Radical Prostatectomy Without Prostate Biopsy Following 18F-PSMA-1007 PET/CT Based on USTC Diagnostic Model: A Single-center, Single-arm, Open-label Study

Clinical study protocol

Version number and date： V1.0/2022-11-10

Clinical research institution： Department of Urology, The First Affiliated Hospital of University of Science and Technology of China

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Protocol summary

Protocol name	Radical Prostatectomy Without Prostate Biopsy Following 18F-PSMA-1007 PET/CT Based on USTC Diagnostic Model: A Single-center, Single-arm, Open-label Study
version and date：	V1.0/2021-11-10
Organizer	Xiao Jun, Tao Tao
Study purpose	This trial takes pathological diagnosis as the gold standard to verify whether the positive predictive value of clinical predictive model combined with prostate-specific membrane antigen positron emission tomography/computed tomography (PSMA PET/CT) (we called "PSMA combined model") in the diagnosis of clinically significant prostate cancer (csPCa) reached the expected level. To evaluate the diagnostic accuracy based on PSMA combined model and the feasibility of performing biopsy-free radical prostatectomy.
Suitable patients	Patients with clinically suspected csPCa by PSMA combined model.
Study endpoints	**Primary endpoint** The detection rate of clinically significant prostate cancer (Gleason score≥3+4); (Positive predictive value of PSMA combined model for clinically significant prostate cancer); **Secondary endpoint** 1) The detection rate of any-grade prostate cancer (Gleason score≥ 3+3); (Positive predictive value of PSMA combined model for any-grade prostate cancer); 2) The detection rate of high-grade prostate cancer (Gleason score ≥

<table>
<tr><td></td><td>4+3). (Positive predictive value of PSMA combined model for high-grade prostate cancer).
Safety endpoint
In the study, the incidence of all adverse events (AEs), adverse reactions (ADRs), and severe adverse events (SAE) are mainly focused.</td></tr>
<tr><td>Study design</td><td>This trial adopts a prospective, single-center, single-arm, open-label study design. Taking pathological diagnosis as the gold standard, to verify whether the positive predictive value of PSMA combined model in the diagnosis of csPCa reached the expected level in patients with suspected PCa or have indication of prostate biopsy. To evaluate the diagnostic accuracy based on PSMA combined model and the feasibility of performing biopsy-free radical prostatectomy.
The PSMA combined model consists of a clinical predictive model based on what we previously report and 18F-PSMA-1007 PET/CT examinations in series. First, the clinical predictive model is used for diagnosis (available online address: https://ustcprostatecancerprediction.shinyapps.io/dynnomapp/). When the clinical predictive model indicated that the patients were csPCa (patient’s risk probability of csPCa ⩾ 0.60), 18F-PSMA-1007 PET/CT is used for further examination.
<table>
<tr><th>Clinical prediction model</th><th>18F-PSMA-1007 PET/CT examinations</th><th>Diagnostic results of PSMA combined model</th></tr>
<tr><td>+</td><td>+</td><td>+</td></tr>
<tr><td>+</td><td>-</td><td>-</td></tr>
<tr><td>-</td><td>Not perform</td><td>-</td></tr>
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For the patients with positive PSMA combined model results</td></tr>
</table>

	(diagnosed with csPCa), the professional clinicians will communicate the diagnosis and treatment plan with patients. Finally, according to the decisions of the patients and their families, we will perform the radical prostatectomy without prostate biopsy directly. The patients with negative PSMA combined model will be excluded of this study. In this study, we screen qualified patients using PSMA combined model. For the patients with positive PSMA combined model (diagnosed with csPCa) results, according to the decisions of the patients and their families, we will perform the radical prostatectomy without prostate biopsy directly or still the traditional prostate biopsy (eligible but not enrolled) and then choose the treatment method based on the biopsy results.
Expected population	Totally, fifty-seven positive patients diagnosed by PSMA combined with model are enrolled in this clinical trial.
Inclusion criteria	1) Male patients with clinically suspected prostate cancer (abnormal digital rectal examination or serum prostate-specific antigen (PSA)); 2) Finish the detection of serum PSA and multi-parameter magnetic resonance imaging (mpMRI); 3) 4 ng/ml≤serum PSA＜100 ng/ml； 4) Prediction threshold of csPCa evaluated by the model (online system) ≥0.60； 5) Finish 18F-PSMA-1007 PET/CT and present positive result; 6) Patients without contraindications of radical prostatectomy.
Exclusion criteria	1) Unable to perform PSA test or mpMRI examination; 2) Serum PSA＜4 ng/ml or ≥100 ng/ml;

	3) Prediction threshold of csPCa evaluated by the model (online system) ＜0.60; 4) Finish 18F-PSMA-1007 PET/CT but negative result; 5) Patients who have negative results in the previous prostate biopsy. 6) Patients refuse radical prostatectomy or still choose prostate biopsy.
Exit criteria	Early withdrawal from the study of the patients can be any of the following, but not limited to the following: 1) Patients requiring exit (withdrawal / revocation of informed consent); 2) If there are any clinical adverse events or changes in the physical condition of the patients, it is not in the best interests of the patients to continue to participate in the study; 3) Patients with poor compliance or unable to truthfully provide relevant information or violate the protocol; 4) Patients who died; 5) Other reasons for withdrawing from the study (need to be recorded in detail);
Statistical analysis	**Sample size estimation** This study is designed for a single group of objective performance criteria. With reference to the opinions of many senior clinical experts and statistical experts, it is considered that the clinically acceptable positive predictive value should not be less than 90%. According to the literature exploration and previous research results, it is expected that the positive predictive value of PSMA combined model is more than 98%. Suppose the significance level is 0.05 (bilateral) and the degree of

power is 80%. The required number of positive samples (positive results in PSMA combined model) is 55. Considering the drop rate of 5%, the study is expected to enroll 57 patients.

