

Official Title: Predictors of Nodal and Distant Metastatic Disease Detected by PSMA PET in Treatment-Naïve High-Risk Prostate Cancer: A Czech Multicentre Cohort Study

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or special term	Explanation
¹⁸F	Fluorine-18 (radiotracer)
⁶⁸Ga	Gallium-68 (radiotracer)
ADT	Androgen Deprivation Therapy
ARPI	Androgen Receptor Pathway Inhibitor
AUC	Area Under the Receiver Operating Characteristic Curve
BCR	Biochemical Recurrence
BCRFS	Biochemical Recurrence-Free Survival
CI	Confidence Interval
CT	Computed Tomography
DICOM	Digital Imaging and Communications in Medicine
DRE	Digital Rectal Examination
EANM	European Association of Nuclear Medicine
EAU	European Association of Urology
EBRT	External Beam Radiotherapy
EMR	Electronic Medical Record
EPV	Events-Per-Variable
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GPP	Good Publication Practice / Good Pharmacoepidemiology Practices
GS	Gleason Score
ICH	International Council for Harmonisation
IQR	Interquartile Range
ISUP GG	International Society of Urological Pathology Grade Group
LASSO	Least Absolute Shrinkage and Selection Operator
LHRH	Luteinising Hormone-Releasing Hormone

Abbreviation or special term	Explanation
miTNM	Molecular Imaging Tumour, Node, Metastasis
MRI	Magnetic Resonance Imaging
OR	Odds Ratio
OS	Overall Survival
PACS	Picture Archiving and Communication System
PB	Prostate Biopsy
PCa	Prostate Cancer
PET	Positron Emission Tomography
PFS	Progression-Free Survival
phi	Prostate Health Index
PI-RADS	Prostate Imaging Reporting and Data System
PLND	Pelvic Lymph Node Dissection
PROMISE	Prostate Cancer Molecular Imaging Standardised Evaluation
PSA	Prostate-Specific Antigen
PSA-D	Prostate-Specific Antigen Density
PSMA	Prostate-Specific Membrane Antigen
PSMA-RADS	PSMA Reporting and Data System
PSMA-TV	PSMA-derived Total Tumour Volume
RP	Radical Prostatectomy
RT	Radiotherapy
SBRT	Stereotactic Body Radiotherapy
SUV_{max}	Maximum Standardised Uptake Value
TNM	Tumour, Node, Metastasis staging
TRUS	Transrectal Ultrasound
VFN	Všeobecná fakultní nemocnice v Praze (General University Hospital in Prague)
WW	Watchful Waiting

RESPONSIBLE PARTIES

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PROTOCOL SYNOPSIS

Study title:

Predictors of Nodal and Distant Metastatic Disease Detected by PSMA PET in Treatment-Naïve High-Risk Prostate Cancer: A Czech Multicentre Cohort Study (CZECH-PSMA trial)

Study sponsor:

Všeobecná fakultní nemocnice v Praze, with its registered seat at U Nemocnice 499/2, 128 08 Nové Město, Czech Republic

Study sites:

9 Urological and affiliated Nuclear Medicine departments across the Czech Republic

Background/Rationale:

Prostate cancer is the second most common malignancy worldwide and the fifth leading cause of male cancer-related mortality. Approximately 15% of localized cases are classified as high-risk for biochemical recurrence. These patients frequently harbour occult metastases undetected by conventional imaging (CT and bone scintigraphy). Consequently, PSMA PET has revolutionized primary staging and is strongly recommended by EAU guidelines.

In the Czech Republic, a transition toward a "PSMA-first" pathway is evident, where molecular imaging increasingly replaces conventional modalities. This "stage-migration" identifies a new cohort of miN1/M1 patients previously classified as having localized disease. However, PSMA PET is a resource-demanding modality and not yet universally available. To optimize its utility, identifying which combinations of routinely available parameters predict metastatic disease and characterizes this new cohort is essential.

Furthermore, real-world evidence regarding early oncological outcomes within this PSMA-only framework is limited. This multicentre cohort study aims to define a multi-parametric predictive model for PSMA-detected metastases and evaluate the real-world therapeutic trajectories and follow-up outcomes of this newly defined high-risk population. By integrating clinical, biological, and molecular data, we seek to refine patient selection and provide a longitudinal perspective on the "PSMA-first" diagnostic era.

Objectives and Hypotheses:

Primary Objective: To identify clinical, pathological and molecular parameters and their combinations associated with nodal (miN1) and/or distant (miM1) metastatic disease on PSMA PET.

Secondary Objectives: To assess the real-world evidence of the "PSMA first" cohort – specifically high-risk PCa patients staged with PSMA PET – and their early oncological outcomes.

Methods:

Study design: A multicentre retrospective observational cohort study.

Data Sources(s): Internal institutional medical records of urological and nuclear medicine departments in the Czech Republic.

Study Population: Male patients ≥ 18 years diagnosed with histologically confirmed high-risk prostate adenocarcinoma (ISUP GG ≥ 4 and/or PSA ≥ 20 $\mu\text{g/l}$ and/or DRE $\geq \text{cT2c}$). Patients must have undergone PSMA PET staging prior to any therapy between January 2016 and December 2025.

Exposure(s): Not applicable; this is an observational retrospective study of patients treated within routine clinical practice.

Outcome(s): Predictors of miN1 and/or miM1 disease on PSMA PET in primary staging of high-risk prostate cancer. Early oncological outcomes and real-world therapeutic trajectories in the PSMA-first cohort.

Sample Size Estimations: A minimum of approximately 400 patients is planned for inclusion.

Statistical Analysis:

A formal sample size calculation was not performed; the number of minimally 400 participants is based on the estimated eligible population. Univariate and multivariate logistic regression analysis will identify the strongest individual or combined parameters to predict nodal and/or distant metastatic disease on PSMA PET. Time-to-event variables, including overall survival, progression-free survival, and time to biochemical recurrence, will be described using Kaplan–Meier estimates. Biochemical persistence after radical prostatectomy, when performed, will be analysed as a binary outcome.

