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Clinical Development of PSMA-Targeted Imaging and Radioligand Therapies in Cancer: A ClinicalTrials.gov-Based Analysis of Completed Studies

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ABSTRACT: Background: Prostate-specific membrane antigen (PSMA) has emerged as one of the most important molecular targets in oncology, enabling both highly sensitive diagnostic imaging and targeted radioligand therapy. Over the past decade, PSMA-directed agents have transformed the management of prostate cancer and are increasingly being explored in other malignancies.

Objective: To characterize completed clinical trials investigating PSMA-targeted imaging and therapeutic interventions registered on ClinicalTrials.gov, with emphasis on study design, clinical phases, enrolment characteristics, disease indications, and therapeutic strategies.

Methods: A registry-based cross-sectional analysis was conducted using ClinicalTrials.gov. The search term “PSMA” was applied with the filter “Completed Studies.” Data were retrieved on study title, condition, intervention, phase, enrolment, study design, study type, and primary outcomes. Descriptive analyses were performed to summarize the characteristics and trends of completed PSMA-related clinical trials.

Results: A total of 175 completed studies were identified. Interventional studies accounted for 147 trials (84.0%), while 28 (16.0%) were observational. The cumulative enrolment across all studies was 15,625 participants. Phase II studies represented the largest proportion of trials (n=40), followed by Phase I studies (n=36), Early Phase I studies (n=17), and Phase III studies (n=10). Prostate cancer was the predominant disease indication, appearing in 88 studies. Diagnostic imaging using 68Ga-PSMA PET/CT and 18F-PSMA PET/CT constituted a major area of investigation, whereas therapeutic studies increasingly evaluated radioligand therapies including 177Lu-PSMA. Most studies focused on diagnostic accuracy, lesion detection, staging, treatment response assessment, and safety evaluation. Despite substantial growth in PSMA-directed research, relatively few completed studies reported posted results on the registry.

Conclusion: Completed PSMA-related clinical trials demonstrate rapid expansion of both diagnostic and therapeutic applications of PSMA-targeted technologies. The field remains heavily focused on prostate cancer, although emerging investigations in other solid tumours are increasing. Continued development of radioligand therapies and theranostic approaches is expected to further advance precision oncology.

INTRODUCTION

Prostate-specific membrane antigen (PSMA) is a transmembrane glycoprotein that is highly expressed in prostate cancer cells and exhibits increasing expression with disease progression, metastatic spread, and castration resistance [1,2]. The emergence of PSMA-targeted molecular imaging has substantially improved the diagnosis and staging of prostate cancer. Radiotracers such as ^{68}Ga -PSMA and ^{18}F -PSMA have demonstrated superior sensitivity for detecting primary tumors, biochemical recurrence, and metastatic lesions compared with conventional imaging modalities [3–5]. These advances have contributed to widespread adoption of PSMA positron emission tomography/computed tomography (PET/CT) in clinical practice.

PSMA has enabled the development of theranostic approaches that combine molecular imaging with targeted radionuclide therapy [6–8]. Radioligand therapies utilizing Lutetium-177 (^{177}Lu) labeled PSMA ligands have shown promising efficacy in metastatic castration-resistant prostate cancer, culminating in regulatory approvals and increasing integration into treatment algorithms [9–11]. Additional therapeutic strategies involving alpha-emitting radionuclides and novel PSMA-targeted compounds are also under active investigation [12,13].

The rapid expansion of PSMA-based technologies has generated a substantial body of clinical research. However, a comprehensive evaluation of completed clinical trials examining PSMA-directed imaging and therapy remains limited. Understanding the evolution of study designs, targeted diseases, therapeutic approaches, and outcome measures is essential for identifying research trends and future opportunities.