The negative samples are all the patients in the study who are negative in the PSMA combined model and should perform prostate biopsy.

Analysis set

1) Full analysis set (FAS): the set of patients determined according to the intention to treat, which refers to the data set of all patients who participated in this study.
2) Per protocol set (PPS): refers to the completed trial and excludes patients who seriously violate the scheme (patients violate the selection criteria or exclusion criteria, etc.).
3) Security data set (SS): all the patients who participated in this study and conducted at least once safety assessment constitute the security population of this study.

Primary endpoint analysis

The primary endpoint of this study is the positive predictive value of PSMA combined model for the diagnosis of csPCa. For the analysis of the primary endpoints, the results of both FAS and PPS will be taken into account. The positive predictive value of PSMA combined model for csPCa diagnosis and its 95% confidence interval (95%CI) will be recorded. When the lower limit of 95%CI is greater than the target value, it is considered that the detection rate of PSMA combined model is up to the standard, which can be used as a proof for a new clinical treatment scheme called biopsy-free radical prostatectomy.

Secondary endpoint analysis

	No target value is set for the secondary endpoint, and only the detection rate and 95%CI are calculated at the time of evaluation. **Safety endpoint analysis** The severity, quantity and incidence of AE, ADR and SAE and their correlation with overall trial, examination or operation and patients are statistically and descriptively analyzed.
Expected duration	12 months

1、Background

Prostate cancer (PCa) has the highest incidence of malignant tumor in male genitourinary system. According to the latest data, the number of new cases of prostate cancer in the United States will reach 216,900 in 2022, with 34,611 deaths, ranking first and second in terms of morbidity and mortality among men. In China, with the rapid development of the economy and the application of early diagnosis technologies, the incidence of prostate cancer is increasing year by year [1]. At the same time, the population structure is also changing, and the aging of the population is a serious challenge for the health care system in the next few decades of China. The incidence of prostate cancer is closely related to age, studies have shown that prostate cancer is extremely rare in men under 50 years of age, but more than 85% of prostate cancer patients are older than 60 years [2]. Therefore, the aging population will inevitably lead to the rapid growth of the number of patients with prostate cancer. In the face of the rapidly growing population of patients, early screening, early diagnosis, and timely treatment of prostate cancer are of great clinical significance to improve the course of disease, reduce the proportion of late patients and prolong the life span of patients [3].

Up to now, the main methods recommended by the guidelines for early diagnosis of

prostate cancer are digital rectal examination (DRE), serum prostate specific antigen (PSA) test, transrectal ultrasound, and multiparameter magnetic resonance imaging (mpMRI). Gene screening can also be performed for patients with family history [4]. Previous studies have shown that although DRE has a certain value in the diagnosis of early PCa, there are great differences among different operators, and the overall sensitivity and specificity are less than 60% [5]. Serum PSA has high sensitivity in the diagnosis of prostate cancer, but the increase of PSA is not specific for prostate cancer, especially in Chinese patients. At the same time, some derivative indexes of PSA, such as PSA density, PSA velocity, PSA double time and free / total PSA ratio, have also been proved to be valuable in the diagnosis of PCa, but more high-quality studies are needed before widespread clinical practice [6]. mpMRI has been widely used in clinical diagnosis of prostate cancer in recent years, and its diagnostic accuracy is significantly better than DRE and PSA. Through prostate imaging-reporting data system (PI-RADS), we can quantitatively evaluate the results of mpMRI, and finally make a diagnosis report. However, mpMRI has poor recognition of small lesions and inflammatory lesions, and a low positive predictive value for the diagnosis of PCa [7, 8]. In summary, current examination methods cannot make a clear diagnosis of PCa.

For patients with suspected PCa, all patients need to undergo prostate biopsy (PB) to confirm the final diagnosis eventually. Although PB is the gold standard for the diagnosis of PCa, it still has some shortcomings. Firstly, prostate biopsy may have some complications, such as urinary tract infection, intestinal bleeding, acute urinary retention and so on [9]. Secondly, prostate biopsy is a local anesthesia operation and costs a lot of money, which will bring certain psychological and economic burden to patients. In addition, after prostate biopsy, patients with definite PCa need to wait a period before surgical treatment, increasing the chance of cancer spread. Finally, patients with negative prostate biopsy cannot completely exclude the possibility of PCa, and if reexaminations still indicate the possibility of PCa, repeated PB is inevitable [10].

In view of the above, we put forward a tentative idea: is there a better diagnostic method for accurate diagnosis of prostate cancer, so that patients do not have to undergo prostate biopsy before surgery? That is, the possibility of radical prostatectomy without prostate biopsy.

To solve this problem, with the support and sponsorship of the key research and development project of Anhui Province (202004J07020022), we retrospectively analyzed the data of 701 patients who underwent prostate biopsy in our hospital from January 2018 to July 2022. A clinical predictive model based on prostate specific antigen density (PSAD) and PI-RADS score is constructed. We find that the combination of PSAD and PI-RADS can significantly improve the diagnostic accuracy of prostate cancer, and the AUC value of diagnostic ROC curve was 0.942 (95%CI: 0.926-0.958). At the same time, in order to avoid the regional differences of the conclusions, we also collect the data of two hospitals from Shanghai city and Nanjing city, and make an external verification of the diagnostic model, and the results also confirmed the reliability of the model [11]. In addition, in order to achieve the purpose of biopsy-free radical prostatectomy, we do further research on the model. We made further updates to the model and an online dynamic system was created. When the cutoff value of the risk threshold by the model is set at 0.60, the specificities and positive predictive values of the model for csPCa are greater than 90% and 80%, respectively. In order to truly achieve biopsy-free radical prostatectomy, we also want to further improve the accuracy of diagnosis and try our best to avoid irreparable damage to patients due to false positive results.