AMENDMENT HISTORY

Date	Section of study protocol	Amendment or update	Reason
06032026	New/initial version	N/A	Not applicable

MILESTONES

Milestone	Planned date
Final Protocol	Q1 2026
Data Collection Completion	Q2 2026
Final Statistical Analysis	Q2 2026
Final Study Report	Q1 2027
Final Manuscript	Q3 2027

1. BACKGROUND AND RATIONALE

1.1 Background

Prostate cancer (PCa) is the second most common malignancy worldwide and the fifth leading cause of cancer-related death in men.¹ In the Czech Republic, the incidence and mortality rates of PCa in 2022 reached approximately 186 and 28 per 100,000 men, respectively.² The rising incidence is primarily attributed to ageing population and growing global population.³ The early diagnosis of PCa is important for disease prognosis.⁴ Following diagnosis a uniform tumour staging is performed to categorize the disease according to the risk of biochemical recurrence. Gleason score as the preferred system of pathological tumour grading, prostate-specific antigen (PSA) levels and digital rectal examination (DRE) findings are also considered.⁵ This, together with factors such as age and comorbidities, further guides patients' treatment options and the need for initial staging. Conventionally, a combination of computed tomography (CT) of the abdomen and pelvis and bone scintigraphy is utilised for staging. However, positron emission tomography/computed tomography using radiolabelled tracers targeting the prostate-specific membrane antigen (PSMA PET/CT) is gaining prominence. According to the European Association of Urology (EAU) guidelines, PSMA PET/CT should be considered the primary staging modality in selected patients, specifically in high-risk PCa as a strong recommendation.⁶ Approximately 15% of localised cases are classified as high-risk for biochemical recurrence and these patients frequently harbour occult metastases undetected by conventional imaging.⁷ The pooled prevalence of extraprostatic PSMA PET positivity in high-risk PCa patients is about 31 %.⁸ High-risk PCa has in general a risk of up to 35 % of prostate cancer specific mortality, if not treated with curative intent and has a ten-year biochemical recurrence-free probability after radical treatment of 39 %.^{9,10}

PSMA PET compared to conventional imaging in initial staging provides higher sensitivity and specificity in assessing the disease extent, while still missing a portion of lymph node micrometastases.^{8,11} Various radiotracers and ligands have been used, most commonly a combination of ⁶⁸Ga (⁶⁸gallium – radiotracer) and PSMA-11 (prostatic specific membrane antigen 11 – ligand). Normal PSMA uptake can be observed in lacrimal and salivary glands, liver, gall bladder, spleen, small intestine and kidney.¹² ⁶⁸Ga-PSMA-11 is primarily excreted via the urinary system and collected in the bladder and this might complicate the assessment of PSMA-ligand uptake in surrounding structures (e.g., prostate and seminal vesicles). Another tracer, ¹⁸F-PSMA-1007, shows high liver uptake, and almost no urinary excretion.¹³ However, F-PSMA-1007 is known to have higher prevalence of equivocal bone lesions.¹⁴ Different anatomical imaging modalities have been used in combination with PSMA PET, specifically CT and MRI (magnetic resonance imaging).¹⁵ Different standardized reporting systems have been proposed such as EANM (European association of nuclear medicine) reporting system, PSMA-RADS (PSMA Reporting and Data System) and PROMISE (Prostate Cancer Molecular Imaging Standardized Evaluation).^{16,17} PROMISE system defines miTNM (molecular imaging TNM) and organises the report into anatomical categories (local tumor, regional nodes, distant metastases), distribution pattern of metastases, PSMA expression level in each location and final diagnosis with exact level of certainty.¹⁸ The new version (PROMISE V2) includes PRIMARY score in assessment of intraprostatic tumor PSMA PET patterns.¹⁹

Thanks to increased accuracy over conventional imaging, PSMA PET can therefore detect disease not seen on bone scan and CT or whole-body MRI. This may lead to significant stage migration and a shift in disease volume in PCa diagnosis creating a discordance between clinical management recommendations as well as prognosis based on criteria from trials using only conventional imaging such as CHAARTED or STAMPEDE.²⁰ Because of these new subgroups of PCa patient, trials investigating new treatment strategies are emerging. For example, investigation of multimodal therapy strategies in oligometastatic disease on PSMA PET, especially metastatic directed therapies combined with local tumor control.^{21,22}

Czech Republic

PSMA PET has been in adoption in Czech Republic as early as 2018 in research but has become more widely used since 2021, when the EAU guidelines for the first time recommended the use of PSMA PET in primary staging in high-risk PCa.^{23,24} Currently, eight nuclear medicine centres in the Czech Republic provides PSMA PET. Currently the only reimbursed indication in Czech Republic in primary staging is for high-risk PCa patients.

1.2 Rationale

The implementation of a "PSMA-first" pathway presents significant clinical and logistical challenges. PSMA PET is a resource-demanding modality with growing but still limited universal geographic and operational availability. Even though PSMA PET is fully reimbursed by insurance companies in high-risk PCa in the Czech Republic, there are still countries, where this imaging modality is being paid by patients out of pocket or reserved for studies only.²⁵ An increased adoption of nuclear medicine molecular imaging methods can be expected in the future, for example, as seen in many studies on its use in renal cancer or in radioligand therapies.²⁶ While a transition toward PSMA PET in primary staging is evident, there remains a need for a multi-parametric predictive model to justify its use. By identifying which combinations of routinely available clinicopathological and molecular parameters accurately predict metastatic disease, we can optimize patient selection and prioritization. Other important consideration is, the fact, that high-risk PCa represents a highly heterogenous cohort and to better guide treatment in the "PSMA-first" pathway era should be further subdivided.¹⁰

While models like PPP2 (Prostate Cancer Molecular Imaging Standardized Evaluation) exist, significant gaps remain in integrating new biomarkers of aggressiveness, such as the presence of cribriform pattern in pathological specimens, or biomarkers, such as the Prostate Health Index (phi), together with molecular metrics to predict biochemical persistence or other early oncological outcomes.²⁷ This study will provide essential real-world evidence for identifying superior prognostic surrogates in a high-risk cohort beyond conventional risk stratification tools.