PSMA expression has also been identified in the neovasculature of several solid tumors, stimulating interest in the broader oncologic applications of PSMA-targeted imaging and therapy [14,15]. Furthermore, ongoing advances in radiochemistry have led to the development of next-generation PSMA ligands with improved tumor uptake, reduced off-target toxicity, and enhanced therapeutic efficacy [16,17]. These innovations continue to expand the clinical potential of PSMA-directed theranostics and support the growing role of precision medicine in oncology.

Therefore, this study aimed to systematically analyze completed PSMA-related clinical trials registered on ClinicalTrials.gov, providing a comprehensive overview of the current clinical development landscape of PSMA-targeted diagnostics and radioligand therapies.

METHODS

Data Source and Search Strategy

A registry-based cross-sectional study was conducted using the ClinicalTrials.gov database. The search term “PSMA” was entered into the registry search engine, and studies were filtered to include only those with a recruitment status of “Completed.” The search was performed on 2 June 2026. No restrictions were applied regarding study phase, participant age, sex, geographic location, or study design. Both interventional and observational studies were considered eligible for screening.

Eligibility Criteria

Studies were included if they met the following criteria: (1) registered on ClinicalTrials.gov, (2) had a status of “Completed,” and (3) investigated PSMA-related applications, including diagnostic imaging, radiopharmaceuticals, radioligand therapy, theranostic approaches, or other PSMA-targeted interventions. Both interventional and observational studies were eligible. Studies that were unrelated to PSMA despite retrieval by the search strategy, duplicate records, withdrawn studies, terminated studies, suspended studies, and studies with recruitment statuses other than “Completed” were excluded.

Study Selection

All retrieved records were screened manually to verify relevance to PSMA-targeted clinical research. Study titles, conditions, interventions, and brief summaries were reviewed to confirm eligibility. Eligible studies were included in the final analysis regardless of whether study results had been posted on the ClinicalTrials.gov platform.

Data Extraction

Data were extracted directly from the ClinicalTrials.gov registry records. The following variables were collected: National Clinical Trial (NCT) identifier, study title, recruitment status, study type, study phase, enrollment size, disease condition,

intervention type, sponsor information, study design characteristics, primary outcome measures, and study completion date. Missing or unavailable information was recorded as reported in the registry.

Data Analysis

Extracted data were compiled and analyzed descriptively using Microsoft Excel. Categorical variables were summarized using frequencies and percentages, while continuous variables such as enrollment size were summarized using descriptive statistics. Studies were categorized according to clinical phase, study type, disease indication, intervention modality, and primary objective. The results were presented in tables and figures to illustrate the distribution and characteristics of completed PSMA-related clinical trials.

Ethical Considerations

This study was based exclusively on publicly accessible data obtained from ClinicalTrials.gov and did not involve direct contact with human participants, identifiable personal information, or access to confidential records. Therefore, institutional review board approval and informed consent were not required.

RESULTS

Study Selection and General Characteristics

A total of 175 completed PSMA-related studies were identified through ClinicalTrials.gov and included in the final analysis. The studies represented a broad spectrum of PSMA-targeted clinical applications, including molecular imaging, radiopharmaceutical development, radioligand therapy, treatment monitoring, dosimetry, and theranostic approaches. Among the included studies, 147 (84.0%) were interventional trials, whereas 28 (16.0%) were observational investigations. The cumulative enrolment across all studies exceeded 15,000 participants, demonstrating substantial global research activity in PSMA-directed oncology. Table 1 summarizes the overall study characteristics.

Table 1. General characteristics of completed PSMA-related clinical studies (n = 175).

