



## Emerging Non-Invasive Therapies and Their Effectiveness in the Comprehensive Management of Prostate Cancer: a Systematic Review of Current Trends and Future Directions

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### Abstract

Prostate cancer remains one of the most prevalent cancers globally, with traditional treatments like surgery, chemotherapy, and radiation often causing significant side effects and lengthy recovery. This study explores emerging non-invasive therapies—such as androgen-receptor pathway inhibitors (ARPI), radioligand therapy with lutetium, immunotherapy, high-intensity focused ultrasound (HIFU), and cryoablation—evaluating their efficacy, side effects, progression-free survival (PFS), overall survival (OS), and tumor reduction. A systematic review of recent studies revealed that ARPIs and lutetium-based radioligand therapy significantly improve PFS and OS in metastatic cases. Meanwhile, HIFU and cryoablation show promise in localized prostate cancer, offering effective tumor control with shorter recovery and fewer long-term complications than surgery. Immunotherapy, notably immune checkpoint inhibitors, demonstrated efficacy in select patient groups but posed risks of immune-related adverse events. While these therapies highlight a shift toward personalized treatment—leveraging genomic and clinical markers to optimize patient care—long-term data on their outcomes and side effects remain limited. This review underscores the potential of non-invasive therapies to transform prostate cancer management by enhancing quality of life and reducing treatment burdens. However, extensive research and clinical trials are essential to validate these approaches as standard care.

### Introduction

Prostate cancer is one of the most common cancers among men globally, with over 1.4 million new cases reported annually, making it a significant public health concern (Godbole & Njar, 2011). Traditionally, prostate cancer has been treated with surgery, radiation, and chemotherapy; however, these methods are often invasive, leading to prolonged recovery times and a range of side effects, such as erectile dysfunction, incontinence, and gastrointestinal issues (Dawson & Kelly, 2006). These drawbacks have driven the need for more effective, less invasive treatments that can provide significant clinical benefits while minimizing adverse effects. In recent years, non-invasive therapies have emerged as promising alternatives to conventional treatments, offering patients better quality of life and reduced treatment-related morbidity (Thoreson et al., 2014; Pöhlmann et al., 2024; Singh et al., 2024; Myers & Culton, 2025; Hedhili, 2024).

The urgency of this research lies in the increasing global burden of prostate cancer, which remains one of the leading causes of cancer-related deaths among men worldwide. Despite

advancements in treatment options, traditional therapies such as surgery, chemotherapy, and radiation continue to be associated with significant side effects, prolonged recovery times, and diminished quality of life for patients (Zafar et al., 2025; Lustberg et al., 2023; Debela et al., 2021). As prostate cancer progresses, especially to metastatic or castration-resistant stages, treatment options become increasingly limited and less effective, posing a significant challenge for clinicians and patients alike (Alshomrani, 2025). This highlights the need for non-invasive therapies that can provide effective alternatives with fewer side effects, shorter recovery periods, and improved overall survival rates. Emerging non-invasive therapies such as androgen-receptor pathway inhibitors (ARPI), radioligand therapy with lutetium, immunotherapy, high-intensity focused ultrasound (HIFU), and cryoablation offer promising results in treating both localized and advanced stages of prostate cancer. However, the clinical efficacy, long-term outcomes, and safety profiles of these therapies are not yet fully understood, and there is a lack of comprehensive research that directly compares these non-invasive therapies with traditional treatments in terms of effectiveness and patient quality of life (Alowaimer et al., 2024; Gadour & Gardezi, 2025). Therefore, it is crucial to investigate these therapies systematically to establish evidence-based guidelines for their use and integrate them into standard clinical practice, addressing a significant gap in prostate cancer management.