Furthermore, as PSMA PET adoption expands across multiple centres, the potential for interobserver variability in image interpretation remains a concern. Evaluating the

reliability of local institutional reports through centralized expert review is essential to ensure the diagnostic consistency required for multi-parametric model implementation in diverse clinical settings.²⁸

The implementation of PSMA PET into clinical guidelines and into PCa diagnostic algorithms has been important for patient's care in the Czech Republic. With its higher accuracy in primary staging more accurate and individualized treatment can be offered. However, most of the recommended managements are based on conventional staging modalities and cannot be automatically extrapolated to this new setting. There is a knowledge gap in the real-world data in Czech Republic on high-risk PCa patients primarily staged with PSMA PET and their subsequent treatment pathways and their early oncological outcomes. By synthesizing real-world clinical data with molecular insights, we evaluate the impact of the "PSMA-first" diagnostic paradigm in the Czech Republic. Our objective is to determine whether prioritizing this pathway yields superior clinical outcomes compared to conventional staging protocols.

Radical prostatectomy has been increasingly used in the high-risk PCa setting, even though additional treatment as part of multimodal approach might have to be applied in some cases. The morbidity of radical prostatectomy with pelvic lymph node dissection is already high, and in the case of need of adjuvant or salvage treatment, for example, radiotherapy, might multiply treatment complications and lower health-related quality of life.^{29,30} Therefore, we aim to establish a combined model using PSMA PET parameters to forecast negative predictive pathological parameters after radical prostatectomy (positive resection margins and/or ISUP GG ≥ 8 and/or \geq pT3a and/or pN1 and the number of positive lymph nodes) as a surrogate for potential biochemical recurrence and the need of subsequent adjuvant or salvage treatment in these patients.³¹ These findings might help us predict outcomes in high-risk PCa patients prior to radical prostatectomy treatment.

2. OBJECTIVES AND HYPOTHESES

The primary goal of this study is to develop a multi-parametric predictive model for nodal (miN1) and/or distant (miM1) metastatic disease detected by PSMA PET and to characterize subsequent real-world clinical management in this cohort.

2.1 Primary Objective

The primary objective is to identify clinical (e.g., PSA-density, phi), pathological (e.g., percentage of positive prostate biopsy cores), and molecular imaging (e.g., SUV_{max}) parameters, as well as their combinations, that are independently associated with the presence of nodal (miN1) and/or distant (miM1) metastatic disease on PSMA PET in treatment-naïve, high-risk prostate cancer patients.

2.2 Secondary Objectives

The secondary objectives aim to provide real-world evidence regarding the "PSMA-first" diagnostic pathway:

To describe real-world therapeutic strategies initiated following PSMA PET staging (e.g., radical prostatectomy, radiotherapy, or systemic therapy, multimodal approaches).

To evaluate early oncological outcomes, including biochemical persistence after radical prostatectomy and biochemical recurrence-free survival.

To quantify stage migration and modifications in patients who underwent both conventional imaging and PSMA PET in the Czech Republic.

2.3 Exploratory objectives

Exploratory outcomes will include interobserver agreement for metastatic disease detection between local and centralized reviews. We will evaluate pre-operative PSMA metrics in predicting adverse pathological features in radical prostatectomy specimens, including positive margins, ISUP GG ≥ 8 , and pN1 status. Additionally, the frequency of management shifts triggered by PSMA PET versus conventional imaging will be quantified, as well as early oncological outcomes in oligometastatic patients receiving definitive local therapy with or without metastasis-directed therapy.

3. METHODOLOGY

3.1 Study Design – General Aspects

This study is designed as a multicentre retrospective observational cohort study. The primary objective is to define a multi-parametric predictive model for metastases detected by Prostate-Specific Membrane Antigen (PSMA) Positron Emission Tomography (PET) and to evaluate real-world therapeutic trajectories and early oncological outcomes within a "PSMA-first" diagnostic framework.

Study steps and responsibilities

Data will be gathered from participating institutions into a centralized database. The principal investigator will be responsible for the administration of this database and will ensure accuracy and completeness of the data. Central review of PSMA PET images from participating institutions will be performed. Data will be analysed according to the Section 5 of this protocol. A designated statistician will be responsible for the statistical analysis. Results will be synthesized and reported by the study's lead investigators.

Central review of PSMA PET images

To ensure the diagnostic validity and consistency of the study findings, all anonymized PSMA PET imaging data including images will be centralized at a single institution and undergo a standardized central re-evaluation by experienced nuclear medicine physician(s). Inter-reader agreement will be evaluated comparing central review and original results from different institutions. At the point of central review, the nuclear medicine physician will be blinded to the results of PSMA PET by participating institutions. As part of the central review, PROMISE V2 reporting system will also be used.

Research design rationale

Retrospective observational multicentre cohort design has been chosen for this study, because it allows for an efficient capture of the real-world evidence of the "PSMA-first" pathway in influencing therapeutic trajectories without interfering with standard-of-care protocols. It allows for collection of sufficient amount of data with necessary statistical power to create and validate a multiparametric predictive model. PSMA PET is a resource-demanding imaging modality, a fact which in prospective setting might prohibit gathering enough data during a similar timeframe. Thanks to the transitioning period from conventional to novel staging methods during this specific study period, it might also allow capturing the stage-migration effect. As an observational retrospective study, no experimental interventions were performed.

Setting and timeline

The retrospective data collected from internal institutional medical records across nine Urological and affiliated Nuclear Medicine departments in the Czech Republic will be eligible for inclusion during the period between January 2016 and December 2025. The

study will not involve active patient contact or prospective follow up. Patients were followed from the date of diagnosis until last documented follow-up or death.