Characteristic	Number of Studies (%)
Interventional	147 (84.0)
Observational	28 (16.0)
Total Studies	175 (100)
Studies with Reported Enrolment	175
Total Enrolment	15,625 participants

Distribution by Clinical Phase

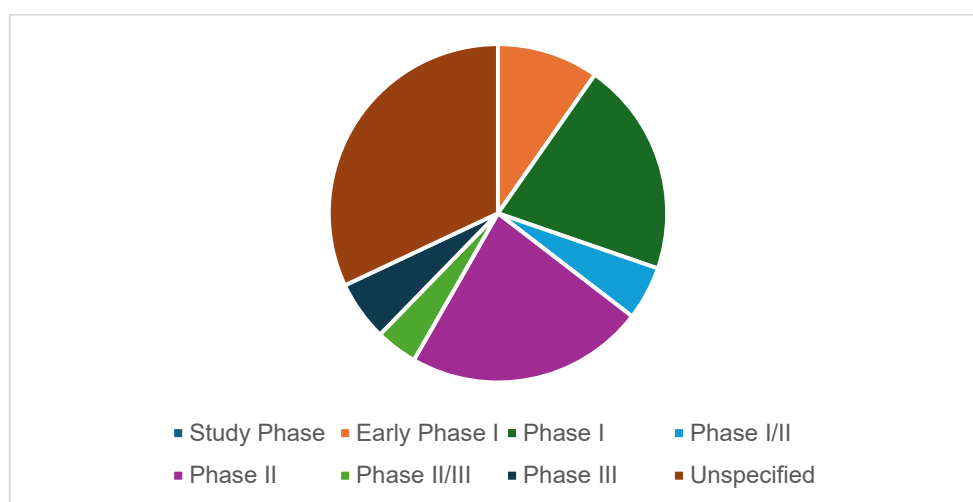
Clinical development was dominated by early- and mid-stage investigations. Phase II studies represented the largest category, accounting for 40 trials (22.9%), followed by Phase I studies (36 trials, 20.6%) and Early Phase I studies (17 trials, 9.7%). Only a limited number of studies progressed to Phase III evaluation. The distribution of studies according to clinical phase is shown in Table 2.

Table 2. Distribution of completed PSMA-related studies by clinical phase.

Study Phase	Number of Studies
Early Phase I	17
Phase I	36
Phase I/II	9
Phase II	40

Phase II/III	7
Phase III	10
Unspecified/Not Applicable	56
Total	175

The predominance of Phase I and Phase II investigations reflects the rapidly evolving nature of PSMA-targeted technologies and the continued optimization of imaging tracers and therapeutic radioligands. Distribution of studies by clinical phase is shown in figure 1.



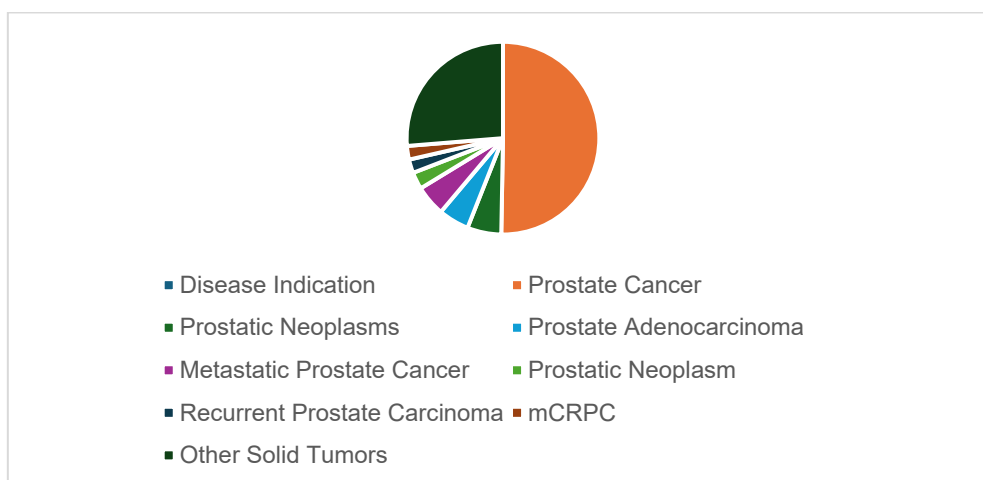
Disease Indications

Prostate cancer was the principal disease indication investigated in the included studies. Various prostate cancer subtypes—including metastatic, recurrent, biochemical recurrence, and castration-resistant disease—accounted for the majority of completed trials. A smaller number of studies evaluated PSMA-targeted approaches in non-prostatic malignancies, including hepatocellular carcinoma, renal cell carcinoma, salivary gland tumors, and adenoid cystic carcinoma. Table 3 presents the most frequently investigated disease indications.