Prostate specific membrane antigen (PSMA) is a transmembrane glycoprotein specifically expressed on the cell membrane of prostate cancer, and its expression is much higher than that of normal prostate cells [12]. Recent studies have shown that the application of small molecular 68Ga and 18F labeled PSMA PET/CT has a good diagnostic ability for prostate cancer. Foreign studies have shown that for patients with

clinically suspected prostate cancer, on the basis of mpMRI, PSMA PET/CT can significantly improve the detection rate of clinically significant prostate cancer [13]. If 'PI-RADS score≥4 and SUMmax≥9.5' was used as the diagnostic criteria for prostate cancer, the specificity and true positive rate was 100% [14]. In addition, Meissner V. H. et al performed biopsy-free radical prostatectomy for 25 patients who met the criteria. Postoperative pathology proves that the positive predictive value of csPCa was 100%. All patients receive radical treatment without prostate biopsy [15]. However, only a single cohort retrospective description is made in this study. So we hope that through the research of our center, we can build a systematic and China-specific prostate cancer diagnosis model and provide a strategy for radical prostatectomy without prior prostate biopsy, so as to improve the efficiency of patients and reduce the waste of medical resources, avoid unnecessary prostate biopsy.

2、Overall design

（1）Study design

1). Study purpose

This trial takes pathological diagnosis as the gold standard to verify whether the positive predictive value of clinical predictive model combined with PSMA PET/CT (we called "PSMA combined model") in the diagnosis of csPCa reached the expected level. To evaluate the diagnostic accuracy based on PSMA combined model and the feasibility of performing biopsy-free radical prostatectomy.

2). Study content

This trial adopts a prospective, single-center, single-arm, open-label study design. Taking pathological diagnosis as the gold standard. To verified whether the positive predictive value of PSMA combined model in the diagnosis of csPCa can reached the expected level in suspected patients who have the indications of prostate biopsy, so as to evaluate the diagnostic accuracy based on PSMA combined model and the feasibility of performing biopsy-free radical prostatectomy.

The PSMA combined model consists of the updated clinical predictive model based on what we previously report and 18F-PSMA-1007 PET/CT examinations in series. First, the clinical predictive model is used for diagnosis (available online address: https://ustcprostatecancerprediction.shinyapps.io/dynnomapp/). When the clinical predictive model indicated that the patients were csPCa (patient’s risk probability of csPCa ≥ 0.60), 18F-PSMA-1007 PET/CT is used for further examination.

Clinical prediction model	PSMA/PET-CT examination	Diagnostic results of PSMA combined model
+	+	+
+	-	-
-	Not perform	-

For the patients with positive PSMA combined model results (diagnosed with csPCa), the professional clinicians will communicate the diagnosis and treatment plan with patients. Finally, according to the decisions of the patients and their families, we will perform the radical prostatectomy without prostate biopsy directly or still the traditional prostate biopsy (eligible but not enrolled) and then choose the treatment method based on the biopsy results. The patients with negative PSMA combined model will be excluded of this study. The finally diagnosis will be recorded according to the repeated prostate biopsy.

3). Selection of study methods

The purpose of the PSMA combined model constructed in this study is to correctly diagnose csPCa patients and provide diagnostic support for biopsy-free radical prostatectomy and this is the first clinical trial in the world to design a strategy for radical prostatectomy without prior prostate biopsy. In order to evaluate its effectiveness and safety, after consulting clinical and statistical experts, we chose pathological examination as the gold standard and adopt a single group of objective

performance criteria for verification. Considering the small number of hospitals that have the conditions to carry out 18F-PSMA-1007 PET/CT in China, this clinical trial is designed by an open-label, single-centre, single-arm method.

4). Measures to reduce and avoid bias

4.1) Centralized film reading

Centralized film reading can reduce the risk of different researchers' subjective judgment of the films, and ensure that all reading results follow the diagnostic criteria of film reading stipulated in this trial.

4.2) Prospective study

The research objects and methods are selected before the study, the relevant influencing factors are included in the statistical scope, the trial quality is strictly controlled during the study, and all cases in accordance with the design method are included in the statistics at the end of the study. In this way, better quality and more reliable clinical data can be obtained, and the bias in case selection and data processing that may be caused by retrospective study can be avoided.

4.3) The training of researchers

Before the start of the clinical trial, the person in charge of the trial center trains the researchers participating in the clinical trial, so that the researchers can understand and be familiar with the whole trial process and related operations.

4.4) Standard implementation of including and excluding standards

The patients are screened according to the inclusion and exclusion criteria of the trial scheme to reduce the selective bias.

4.5) Monitoring of clinical trials

Key researchers formulate monitoring plans and appoint independent inspectors to conduct regular on-site monitoring visits to experimental hospitals to ensure that all contents of the research program are strictly observed, and regularly check the database to ensure consistency with the contents of the original materials.

4.6) Blind evaluation

The centralized film reading is blinded, and the image is blinded by the statisticians to prevent the central film reviewers from knowing the subject's disease diagnosis, subject number and other information which can cause bias.

5）. Patients selection criteria

5.1） Inclusion criteria

1) Male patients with clinically suspected prostate cancer (abnormal digital rectal examination or serum PSA);
2) Finish the detection of serum PSA and multi-parameter magnetic resonance imaging (mpMRI);
3) 4 ng/ml≤serum PSA＜100 ng/ml；
4) Prediction threshold of csPCa evaluated by the model (online system) ≥ 0.60；
5) Finish 18F-PSMA-1007 PET/CT and present positive result;
6) Patients without contraindications of radical prostatectomy.

5.2） Exclusion criteria

1) Unable to perform PSA test or mpMRI examination;
2) Serum PSA＜4 ng/ml or ≥100 ng/ml;
3) Prediction threshold of csPCa evaluated by the model (online system) ＜ 0.60;
4) Finish 18F-PSMA-1007 PET/CT but negative result;
5) Patients who have negative results in the previous prostate biopsy.
6) Patients refuse radical prostatectomy or still choose prostate biopsy.