3.1.1 Data Source(s)

The data for this retrospective observational study will be sourced from the internal institutional medical records of planned nine participating Urological and affiliated Nuclear Medicine departments across the Czech Republic. These sources are selected to provide a comprehensive and longitudinal overview of the patient journey within the "PSMA-first" diagnostic era.

To ensure that the necessary data points are captured in a consistent and structured manner for statistical analysis, information will be extracted via centralized data capture sheets designed to capture clinical, biological, and molecular parameters.

The inclusion of both urological and nuclear medicine departments ensures a complex and representative description of the patient pathway through the national healthcare system.

Participating centres represent tertiary referral institutions providing molecular imaging across the Czech Republic. The resulting dataset will provide a robust foundation for identifying predictors of metastatic disease and evaluating real-world therapeutic trajectories.

3.2 Study Population

Persons: Male patients aged ≥ 18 years with histologically confirmed prostate adenocarcinoma.

Place: The Czech Republic, including patients diagnosed and treated in Urological and affiliated Nuclear Medicine Departments.

Time period (Study Window): January 1, 2016 to December 31, 2025, capturing the transition toward molecular imaging in primary staging.

Selection Criteria: Patients with histologically confirmed high-risk prostate cancer according to EAU guidelines who underwent primary staging with PSMA PET within the study window.⁶

Sample Size: A minimum of 400 patients is planned for inclusion to ensure a statistically robust dataset for the development of the predictive model. Based on a reported prevalence of approximately 31% for mN1/M1 disease in high-risk PCa staged with PSMA PET, we anticipate approximately 120 events.⁸ This event rate allows for multivariable modelling with an Events-Per-Variable (EPV) ratio of up to 12 candidate predictors. To mitigate the risk of overfitting and ensure model stability, if needed, internal validation using bootstrapping techniques will be employed. This sample size provides sufficient power to identify independent predictors with a clinically relevant effect size.

3.3 Inclusion Criteria

Male patients will be included if:

- Male patients aged ≥ 18 years with histologically confirmed prostate adenocarcinoma,
- high-risk disease defined as ISUP GG ≥ 4 and/or PSA ≥ 20 ng/ml and/or clinical stage assessed by DRE \geq cT2c,
- PSMA PET performed for primary staging within study window.

3.4 Exclusion Criteria

Patients with:

- definitive local treatment (e.g., radical prostatectomy or radiation therapy) or systemic treatment (e.g., androgen deprivation therapy) administered prior to primary staging with PSMA PET,
- low or intermediate-risk PCa as defined by failing to meet any of the inclusionary high-risk parameters,
- incomplete or fragmented medical records that preclude the accurate extraction of primary staging parameters (PSA, ISUP GG, clinical T-stage) or PSMA PET results (miN/miM status),
- active malignancy requiring systemic treatment at the time of PSMA PET.

4. VARIABLES AND EPIDEMIOLOGICAL MEASUREMENTS

A formal sample size calculation was not performed. The number of minimally 400 participants is based on the estimated number of patients meeting the pre-defined selection criteria.

The entire cohort of patients eligible for the study will be entered into the dataset with the variables of interest recorded.

The information about:

- the clinical characteristics of patients,
- dates
- clinical, laboratory and pathological data
- imaging modalities results including PSMA PET date and site
- treatment planned prior PSMA PET and/or treatment after PSMA PET results
- follow-up and outcomes

will be collected.

Anonymized PSMA PET images will be reviewed centrally in the lead institution and the information required will be put in a separate data sheet.

General descriptions of study variables are recorded below:

Patient and baseline

- **Age** – Calculated as the difference between date of birth and date of PSMA PET and recorded in years with one decimal place: number (e.g., 57.0)
- **Initial PSA** – Highest prostate specific antigen (PSA) level at diagnosis: number
- **Phi** – Prostate Health Index (phi) score at diagnosis: number
- **Prostate Volume** – Prostate Volume in ml: number
 - preferably measured on magnetic resonance imaging (MRI)
 - if not available from MRI, then measured by transrectal ultrasound (TRUS)
- **cT stage** – Clinical T (tumor) stage assessed by digital rectal examination (DRE) at diagnosis
 - 1 = cT1
 - 2 = cT2a
 - 3 = cT2b
 - 4 = cT2c
 - 5 = cT3a
 - 6 = cT3b
 - 7 = cT4
- **Any notes to patient and baseline**: free text

MRI

- **PI-RADS score** – Highest Prostate Imaging Reporting and Data System (PI-RADS) score on MRI before last PB before primary staging with PSMA PET:
 - PI-RADS 1 = 1
 - PI-RADS 2 = 2
 - PI-RADS 3 = 3
 - PI-RADS 4 = 4
 - PI-RADS 5 = 5
- **Date of MRI** – Date of MRI before last PB: dd.mm.yyyy, if exact day not known, default day 15.mm.yyyy, if exact month not known, default 15.6.yyyy
- **Any notes to MRI:** free text

Prostate Biopsy

- **Date of PB** – Date of last PB before initial staging with PSMA PET: dd.mm.yyyy, if exact day not known, default day 15.mm.yyyy, if exact month not known, default 15.6.yyyy
- **Type of PB** – Type of PB performed:
 - 1 = fusion
 - 2 = systematic
 - 3 = other (specified in notes)
- **ISUP GG** – Highest International Society of Urological Pathology (ISUP) grade group (GG) or combined Gleason Score (GS) from PB:
 - 1 = ISUP GG 1 (GS 3+3)
 - 2 = ISUP GG 2 (GS 3+4)
 - 3 = ISUP GG 3 (GS 4+3)
 - 4 = ISUP GG 4 (GS 3+5 / 4+4 / 5+3)
 - 5 = ISUP GG 5 (GS 4+5 / 5+4 / 5+5)
- **Number of positive cores** – Number of cores with detection of any prostate cancer cells: number
- **Number of total cores** – Number of all cores taken during the PB: number
- **Cribriform pattern** – Presence of cribriform pattern in PB:
 - 0 = no
 - 1 = yes
- **Any notes to Prostate Biopsy:** free text