Table 3. Most frequently investigated disease indications in completed PSMA-related studies.

Disease Indication	Number of Studies
Prostate Cancer	88
Prostatic Neoplasms	10
Prostate Adenocarcinoma	9
Metastatic Prostate Cancer	9
Prostatic Neoplasm	5
Recurrent Prostate Carcinoma	4
Metastatic Castration-Resistant Prostate Cancer	4
Other Solid Tumors	46

The overwhelming representation of prostate cancer reflects the biological relevance of PSMA expression in prostate malignancies and the clinical success of PSMA-targeted imaging and therapeutic strategies. Distribution of PSMA technologies (68Ga-PSMA, 18F-PSMA, 177Lu-PSMA, others) is shown in figure 2.



Temporal trend of completed PSMA studies

Temporal trend of completed PSMA studies by completion year is shown in figure 3.

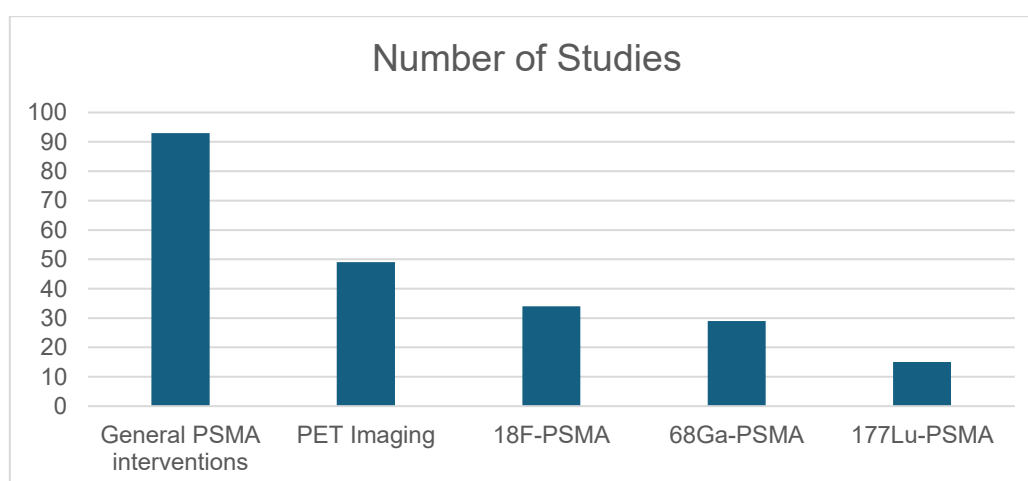


Figure 3. Temporal trend of completed PSMA studies by completion year

PSMA-Targeted Imaging and Radioligand Therapies

Analysis of interventions revealed a predominance of molecular imaging studies utilizing PSMA-targeted positron emission tomography (PET) tracers. Both 68Ga-PSMA and 18F-labeled PSMA agents were widely investigated for disease detection, staging, restaging, and treatment response assessment. Therapeutic radioligand approaches involving 177Lu-PSMA constituted a substantial proportion of interventional studies, reflecting increasing clinical interest in PSMA-directed radionuclide therapy. Table 4 summarizes the major PSMA-directed technologies identified in the included studies.

Table 4. Major PSMA-targeted technologies investigated in completed studies.

Technology Category	Number of Studies
General PSMA-based interventions	93
PET Imaging Studies	49
18F-PSMA Tracers	34
68Ga-PSMA Tracers	29
177Lu-PSMA Radioligand Therapy	15

The increasing number of completed radioligand therapy studies highlights the growing clinical adoption of theranostic approaches, where PSMA imaging is integrated with targeted radionuclide treatment to support precision oncology.

