the most common adverse events (AEs) in the trial included dysgeusia (2.6%), headache (1.8%), and fatigue (1.3%), which were observed across all grades of severity (11, 12). These were no serious adverse effects attributable to intravenous administration of 18F-DCFPyL PSMA.

An adverse event to either 18F-DCFPyL PSMA PET scan, or mpMRI, will be considered as any unfavourable and unintended sign, symptom, or disease temporally associated with their use, whether or not they are directly related to the 18F-DCFPyL PSMA PET scan, or mpMRI. No serious adverse effects due to intravenous administration of 18F-DCFPyL PSMA PET for imaging have been reported in the published literature. Overall, 18F-DCFPyL PSMA may be used in clinical research with no risk to patients with prostate cancer.

As per the US Food and Drug Administration (FDA) requirements, a single-organ dose of 0.05 Sv is allowed. This corresponds to an activity of 289.9–414 MBq of 18F-DCFPyL PSMA for a 70–100kg male patient. Accordingly, the effective dose expected to the whole body is 0.01 Sv, which is below the 0.03-Sv upper limit recommended by the FDA. The total (combined 18F-DCFPyL PSMA-PET and CT) effective dose would thus be significantly below the 10 mSv range that the Australian Radiation Protection and Nuclear Safety Agency states has no direct effects on human health, and probably below 5 mSv in any 1 year, as described in the code of practice for exposure to humans to ionizing radiation for research purposes (13).

Exposure to ionizing radiation in this study is standard of care and required for re-staging of their underlying prostate cancer. Participation in this study will not expose the participants to additional ionizing radiation as this is standard of care and required for re-staging of their underlying prostate cancer. In this study, A total of 10 participants will be exposed to ionizing PSMA PET/CT radiation.

The exposure to radiation will be addressed with a formal Radiation Safety Report. Radiation risks will be outlined as per the **Code of Practice** from the Australian Radiation Protection and Nuclear Safety Agency (13)

# STATISTICAL METHODS

* 1. **Sample Size Estimation**

n= 10

* 1. **Population to be analysed**

Men ≥ 50yo who have undergone radical prostatectomy for NCCN defined high risk prostate cancer who have a PSA level greater than or equal to 0.20ng/mL. Final pathology will have negative surgical margins. No detectable local, nodal or metastases observed on F18-DCFPyL PSMA PET/CT and mpMRI at study entry.

* 1. **Statistical Analysis Plan**

Basic descriptive statistics for a pilot case series. This study will form the basis of a subsequent larger scale study.

* 1. **Interim Analyses**

As this is a pilot study examining an aspect of imaging for which there is limited data, no power calculations have been undertaken. This study will form the basis of a subsequent larger scale study.

# DATA MANAGEMENT

* 1. **Data Collection**

Data collection will be conducted by interrogating hospital electronic medical records and will include:

* Name
* Age
* Date of birth
* Medical record number
* Medical history
* Urological history
* Social history
* Allergy history
* Serum biochemistry
  + Record of serial PSA results before, at the time and after radical prostatectomy
* Histopathology
* PSMA PET/CT reports
* Multiparametric MRI reports

Progress and follow-up data will be collected at the 6-week clinic visit and then at every subsequent 3-monthly visit. Data entry will be conducted by the primary investigator. This information will also be shared with the associate investigators.

* 1. **Data Storage and Study Record Retention**

Information collected from this study will have identifying information removed and will be kept confidential and secure. Medical files containing participants’ personal details will remain at the site where they are collected. All research data will be stored, including the original copies of consent, at Sydney Adventist Hospital, Prostate Centre of Excellence (Level 2, Clark building). All data collected in paper format will be stored in a locked cabinet (with access limited to study investigators only) and will be transcribed into an electronic database on password secure computer and file at Sydney Adventist Hospital. Any data transcribed into online systems will only be identifiable by the participant’s enrolment code. In addition, access to the database will be password- protected, monitored and restricted to registered users. The principal investigator will be responsible for data management. Data will be retained for 15-years as per NHMRC Australian Code for the Responsible Conduct of Research, unless required longer by a publishing journal or a change in guidelines.

* 1. **Data Confidentiality**

Data used for reporting purposes will be de-identified and only group data will be used in any publications arising from this study. Case report forms will be placed in opaque folders and filed securely in a locked cabinet at the Prostate Centre of Excellence (key to cabinet provided to PI and AI only). The Prostate Centre of Excellence is a located-on level 2 Clark building at Sydney Adventist Hospital and is swipe access protected. The case report forms are transcribed as de-identified data onto a password protected excel spreadsheet and the case report form is uploaded electronically to a password protected shared network drive that is only accessible by the principal investigator. The hardcopy is shredded and discarded in confidentiality bin. The principal investigator will retain the keys to access and de-code the case report forms to unblind the data. AHCL information services backs the drive up every 24hrs and therefore risk of data loss is negligible

* 1. **Participant reimbursement**

No participant shall receive financial or any other forms of reimbursement for enrolment and participation in this clinical trial

* 1. **Financial disclosure and conflicts of interest**

None to disclose

This pilot case series is self-funded. Payments will be made directly to San radiology and nuclear medicine. Out of pocket cost will be approximately AUD 11,250$

|  |  |  |  |
| --- | --- | --- | --- |
| **Item** | **Unit** | **Cost** | **Funding** |
| Lu-PSMA-177 | 1x | $5,500 | Self-funded |
| SPECT scan | 3x | $300 | Self-funded |
| mpMRI | 1x | $450 | Self-funded |
| San radiology staff and consumables | 1x | $5000 | Self-funded |

# USE OF DATA AND PUBLICATIONS POLICY

This study will be published in peer reviewed journal(s) or presented at national and international conferences. Individual participants will not be identifiable in any analysis, publications, or presentations. Participants will always remain de-identified regardless of journals’ data sharing policies

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# APPENDIX 1