Other Imaging

- **CT abdomen and pelvis and/or bone scintigraphy** – Contrast-enhanced Computed Tomography (CT) scan of abdomen and pelvis and/or ^{99m}Tc bone scintigraphy (as conventional staging) performed before PSMA PET:
 - 0 = no
 - 1 = yesIf yes,
- **cN** – clinical (node) N status based on conventional staging imaging (not PSMA PET):

- 0 = negative
- 1 = suspicious
- 2 = positive (location(s) and number in notes)
- **Any notes to cN status based on conventional imaging:** free text
- **cM** – clinical metastasis (M) status based on conventional staging imaging (not PSMA PET):
 - 0 = negative
 - 1 = suspicious
 - 2 = positive (location(s) and number in notes)
- **Any notes to cM status based on conventional imaging:** free text

Plan of therapy based on conventional imaging

- **Therapy type** – Type of therapy planned based on conventional staging imaging, before PSMA PET:
 - 0 = no plan before PSMA PET
 - 1 = RP + PLND
 - 2 = RT prostate + ADT (if yes, specify in notes: prostate / prostate and pelvis/other)
 - 3 = systemic treatment (specify in notes, e.g., LHRH+ARPI)
 - 4 = WW
 - 5 = other (specify in notes)
- **Treatment change** – Treatment plan changed after the results of PSMA PET were known:
 - 0 = no
 - 1 = yes
- **Any notes to Plan of therapy based on conventional imaging:** free text

PSMA PET

- **Date of PSMA PET** – Date of PSMA PET performed as primary staging for high-risk prostate carcinoma: dd.mm.yyyy, if exact day not known, default day 15.mm.yyyy, if exact month not known, default 15.6.yyyy
- **Institution** – Institution, where PSMA PET was performed:
 - VFN (= Všeobecná fakultní nemocnice Praha)
 - ÚVN (= Ústřední vojenská nemocnice Praha)
 - NNH (= Nemocnice Na Homolce)
 - FN Plzeň (= Fakultní nemocnice Plzeň)
 - ČB (= Nemocnice České Budějovice)
 - MOÚ (= Masarykův Onkologický ústav Brno)
 - Liberec (= Krajská nemocnice Liberec)
 - Olomouc (= Fakultní nemocnice Olomouc)
 - other (specify in notes)
- **Any notes to PSMA PET:** free text

Treatment after PSMA PET

- **Type of treatment** – Type of therapy chosen after PSMA PET results:
 - RP + PLND (= radical prostatectomy and pelvic lymph node dissection)
 - RT + ADT (= radical radiotherapy and androgen deprivation therapy)
 - systemic treatment
 - WW (= watchful waiting)
 - other (specify in notes)
- **Date of therapy** – Date of any therapy start: dd.mm.yyyy, if exact day not known, default day 15.mm.yyyy, if exact month not known, default 15.6.yyyy
- **Any notes to treatment after PSMA PET:** free text

If surgery

- Final ISUP GG – Final International Society of Urological Pathology (ISUP) grade group (GG) or combined Gleason Score (GS) from RP (= radical prostatectomy):
 - 1 = ISUP GG 1 (GS 3+3)
 - 2 = ISUP GG 2 (GS 3+4)
 - 3 = ISUP GG 3 (GS 4+3)
 - 4 = ISUP GG 4 (GS 3+5 / 4+4 / 5+3)
 - 5 = ISUP GG 5 (GS 4+5 / 5+4 / 5+5)
- pT – Final pathological T (tumor) stage from RP:
 - 0 = pT0
 - 1 = pT2
 - 2 = pT3a
 - 3 = pT3b
 - 4 = pT4
- pN – Pathological N (node) stage from RP:
 - 0 = pN0
 - 1 = pN1
 - 2 = pNx
- R – resection margins from RP:
 - 0 = R0
 - 1 = R1

If radiation

- Type of RT – Type of radical radiotherapy:
 - 1 = EBRT (= External Beam Radiotherapy)
 - 2 = SBRT (= Stereotactic Body Radiotherapy)
 - 3 = Brachy (= Brachytherapy)
 - 4 = Proton (= Proton Radiotherapy)
 - 5 = other (specify in notes)
- Targeted area – Targeted area during radiotherapy:
 - 1 = prostate
 - 2 = prostate + pelvis
 - 3 = other (specify in notes)

If systemic therapy

- Type of systemic therapy:
 - 0 = ADT mono (= androgen deprivation therapy in monotherapy)
 - 1 = ADT + ARPI (= androgen deprivation therapy in monotherapy and androgen receptor pathway inhibitors)
 - 2 = ADT + docetaxel (= androgen deprivation therapy in monotherapy and docetaxel)
 - 3 = ADT + ARPI + docetaxel (= androgen deprivation therapy in monotherapy and androgen receptor pathway inhibitors and docetaxel)
 - 4 = other (specify in notes)

Follow-up

- **Date of last follow-up:** dd.mm.yyyy, if exact day not known, default day 15.mm.yyyy, if exact month not known, default 15.6.yyyy
- **Survival status** – Survival status at last follow-up:
 - 0 = alive
 - 1 = death because of PCa
 - 3 = death because of other cause
- **PSA persistence** – PSA persistence status according to investigator's judgement (e.g., PSA persistence = PSA \geq 0.1 ng/mL measured within 4 to 8 weeks after radical prostatectomy):
 - 0 = no
 - 1 = yes
- **BCR** – biochemical recurrence status according to investigator's judgement (e.g., after RP: PSA \geq 0.2 ng/mL and confirmed; after RT: nadir + 2 ng/mL – Phoenix criteria):
 - 0 = no
 - 1 = yes
- **Date of BCR** – Date of BCR detection: dd.mm.yyyy, if exact day not known, default day 15.mm.yyyy, if exact month not known, default 15.6.yyyy
- **Metastatic progression** – Radiological metastatic progression according to investigator's judgement on imaging modality:
 - 0 = no
 - 1 = yes
- **Date of metastatic progression:** dd.mm.yyyy, if exact day not known, default day 15.mm.yyyy, if exact month not known, default 15.6.yyyy
- **Any notes to follow-up:** free text