Primary Study Objectives

The primary objectives of the included studies were highly diverse. Diagnostic investigations predominantly focused on lesion detection, staging accuracy, and biochemical recurrence localization. Therapeutic studies frequently evaluated safety, dosimetry, treatment response, progression-free survival, and radioligand efficacy. Several studies also assessed pharmacokinetics, biodistribution, and radiation exposure associated with novel PSMA-targeted agents. Collectively, the results demonstrate a mature and rapidly expanding clinical research landscape centered on PSMA-directed imaging and radiopharmaceutical therapies, with prostate cancer remaining the principal focus of investigation.

DISCUSSION

This ClinicalTrials.gov-based analysis demonstrates the remarkable expansion of PSMA-directed clinical research and highlights the central role of PSMA as a molecular target in precision oncology. The predominance of interventional studies reflects substantial translational activity and continued efforts to optimize both diagnostic and therapeutic applications. A notable finding was the overwhelming focus on prostate cancer, which accounted for approximately half of all completed studies. This observation is consistent with the biological importance of PSMA expression in prostate malignancies and the increasing clinical integration of PSMA-targeted imaging and therapy [18,19].

Diagnostic imaging remains the largest area of investigation. The widespread evaluation of ^{68}Ga -PSMA and ^{18}F -PSMA tracers reflects their established role in staging, detection of biochemical recurrence, and treatment planning. Several studies explored optimization of imaging protocols, lesion detection rates, and comparative performance against conventional modalities [20–22]. The increasing number of completed ^{177}Lu -PSMA studies reflects the rapid expansion of PSMA-targeted radioligand therapy and the growing adoption of theranostic approaches in prostate cancer. This trend is supported by pivotal trials demonstrating improved clinical outcomes in metastatic castration-resistant prostate cancer, which led to regulatory approvals and accelerated global research interest in PSMA-directed therapies [23,24]. Although prostate cancer dominated the dataset, completed studies involving hepatocellular carcinoma, salivary gland cancers, renal cell carcinoma, and other malignancies suggest expanding applications beyond traditional prostate cancer indications. Such diversification may represent an important future direction for PSMA-based oncology research.

Despite substantial growth, several challenges remain. Many completed studies had not posted results on ClinicalTrials.gov, limiting comprehensive assessment of efficacy and safety outcomes. Furthermore, the predominance of early-phase investigations indicates that many PSMA-based technologies are still undergoing clinical validation. Future research should focus on comparative effectiveness studies, long-term outcomes, combination treatment strategies, alpha-emitting radionuclides, and expansion of PSMA-targeted therapies into additional cancer types.

CONCLUSION

Completed PSMA-related clinical trials reveal a rapidly evolving field characterized by extensive development of molecular imaging and radioligand therapies. Prostate cancer remains the principal focus of investigation, although emerging studies demonstrate increasing interest in other malignancies. The continued advancement of PSMA-targeted theranostics is likely to play a major role in the future of precision oncology and radiopharmaceutical medicine.

Limitations

This study was limited to completed studies registered on ClinicalTrials.gov and may not capture trials registered in other databases. Many studies lacked posted results, restricting detailed evaluation of clinical outcomes. Additionally, heterogeneity in study designs, disease indications, and interventions limited direct comparisons across studies.

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Conflicts of Interest

The author declares no conflicts of interest.

Ethics Statement

Ethical approval was not required because this study analyzed publicly available registry data.

Consent to Participate

Not applicable.

AI tool and assistive technologies

ChatGPT (OpenAI) was used solely to assist with proofreading, language editing, grammar correction, and improving the clarity and formatting of the manuscript. The authors reviewed and verified all edits and take full responsibility for the final content of the manuscript.

Data Availability

All data analysed in this study were obtained from publicly accessible database on www.ClinicalTrials.gov.

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