6). Effectiveness evaluation

6.1) Definition

1) True positive：The diagnosis results of PSMA combined model and pathological examination are both csPCa.

2) False positive：The diagnosis result of PSMA combined with model is csPCa, while the pathological examination is not.

6.2）Main effectiveness index

Positive predictive value

Definition：The patients with positive results of PSMA combined model and pathological examination accounted for the proportion of all patients with positive results of PSMA combined model.

Calculation method：Positive predictive value= $\frac{\text{true positive}}{\text{true positive+false positive}} \times 100\%$

6.3）Secondary effectiveness index

1) Misdiagnosis rate

Definition：The patients with positive results of PSMA combined model and negative results of pathological examination accounted for all patients with positive results of PSMA combined model.

Calculation method：Misdiagnosis rate= $\frac{\text{false positive}}{\text{true negative+false positive}} \times 100\%$

7. Safety evaluation

The severity, quantity and incidence of AE, ADR, and SAE and their correlation with overall trial, examination or operation and individual patients are statistically and descriptively analyzed.

(2) Study flow

1). Study flow chart

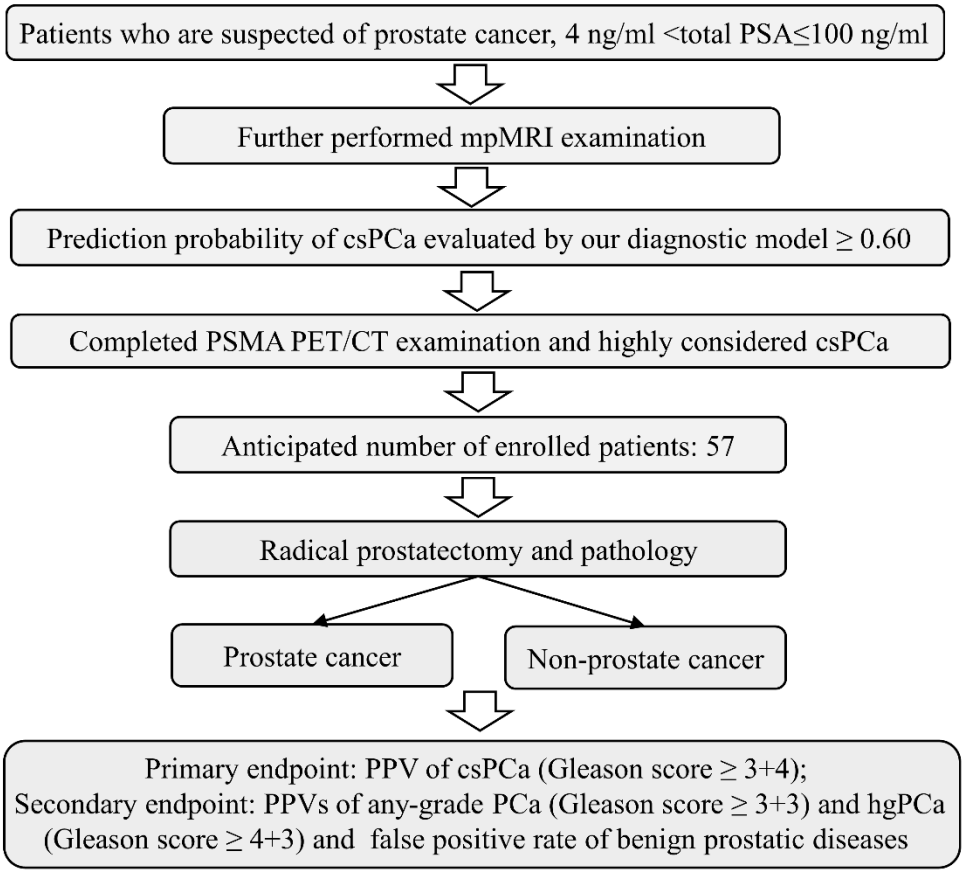

Table 1 The schedule of the screening period, perioperative period, and evaluation period for this trial.

Items	Screening period（-7~0 days）	Perioperative period of radical prostatectomy (1-14 days)	Evaluation period
Demographic data	▲		
Signs and symptoms	▲		
Completed the blood test[a] and mpMRI examination	▲		
Evaluation by the online diagnostic model	▲		
Signing of informed consent forms	▲		
^{18}F-PSMA-1007 PET/CT examination[b]	▲		
Enrollment	▲		
Radical prostatectomy[c]		▲	

Reading of pathological slices			▲
Follow up and adverse events	▲	▲	▲

[a] Prostate cancer marker test (Serum total PSA).

[b] The researchers decide whether an ^{18}F-PSMA-1007 PET/CT examination is performed based on the results of the risk probability by online diagnostic model evaluation.

[c] The researchers decide whether the radical prostatectomy is performed based on the decisions of the patients and their relatives. Full preoperative communication is needed.

mpMRI, multi-parameter magnetic resonance imaging; ^{18}F-PSMA-1007 PET/CT, ^{18}F-prostate-specific membrane antigen-1007 positron emission tomography/computed tomography; PSA, prostate specific antigen.