PSMA PET by central review

- **T stage** – miT (tumor) stage assessed PSMA PET (miTNM PROMISE V2):
 - 0 = miT0
 - 1 = miT2u

- 2 = miT2m
- 3 = miT3a
- 4 = miT3b
- 5 = miT4
- **N stage** – miN (nodal) stage assessed PSMA PET (miTNM PROMISE V2):
 - 0 = miN0
 - 1 = miN1
 - 2 = miN2
- **M stage** – miM (metastasis) stage assessed PSMA PET (miTNM PROMISE V2):
 - 0 = miM0
 - 1 = miM1a
 - 2 = miM1b
 - 3 = miM1c
- **PSMA-expression score according to PROMISE V2:**
 - 0 = 0
 - 1 = 1
 - 2 = 2
 - 3 = 3
- **SUV_{max} of the primary index lesion (prostate):** number
- **PSMA Total Tumor Volume (cm³):** number
- **Total number of metastatic lesions:** number
- **Any notes to PSMA PET:** free text

Written radiological reports from PSMA PET examinations performed at participating institutions will be collected in pseudonymized form. In addition, corresponding imaging data (DICOM format) will be securely transferred from local PACS systems to the coordinating centre. All imaging studies will undergo centralized re-evaluation by experienced nuclear medicine physicians according to PROMISE V2 criteria to ensure standardized staging and data extraction.

4.1 Exposures

Not applicable.

4.2 Outcomes

Describe: This section characterizes the predictors of metastatic disease on PSMA PET and the clinical progression of the "PSMA-first" cohort within the Czech Republic. The objectives involve identifying clinical, biological, and molecular parameters associated with nodal or distant spread and evaluating subsequent therapeutic trajectories and early oncological outcomes.

4.2.1 Primary Outcomes

The primary outcome is the presence of nodal (miN1) and/or distant (miM1) metastatic disease on PSMA PET, as defined according to PROMISE V2 criteria.

- The primary analysis will evaluate the association between clinicopathological parameters and this outcome. Candidate predictors will include serum PSA, Prostate Health Index (phi), PSA density (PSA-D), clinical T stage (based on DRE), ISUP grade group from prostate biopsy, percentage of positive biopsy cores, presence of cribriform pattern in biopsy specimens, and PI-RADS score on prostate MRI.
- In addition, selected molecular imaging metrics derived from PSMA PET will be analysed, including the highest SUV_{max} of the primary intraprostatic lesion (prostate \pm seminal vesicles) and PSMA-derived total tumor volume (PSMA-TV).

4.2.2 Secondary Outcomes

The secondary outcomes focus on real-world evidence and early oncological results of patients staged with PSMA PET prior to therapy. Specifically:

- Analysis of the combination of PSMA molecular and clinicopathological parameters (e.g., cribriform pattern and SUV_{max} , phi and SUV_{max}) as mentioned above and early oncological outcomes (biochemical persistence, BCR, PFS, and OS) in high-risk PCa with PSMA PET as primary staging.
- Evaluation of the correlation of miT (tumor) and miN (nodal) findings according to PROMISE V2 criteria on primary staging PSMA PET and final radical prostatectomy pathological TNM staging.

4.2.3 Exploratory Outcomes

Specifically, we aim to analyse:

- Analysis of the interobserver agreement between local institutional PSMA PET interpretations and a centralized expert review to assess the reliability of metastatic disease detection across participating centres.
- Evaluation of pre-operative clinical and per-lesion molecular PSMA metrics (e.g., SUV_{max} , miT stage according to PROMISE V2, PSMA-TV) in predicting these BCR surrogate endpoints in radical prostatectomy cohort: pathological positive resection margins and/or ISUP GG ≥ 8 and/or \geq pT3a and/or pN1 and the number of positive lymph nodes.
- Additional analysis of the frequency and nature of changes in clinical management in time (e.g., change from curative intent to systemic therapy, or addition of

metastasis-directed therapy) triggered by PSMA PET findings compared to initial plans based on conventional imaging.

- Comparison of early oncological outcomes in patients with oligometastatic disease (defined as 1 – 5 lesions in any organ) who underwent definitive local treatment to the primary tumor with or without other form of therapy (e.g., metastasis directed therapy, systemic therapy).

Time for Assessment

Outcomes will be assessed retrospectively from patient data collected within the study window of January 1, 2016, to December 31, 2025. This window allows for a longitudinal perspective on the adoption of molecular imaging and provides sufficient follow-up for early oncological outcomes.

Handling Missing or Erroneous Data

To ensure the validity and integrity of the finding and to minimize bias, missing or erroneous data will be handled as described in study protocol section 5.

4.3 Other Variables and Covariates

Not applicable.

5. STATISTICAL ANALYSIS PLAN

5.1 Statistical Methods – General Aspects

All statistical analyses will be performed using R software (version 4.3.0 or higher; R Foundation for Statistical Computing, Vienna, Austria) and/or SAS® software (version 9.4 or higher; SAS Institute Inc., Cary, NC, USA). A two-sided p-value < 0.05 will be considered statistically significant where applicable. Continuous variables will be summarized using mean and standard deviation or median and interquartile range (IQR), as appropriate. Categorical variables will be presented as absolute and relative frequencies. The functional form of continuous predictors will be assessed using graphical inspection and, where appropriate, formal tests. Non-linear relationships may be explored, and transformations (e.g., logarithmic transformation for PSA) may be applied to improve model fit and stability. The extent and pattern of missing data will be assessed for all variables. If the proportion of missing data for key predictors is considered clinically relevant, appropriate methods such as multiple imputation may be applied. Sensitivity analyses will be performed where necessary. All analyses will be conducted according to a pre-specified statistical analysis plan to minimize the risk of data-driven model overfitting.

Primary Endpoint Definition

The primary endpoint is presence of nodal (miN1) and/or distant (miM1) metastatic disease detected by PSMA PET at primary staging, according to PROMISE V2 criteria. This endpoint will be analysed as a binary outcome (metastatic vs. non-metastatic).

Secondary analyses may separately evaluate:

- miN1 vs. miN0,
- miM1 vs. miM0,
- multinomial outcome (miN0M0 / miN1 / miM1).

5.1.1 Primary Objectives

Univariate Analysis

Associations between candidate predictors and metastatic disease will initially be evaluated using:

- Logistic regression for categorical and continuous variables
- Odds ratios (OR) with 95% confidence intervals (CI)

Candidate predictors include:

- Clinical variables (PSA, PSA density, phi, cT stage, etc.)
- Pathological variables (ISUP Grade Group, % positive biopsy cores, cribriform pattern, etc.)
- Imaging variables (PI-RADS score)

- Molecular PSMA PET metrics (SUVmax of index lesion, PSMA total tumor volume etc.)

Multivariable Model Development

A multivariable logistic regression model will be constructed to identify independent predictors of metastatic disease.

Variable selection will be performed using:

- Clinical relevance criteria
- Penalized regression methods (e.g., LASSO), if necessary
- Events-per-variable considerations (minimum 10 events per parameter)

Continuous variables will be retained as continuous whenever possible to preserve statistical power.

Model Performance Assessment

Model performance will be evaluated using:

- Discrimination: Area under the Receiver Operating Characteristic curve (AUC)
- Calibration: Calibration plots and Hosmer–Lemeshow test
- Internal validation: Bootstrap resampling (≥ 1000 iterations)

If feasible, a nomogram may be derived from the final model.

Decision curve analysis may be performed to assess clinical utility.

5.1.2 Secondary Objectives

Real-World Therapeutic Trajectories

Treatment strategies before and after PSMA PET will be described descriptively.

Changes in treatment plan will be quantified using:

- Absolute and relative frequencies
- McNemar test for paired categorical comparison

Stage Migration Analysis

In patients who underwent both conventional imaging and PSMA PET:

- Agreement will be assessed using Cohen's kappa statistic
- Upstaging and downstaging rates will be calculated
- Treatment modifications triggered by PSMA PET will be quantified

Early Oncological Outcomes

Time-to-event outcomes will include:

- Overall survival (OS)
- Progression-free survival (PFS)

- Biochemical recurrence-free survival (BCRFS)

Time-to-event variables will be analysed using:

- Kaplan–Meier estimates
- Log-rank tests
- Cox proportional hazards regression (if appropriate)

Biochemical persistence after radical prostatectomy will be analysed as a binary outcome.

5.1.3 Exploratory Objectives

Exploratory analyses will include:

- interobserver agreement between local and central PSMA PET interpretation (Cohen’s kappa, Intraclass Correlation Coefficient),
- correlation between PSMA PET findings and final pathological stage in RP cohort,
- subgroup analysis of oligometastatic patients (1–5 lesions).

Exploratory analyses will be considered hypothesis-generating.

5.2 Bias and Confounding

Potential sources of bias include selection bias related to the tertiary-centre population, information bias inherent to retrospective data extraction, and heterogeneity across participating centres. To mitigate these risks, centralized PSMA PET image review will be performed to ensure consistency of staging, and multivariable modelling will be applied to adjust for potential confounders. In addition, centre effects may be explored in sensitivity analyses using fixed or random effects modelling where appropriate.

5.3 Sample Size and Power Calculations

A formal sample size calculation was not performed. Assuming a total sample size of approximately 400 patients and an estimated metastatic rate of 30%, this would yield roughly 120 metastatic events. Such a sample size is expected to allow the inclusion of approximately 10–12 predictor variables in a multivariable logistic regression model, in accordance with commonly accepted event-per-variable recommendations.

5.4 Strengths and Limitations

This study has several strengths, including its multicentre design, centralized imaging review to ensure consistency of PSMA PET interpretation, internal validation of the predictive model, and the integration of molecular imaging metrics with clinicopathological parameters.

However, limitations inherent to the retrospective design must be acknowledged, including potential heterogeneity across participating centres, variable duration of follow-up, and the possibility of residual confounding despite multivariable adjustment.

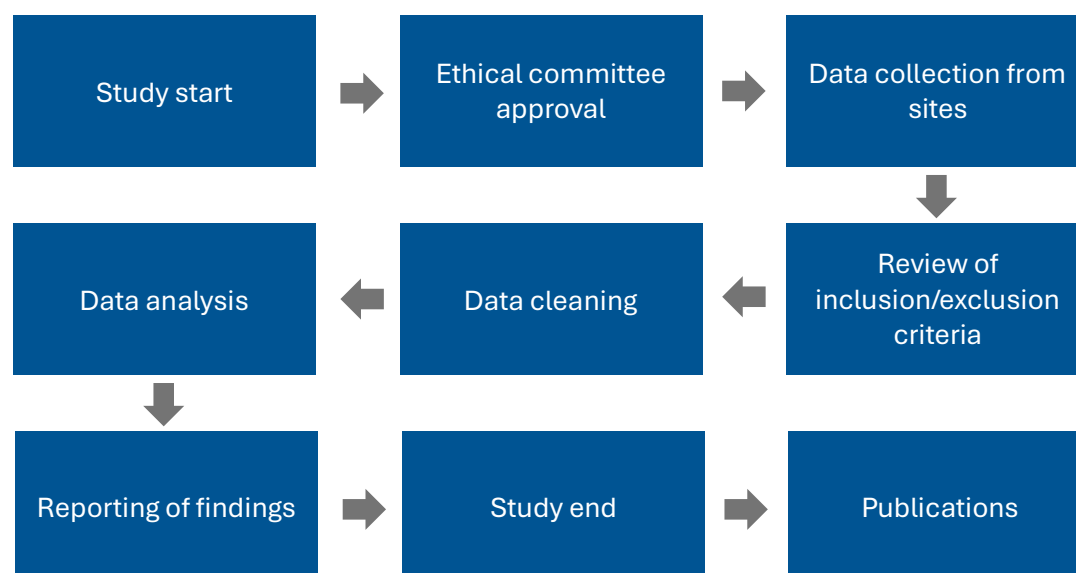
5.3 Interim Analyses

Not applicable due to retrospective design.