2). Screening period（-7~0 day）

The following process will be completed during the screening period：

- Allocation of patient's number;
- Collection of demographic information (age, place of origin, height, weight, and healthy condition, etc.);
- Collection of medical history information (allergic history, medical history, surgical history, family history of disease);
- Acquisition of signs and symptoms;
- Blood test of PSA and mpMRI examination;
- 18F-PSMA-1007 PET/CT examination;
- Acquisition the risk probability of csPCa by online dynamic nomogram;
- Review of inclusion / exclusion criteria
- Obtain the indication radical prostatectomy

The risk of csPCa is assessed by clinical predictive model (an online system). The prostate volume is calculated according to the maximum anteroposterior diameter, transverse diameter, and longitudinal diameter of prostate from mpMRI images. PSAD is the ratio of serum total PSA to prostate volume. The result of prostate mpMRI is quantified by PI-RADS (version 2.1). The range of scores is 1-5. The online dynamic nomogram is used to quantitatively evaluate the risk probability of patients, and the patients whose risk threshold reach 0.60 are defined as the positive patients of the

diagnostic model, and the 18F-PSMA-1007 PET/CT examination will be further completed and evaluated.

3). Perioperative period of radical prostatectomy（**1~14 day**）

The following procedures will be completed during the perioperative period of radical prostatectomy：

- Enrollment of patients;
- Signing of informed consent forms;
- Radical prostatectomy and get prostate specimen;
- AEs records

4). Evaluation period

4.1) Evaluation of the diagnostic results of PSMA combined model

Patients with risk probability ≥0.60 after assessing by the online dynamic nomogram. Meanwhile, further 18F-PSMA-1007 PET/CT examination also indicate the diagnosis of csPCa, that is, the patients have positive results by PSMA combined with model.

4.2) Reading of pathological slices

We set up blindness for reading of pathological slices. Three senior pathological physicians are randomly selected to form slices reading group as evaluators. The statisticians blind the pathological specimens, and the reading group interprets and analyzes the pathological specimens subsequently. Finally, a consensus is obtained.

The qualification requirements for senior pathologists are as follows：

1）A tertiary hospital doctor with GCP qualification；

2）Clinicians with 5 or more years of experience in reading pathological images of prostate cancer；

3）Do not participate in the screening process of patients.

3、Statistical analysis

（1）Statistical design, methods, and analysis

1). Sample size

This study is designed for a single group of objective performance criteria. With reference to the opinions of many senior clinical experts and statistical experts, it is considered that the clinically acceptable positive predictive value should not be less than 90%. According to the literature exploration and previous research results, it is expected that the positive predictive value of PSMA combined model is more than 98%. Suppose the significance level is 0.05 (bilateral) and the degree of power is 80%. The required number of positive samples (positive results in PSMA combined model) is 55. Considering the drop rate of 5%, the study is expected to enroll 57 patients.

2). Statistical analysis set

1) Full analysis set (FAS): the set of patients determined according to the intention to treat, which refers to the data set of all patients who participated in this study.

2) Per protocol set (PPS): refers to the completed trial and excludes patients who seriously violate the scheme (patients violate the selection criteria or exclusion criteria, etc.).

3) Security data set (SS): all the patients who participated in this study and conducted at least once safety assessment constitute the security population of this study.

3). Principle of statistical analysis

1）IBM SPSS (version 25.0) statistical software is used for statistical analysis.

2）All statistical tests use two-sided tests, and a P value of less than 0.05 will be considered to be statistically significant normally.

3）Description statistics: the measurement of continuous variables is described by means, standard deviation, and median, interquartile range; categorical variables are described by number and proportion (%).

4）The comparison of the two groups of variables will be analyzed by appropriate methods according to the type of variables. T-test or Wilcoxon rank sum test is used to compare measurement indexes between groups. χ^2 test or Fisher exact test is used to compare categorical variables between groups.

4). Group completion status

The selection and completion of the cases are described respectively, and the corresponding statistical analysis of the population is summarized and listed by the enrollment, drop, elimination, completed cases, and the number of cases of each analysis set.

5). Equilibrium analysis of baseline data

Baseline analysis based on full data set（FAS）

The number of patients enrolled in the group, the number of completions, and the total drop rate are described respectively, and the list of excluded cases and the detailed list of unfinished reasons are listed. The baseline features of the patients are statistically described.

6). Evaluation indexes

The analysis of effectiveness indexes is based on the full analysis set (FAS) and the per-protocol set (PPS) and is described in the table below.

Table 2 Statistical analysis of main indicators [f]

		Results of pathological diagnosis		
		positive	negative	total
PSMA combined model	positive	A	B	A+B
	negative	C	D	C+D
	total	A+C	B+D	N=A+B+C+D

Positive predictive value (true positive rate)= A/(A+B) ×100%;
Misdiagnosis rate=B/(A+B) ×100%.

6.1) Main effectiveness indexes

The most important effectiveness index of this study is the positive predictive value (true positive rate) of PSMA combined model, which is the proportion of the positive results of postoperative pathological diagnosis to all enrolled patients. For the analysis of the primary endpoint, the results of both FAS and PPS will be considered. The positive predictive value of PSMA combined model for csPCa diagnosis and its 95%

CI will be calculated, when the lower limit of 95%CI is greater than the set target value, it is considered that the detection rate of PSMA combined model is up to the standard, which can be used as a proof for a new clinical treatment scheme called biopsy-free radical prostatectomy.

6.2) Secondary effectiveness evaluation index

The secondary endpoint of the study is the detection rate of any-grade PCa (Gleason score ≥3+3) and high grade PCa (hgPCa) (Gleason score ≥4+3) by PSMA combined model, the positive predictive value and misdiagnosis rate of any-grade PCa and hgPCa will be assessed.

Notably, no target value is set for the secondary endpoint indexes, and only the point estimated value and 95% CI are calculated at the time of evaluation.

Safety endpoint analysis

6.3) Safety evaluation

The severity, quantity and incidence of AE, ADR and SAE and their correlation with overall trial, examination or operation and patients are statistically and descriptively analyzed. In addition to the above statistical methods, detailed and additional exploratory analysis may be required and confirmed in the Statistical Analysis Program (SAP).