6. STUDY CONDUCT AND REGULATORY DETAILS

6.1 Study Conduct

6.1.1 Study Flow Chart and Plan



The study is designed as an observational retrospective study enrolling male patients diagnosed with high-risk prostate cancer who have undergone primary staging with PSMA PET within the study window.

6.1.2 Procedures

Data regarding patients, disease and treatments characteristics will be collected in the frame of the observational retrospective study. The detailed information about the diagnostics (patient and baseline PSA level, MRI results, prostate biopsy, other imaging), plan of therapy based on conventional imaging, treatment after PSMA PET and follow-up will be collected. Anonymized written PSMA PET result reports as well as anonymized PSMA PET images will be reviewed centrally in the lead institution and specific molecular parameters (miTNM, SUV_{max} , PSMA-TV, etc.) will be retrieved.

6.1.3 Quality Control

Quality control and assurance are integral to the integrity and credibility of the study findings. For this retrospective observational study, several mechanisms and procedures will be implemented to ensure the quality and integrity of the data collected and analysed.

Centralized data capture sheets and centralized review of PSMA PET imaging

Data will be collected from internal institutional medical records of urological and nuclear medicine departments across the Czech Republic designed to capture all relevant information in a consistent and structured manner ensuring that it captures the necessary data points for analysis. This will be done via:

- completion of centralized data capture sheets,
- centralized expert review of PSMA PET images.

Data Collection and Verification

Multiple personnel will be involved in the data collection and review process to ensure accuracy. Data will be extracted from electronic medical records (EMRs) and entered into the centralized data capture sheets by trained data abstractors. Diagnostic validity will be ensured by central re-evaluation of all anonymized PSMA PET imaging by experienced nuclear medicine physician(s) at a single lead institution.

Data Management Plan

A data management framework will be established at the coordinating centre. This framework will define procedures for data collection, pseudonymization, centralized integration, data cleaning, query resolution, and database lock prior to statistical analysis. Detailed operational procedures will be maintained internally at the coordinating institution.

Statistical Software and Programming Validation

Statistical programming will be conducted by a designated statistician. Analytical scripts and outputs will undergo internal review to ensure accuracy, consistency, and reproducibility of the analyses. All statistical analyses will be performed using SAS® software (version 9.4 or higher; SAS Institute Inc., Cary, NC, USA) for data analysis and R software (version 4.3.0 or higher; R Foundation for Statistical Computing, Vienna, Austria) for graphical outputs.

Data Flow

The flow of observational study data for CZECH-PSMA will be as follows:

- Data Entry: Data will be extracted from institutional medical records and entered into anonymized centralized data capture sheets (excel sheet) at each participating site.
- Training: Personnel responsible for data extraction will be trained on specific data point definitions and anonymization protocols to ensure consistency.
- Transfer and Central Review: Anonymized data sheets and PSMA PET imaging files will be securely transferred to the lead institution. All PSMA PET images will undergo a standardized central re-evaluation by experienced nuclear medicine physician(s), with findings recorded in a dedicated separate data sheet.

- Integration and Verification: Once local clinicopathological data and central review results are integrated, the dataset will be reviewed for accuracy and completeness.
- Database Lock: After final verification and editing, the database will be locked to prevent further changes prior to statistical analysis.
- Archiving: A copy of the final anonymized data sheets will be archived at the lead institution in accordance with regulatory requirements.

Training of Study Site Personnel

The principal investigator will ensure that appropriate training relevant to the observational study is given to investigational staff, and that any new information relevant to the performance of this observational study is forwarded to the staff involved.

Protection of Human Subjects

The observational study will be performed in accordance with ethical principles that are consistent with the Declaration of Helsinki, ICH GCPs, GPP and the applicable legislation on Non-Interventional Studies and/or Observational Studies. The Investigator will perform the observational study in accordance with the regulations and guidelines governing medical practice and ethics in the country.

6.1.4 Subject Informed Consent (Primary Data Collection Only)

Due to the retrospective nature of the study and the use of pseudonymized data collected during routine clinical practice, individual informed consent is not anticipated to be required. However, the final determination regarding the requirement for informed consent will be made by the respective institutional ethics committees at each participating centre.

6.1.5 Confidentiality of Study/Subject Data (Primary Data Collection Only)

All study data will be stored in a secure electronic database in compliance with the General Data Protection Regulation (GDPR; Regulation (EU) 2016/679) and Act No. 110/2019 Coll. on the Processing of Personal Data, as applicable in the Czech Republic. Patient data collected at participating sites will be pseudonymized prior to transfer to the coordinating centre. Each patient will be assigned a unique study identifier, and no directly identifiable personal information will be shared outside the originating site. Access to study data will be restricted to authorized study personnel, and appropriate technical and organizational safeguards will be implemented to prevent unauthorized access.

6.1.6 Storage and Retention

Pseudonymized study data will be securely stored at the coordinating centre using appropriate technical and organizational safeguards to prevent unauthorized access, alteration, or loss. Data transfer between participating sites and the coordinating centre will be conducted via secure, encrypted channels. Access to study data will be restricted to authorized study personnel only. Data storage and retention will comply with the General Data Protection Regulation (GDPR; Regulation (EU) 2016/679) and Act No. 110/2019 Coll. on the Processing of Personal Data. Study data will be retained for a period required by applicable national regulations and institutional policies, after which they will be securely destroyed. Study results will be disseminated through peer-reviewed publications and scientific presentations.

6.2 Collection and Reporting of Adverse Events

As this is a retrospective observational study without administration of investigational medicinal products, adverse event reporting is not applicable.

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APPENDICES

Not applicable.

ATTACHMENTS

Not applicable.

7. SIGNATURES