3、Data management

（1）Raw data verification

The inspector certifies that every piece of information in the analytical data set corresponds to the original record. The project leader will receive a challenge in the form of an electronic challenge form if there are any errors or omissions, and the person he or she designates will examine the original data piece by piece against the query list and rectify it. By doing this, it is made sure that the data in the database and the original record table are identical.

（2）Questioning management

The data management unit follows standard operating procedures to review the data recorded in the database to ensure data quality. For any queries in the data, the data management staff will send a query to the project leader in the form of an electronic query form and ask the person designated by the project leader to respond to the query and make some necessary changes to the data. All data changes and related operations need to be recorded with traces.

（3）Database locking and exporting

The data manager writes the data review report based on the trial protocol, database, and the requirements of the sponsor. The data review meeting is attended by the principal investigator, statistician, and data administrator to review the data, and the representatives of all parties attending the meeting sign the review resolution. After all parties approve the locking of data, the data administrator organizes the execution of data locking and submits the locked data to the statistical analyst, who performs the statistical analysis as required by the statistical analysis plan. After completing the statistical analysis, the statistical analysts will write the statistical analysis report. The locked data cannot be edited again, and the problems found after data locking can be corrected in the statistical analysis program after confirmation. If there is definite evidence that unlocking is necessary after data locking, the researcher and the sponsor need to sign relevant documents.

4、Feasibility analysis

（1）Analysis of the possibility of success

The research of this project will rely on The First Affiliated Hospital of University of Science and Technology of China, which is the largest clinical medical center in Anhui Province. The Department of Urology, where the applicant is located, is the main committee designates of the Urology Branch of the Anhui Medical Association and the Genitourinary Tumor Branch of the Anhui Anti-Cancer Society, with strong clinical and scientific research strength. Before the implementation of this project, the subject group has made sufficient preparation, and the patient enrollment conditions are all based on the theoretical foundation of big data analysis, which is solid and reliable. The reduction

of prostate biopsy for patients reduces the pain and burden during the visit, and patient compliance is high. Therefore, this project has a great possibility of success.

（2）Analysis of the possibility of failure

The project is fully prepared, well-staffed, solid theoretical basis, and the possibility of failure is extremely low.

5、Adverse event

（1）Definition

1）Adverse Event (AE）： It refers to adverse medical events that occur during a clinical trial, whether or not it is related to the trial.

2）Serious Adverse Event (SAE）： It refers to events that lead to death or serious deterioration of health in the course of clinical trials, including fatal diseases or injuries, permanent defects in body structure or function, the need for hospitalization or extension of hospitalization, and the need for medical or surgical intervention to avoid permanent defects in body structure or function.

（2）Classification of adverse event degree

1）I： Any deviation from the normal postoperative course that does not require medication or surgical, endoscopic and radiation intervention, the main treatment options are antiemetic, antipyretic, analgesic, diuretics and electrolytes, as well as physiotherapy.

Mainly including Acute urinary retention, Fever, Infection, Dislodged catheter requiring replacement, Inadvertent cystotomy, Anastomotic leak, Rectus hematoma, ulnar neuropathy, Chronic abdomen pain, Genital femoral nerve irritation, Seroma, Vasovagal syncope, Clot retention, Urinary leakage, Subcutaneous emphysema, Drug reaction, Infected pelvic hematoma, Obturator neuropathy.

2）II： It needs to be treated with drugs and may be complicated with grade I complications.

Mainly including Blood transfusion, Cardiovascular complications, Ileus, Calf myositis, Obturator nerve palsy, Deep-vein thrombosis, Bladder neck contracture, Pelvic hematoma, Blood loss, Postoperative bleeding, Neuropraxia, Lymphorrhagia, Nerve damage/injury, Intra-abdominal drain retraction, Lymph leakage,

Gastrointestinal symptoms, Delirium, Hemorrhage/hematoma, Postoperative neuropathy.

3）III： Surgical complications that require surgical, endoscopic or radiotherapy intervention.

IIIa (No need for general anesthesia)： Lymphocele, Abdominal abscess, Prolonged urinary leakage, Ureter wound.

III b (Need for general anesthesia)：Rectal injury/lesion, Bladder neck contracture, Epigastric artery/vessel injury, Hydroureteronephrosis, Postoperative hydrocele, Ureteral injury, Surgical reintervention, Bowel injury, Hematoma leading to contracture, Hematuria, Meatal stricture, Wound dehiscence, Surgical re-exploration, Colon lesion, Bladder injury, Inferior epigastric injury, Revision, Ureteric obstruction, Hernia, ureter entrapment, Anastomotic stricture, Dehiscence/rupture of wound, Bladder neck sclerosis, Blood vessel damage, Wound hernia.

IV： Life-threatening complications (including central nervous system complications) *

IV a：(Single organ dysfunction requires IC/ICU management, including dialysis)：Pulmonary embolism, Myocardial infarction, Re-exploration due to bleeding, Cerebral vascular accident, Acute tubular necrosis, Renal failure, Stroke, Embolic stroke, Cardiovascular including arrhythmias and myocardial infarction, Respiratory insufficiency, Renal insufficiency

IV b： Multiple organ failure

V： Patients died, mainly including fatal cardiac arrest, cerebrovascular accident death, and pulmonary embolism death.

（3）Adverse event handling

Once an adverse event occurs, the researcher should ensure that the patients are provided with adequate and timely treatment. All adverse events / serious adverse events must be followed up until one of the following events occurs:

1）Event mitigation

2）Event stability

3）If a baseline value is acceptable, the event returns to the baseline level

4）It is impossible to obtain other information (patients or people who take care of their health refuse to provide other information to prove patients who have lost follow-up after follow-up efforts).

（4）Reporting procedures and contact person information

1). Reporting procedures

For all adverse events that occur during the clinical trial, the researcher shall record and analyze the causes of the event, form a written analysis report, put forward opinions on the continuation, suspension, or termination of the trial, and submit it to the Ethics Committee for review.

In case of serious adverse events, the researcher should immediately take appropriate treatment measures for the patients and report to the clinical trial management department in writing. For deaths, clinical trial institutions and researchers should provide the ethics committee with all the information needed.

For serious adverse events, the main researcher should report to the competent department of health at the same level within 5 working days after being informed, and promptly notify the ethics committee of the clinical trial institution.

2). Contact person information

Dr. Wang, Telephone number：15840256553

6、Quality control of clinical trials

（1）Monitoring of clinical trials

In the course of clinical trials, inspectors will regularly visit the research center according to the monitoring plan to ensure that all contents of the research program are strictly followed, and check the original data to ensure that the contents of EDC are true, complete, and correct.

（2）Filling in the case report form

Authorized users input data to ensure that the original data is consistent with EDC data.

（3）Preservation of original materials

The original materials of this trial, including signed informed consent forms, relevant laboratory inspection reports, medical records, and other related records,

should be kept in the national drug clinical trial institutions of the hospitals where the research centers are located. All raw data and printed CRF should be preserved until 10 years after the end of the clinical trial.

7、Ethical issues and informed consent in clinical trials

（1）Ethical considerations

Clinical research will follow the relevant provisions of the Helsinki Declaration of the World Medical Congress. Prior to the commencement of the study, the study shall be approved by the Ethics Committee before it can be implemented. Before each subject enrolls in this study, the researcher has the responsibility to fully and comprehensively introduce the purpose, procedure, and possible risks of the study to the subject or his agent, and to sign a written informed consent form. The patients should know that they have the right to withdraw from the study at any time, and the informed consent should be kept as a clinical research document for reference. In the course of the study, the patient's personal privacy and data confidentiality will be protected.

（2）Examination and approval of the trial scheme

The approval of the clinical trial program is carried out by the ethics committee, and the clinical trial can only be carried out after the final ethical approval has been obtained.

（3）Informed consent process and informed consent form text

Before being enrolled in this study, the researcher must explain the details of the clinical trial to the subject or his guardian, including the trial content, trial purpose, expected efficacy, possible adverse events, and countermeasures. Only after the patients fully understand the experiment and sign the informed consent form can they be selected.

Incapacitated patients can also enter clinical trials if the ethics committee agrees in principle and the researchers believe that it is in their own interest to participate in clinical trials, but their guardians should sign and date them before the trial. Patients

with acute ischemic stroke may not be in a coma clinically, but their cognitive ability and hand function are affected. Such patients should be signed and dated by their guardians before the trial.

When the subject or his guardian is unable to read, there shall be a witness present in the informed process. After a detailed explanation of the informed consent form, the witness reading the informed consent form is consistent with the oral informed content. With the oral consent of the subject or his guardian, the witness shall sign and date the informed consent form, and the signature of the witness shall be on the same day as that of the researcher.

8、Deviation of the clinical trial scheme and provisions for revision of the clinical trial scheme

Before the beginning of clinical verification, the trial scheme is finalized and signed by various researchers after joint discussion and revision, and submitted to the Ethics Committee for approval before implementation.

If there are problems in the actual implementation of the clinical verification, the scheme needs to be revised, and it should be proposed to the implementer that, after multi-center consultation and discussion, the responsible unit shall revise the scheme, submit it in writing to the implementer and each participating research unit for signature and approval, and then submit it to the ethics committee for approval.

In the course of the clinical trial, if the existing clinical trial center fails to pass the examination and approval of the clinical trial management department or the ethics committee, which leads to the trial progress being significantly lower than the expected plan, the organizer shall make adjustments to the participating center (abandon selection or increase) after full communication with the coordinating researcher, but can only update the list of clinical trial institutions in the attachment without amending the text of the plan. The final list of participating clinical trial centers should be

submitted to the clinical trial management departments and ethics committees of all participating units for the record.

If important and new information relating to the experimental group is discovered, the informed consent form must be submitted to the Ethics Committee for approval and the consent of the patients must be obtained again.

If the trial deviates from the trial plan, the researcher must inform the ethics committee in a timely manner.

9、Direct access to source data and files

In this clinical study, the main researchers and their authorized researchers can access and generate outpatient medical records, patients' informed consent (ICF), EDC, and original medical records in the HIS system.

Laboratory inspectors and researchers can access and produce their own report forms of test results.

Data managers can access and generate data management data; statistical analysts can access and generate statistical analysis data.

The access and editing rights of the rest of the source data shall be specified in detail by the SOP of the corresponding departments in accordance with the requirements of the relevant laws, regulations, and technical specifications of China.

10、Finance and Insurance

The key researchers will make a written agreement and submit it to the relevant departments of their clinical research institutions for review, which will specify in detail the financial situation and payment method of this clinical trial. For details, please see the agreement signed.

11、Content covered by the clinical trial report

The main researchers organize statistical professionals to complete the statistical analysis report and complete the clinical trial summary report according to the contents

of the statistical analysis report. The statistical analysis report should at least include the general situation of clinical trials, clinical general data, safety and effectiveness data sets, the incidence and treatment of adverse events, and the description of program deviation, together with the original cases of the patients.

The clinical trial report should be consistent with the clinical trial scheme, and the contents should include:

（1）General information;

（2）Abstract;

（3）Introduction;

（4）Clinical trial purpose;

（5）Clinical trial method;

（6）Clinical trial content;

（7）General clinical information;

（8）Control diagnosis and treatment methods;

（9）Statistical analysis methods and evaluation methods;

（10）Clinical evaluation criteria;

（11）Organizational structure of clinical trial;

（12）Ethical explanation;

（13）Clinical trial results;

（14）Adverse events found in clinical trials and their management;

（15）Analysis and discussion of clinical trial results, especially indications, scope of application, contraindications and matters needing attention;

（16）Conclusion of clinical trial;

（17）Existing problems and suggestions for improvement;

（18）List of trial personnel;

（19）Other circumstances to be explained;

12、Principle of confidentiality

This agreement and the contents of this clinical trial and all ancillary materials are confidential and belong exclusively to the team of researchers, and all researchers participating in the project shall be held confidential. The patent application, research process, and unpublished data shall not be disclosed to any third party except with the consent of the research team. This obligation of confidentiality shall remain valid after the termination of this trial.

13、Responsibilities of the researcher

（1） Provide hospital supervision department with the trial scheme, EDC, informed consent form, etc;

（2） Pre-trial training for clinical trial researchers;

（3） Bear the costs related to the trial;

（4） Before suspending the clinical trial, the major researcher shall notify the medical institution and the ethics committee and explain the reasons;

（5） Promptly study serious adverse events, take necessary measures to ensure the safety and interests of the patients, and report them in a timely manner;

（1） Personnel and facilities can conduct clinical trials safely and effectively;

（2） Clinical trials always have an appropriate number of patients;

（3） Acquisition of informed consent form;

（4） In accordance with national regulations, the case record table should be recorded in time, and its data should be consistent with the recorded data of the object;

（5） Records of patients withdrawing, disobeying doctor's orders and any termination of clinical trials;

（6） Responsible for the correctness, clarity and reliability of the report;

Investigator statement

I agree：

1. This clinical trial is conducted in strict accordance with the Helsinki Declaration, China's current regulations, and the requirements of the trial program.

2. This clinical trial ensures the authenticity, validity, and integrity of EDC data, and completes the electronic data signature on time.

3. In the course of clinical trials, complete and accurate records are recorded and records are kept.

4. This clinical trial allows inspectors, verifiers, and regulatory authorities authorized or dispatched by key researchers to monitor, verify and examine the clinical trial.

5. The terms of the clinical trial contract/agreement signed by the parties will be strictly enforced;

I have read all the clinical trial plans, including the above statement, and I agree with all of the above.

Researcher's opinion Signature： Date:

14、Research risk/benefit assessment

（1）Benefit

The patients of this study are clinically suspected to be PCa patients with prostate cancer biopsy indications. We will take a small number of tissue, blood, and prostatic fluid samples from the patients for diagnostic verification or further research. The samples mainly come from the remaining samples in the process of clinical diagnosis and treatment of patients, which will not affect the normal diagnosis and treatment of patients. The acquisition of clinical data and the collection and preservation of samples will not increase the additional pain or health impact on patients.

Patients with low and medium risk of PCa assessed by PSAD+PI-RADS score clinical diagnostic model cannot benefit directly from this study. However, the clinical information and samples provided by patients will help to verify the accuracy and clinical application of the clinical diagnostic model of PSAD+PI-RADS score, so as to obtain a more effective method of PCa diagnosis, which is the common interest of all PCa-related patients.

For patients with a high risk of PCa assessed by the PSAD+PI-RADS score clinical diagnostic model for radical prostatectomy without prostate biopsy, the benefits include: ①to avoid complications of prostate biopsy; ②to avoid the economic burden caused by prostate biopsy and the psychological and physical burden caused by prostate biopsy; ③to avoid the possibility of tumor spread after prostate biopsy; ④to avoid the possibility of repeated prostate biopsy; ⑤to avoid the risk of developing PCa in the future.

（2）Risk

The main risk in this study is the risk of performing biopsy-free radical prostatectomy. It is possible that the clinical diagnostic model of PSAD+PI-RADS score is evaluated as high risk and PSMA/PET-CT examination is positive, but the postoperative pathology indicates the possibility of non-malignant tumor, which

indicates that the prostate organ without tumor will be removed.

（3）Risk/benefit assessment

For patients undergoing biopsy-free radical prostatectomy, the doctor will fully inform the patients and their families of the relevant information and risks before the operation. The postoperative pathology of the patient suggests that it is a malignant tumor, and the patient effectively avoids the related risks caused by prostate biopsy. The postoperative pathology suggests that the patient is non-malignant, and the patients with high risk evaluated by PSAD+PI-RADS score clinical diagnostic model and positive PSMA/PET-CT examination are still at high risk of prostate cancer, and they have a great risk of developing prostate cancer, which required regular follow-up and even repeated prostate biopsy, and finally could not avoid the treatment of radical surgery, which is a great burden and injury to the patients themselves. Biopsy-free radical prostatectomy can effectively reduce the risk of prostate cancer in high-risk groups, decrease the physical and psychological burden of patients, and the benefits outweigh the risk. In addition, the construction of a prostate cancer diagnosis model suitable for the Chinese population can be beneficial to early screening, early diagnosis, and early treatment of prostate cancer, reduce the proportion of patients with advanced prostate cancer, improve the survival rate of patients, and reduce the consumption of medical resources and unnecessary prostate biopsies.

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Annex I. List of researchers

List of researchers

Name	Department	Degree	Professional title	Participated in GCP	Division of responsibilities
Xiao jun	Department of urology	**Doctor**	Chief physician	Yes	Project leader
Tao tao	Department of urology	**Doctor**	Chief physician	Yes	Project planning, surgery
Wang changming	Department of urology	**Master**	Doctoral candidate	No	Data analysis

Shen deyun	Department of urology	**Master**	Doctoral candidate	No	Patient screening and communication
Zhang bin	Department of urology	**Bachelor**	Master degree candidate	No	Data collection, collation
Wu baorui	Department of urology	**Bachelor**	Master degree candidate	No	Data collection, collation

Annex II. Annual implementation plan

December 2022-August 2023: Fifty-seven patients who met the requirement of radical prostatectomy without prostate biopsy are enrolled in the group. The basic personal and clinical information of the patients are recorded in detail.

September 2023-December 2023: We will collate all data, statistical analysis, article writing and contribution.