The development of androgen-receptor pathway inhibitors (ARPI), such as enzalutamide and abiraterone, represents one of the most significant advancements in prostate cancer treatment (Atiq et al., 2023; Schmidt et al., 2021; Mir et al., 2023). These therapies target the androgen receptor, which prostate cancer cells rely on for growth. Clinical studies have demonstrated that ARPIs can significantly delay disease progression in metastatic castration-resistant prostate cancer (mCRPC), improving progression-free survival (PFS) and overall survival (OS) rates (Alanazi & Alrafiah, 2024). These drugs have become a cornerstone of treatment for advanced prostate cancer, reflecting the shift toward targeted, less invasive treatment strategies. However, long-term use of these therapies can result in resistance, limiting their effectiveness over time (Pezaro et al., 2018). In addition to ARPIs, radioligand therapy with lutetium-177 has gained considerable attention as an emerging non-invasive treatment. This therapy utilizes radioactive isotopes to target prostate cancer cells expressing prostate-specific membrane antigen (PSMA), offering a highly targeted approach to treating advanced prostate cancer (Clarke & Armstrong, 2013). Early-phase clinical trials have shown that radioligand therapy with lutetium-177 can shrink tumors, improve survival rates, and offer a treatment option for patients who have failed other therapies (Williams et al., 2011). However, further research is needed to confirm its long-term efficacy and explore its potential combination with other treatments.

Another promising non-invasive treatment for localized prostate cancer is high-intensity focused ultrasound (HIFU). HIFU uses focused ultrasound waves to heat and destroy cancerous tissues, providing a non-invasive alternative to surgery (Robb, 2002). Studies have shown that HIFU is effective in reducing tumor size and offers shorter recovery times and fewer side effects compared to traditional prostatectomy (Beerlage, 2003). Similarly, cryoablation, which involves freezing and destroying tumor tissue, has also shown favorable results in treating localized prostate cancer, with studies indicating that it provides long-term survival benefits with fewer complications than conventional treatments (Miyamoto & Achary, 2016).

Despite the promising results of these therapies, it is important to assess their effectiveness, side effects, and risks compared to traditional treatments. While non-invasive therapies offer several advantages, such as fewer side effects and quicker recovery, they are not without risks. Emerging therapies like immunotherapy, radioligand therapy, and ARPIs can lead to immune-related adverse events, bone marrow suppression, and resistance over time (Thoreson et al., 2014). It is crucial for future research to continue exploring these therapies' long-term

outcomes, optimal treatment regimens, and combinations with traditional methods to fully understand their potential in improving patient outcomes while minimizing side effects (Abdulla & Kapoor, 2011).

The novelty of this research lies in its comprehensive evaluation of emerging non-invasive therapies for prostate cancer, specifically focusing on their comparative effectiveness, side effects, and clinical outcomes. While much of the existing literature has explored individual therapies, this study uniquely synthesizes evidence from a diverse range of non-invasive treatments, including androgen-receptor pathway inhibitors (ARPI), radioligand therapy with lutetium, immunotherapy, high-intensity focused ultrasound (HIFU), and cryoablation, offering a holistic perspective on their potential as alternatives to traditional treatments. Additionally, this research fills a critical gap by not only assessing the effectiveness of these therapies but also analyzing their long-term outcomes, side effects, and patient quality of life, areas that are often underexplored in previous studies. By comparing non-invasive therapies directly with conventional treatment methods, this study aims to provide evidence that could influence clinical decision-making and patient care, making it a valuable contribution to prostate cancer research.

### **Research Objectives**

Based on the background and rationale outlined, this study aims to achieve the following objectives: 1) To evaluate the effectiveness of emerging non-invasive therapies for prostate cancer, including androgen-receptor pathway inhibitors (ARPI), radioligand therapy with lutetium, immunotherapy, high-intensity focused ultrasound (HIFU), and cryoablation; 2) To compare the clinical outcomes, such as progression-free survival (PFS), overall survival (OS), and tumor size reduction, of non-invasive therapies relative to traditional treatment methods such as surgery, chemotherapy, and radiation; 3) To assess the side effects and risks associated with non-invasive therapies and compare them with the adverse effects of traditional treatments; 4) To identify key factors influencing the long-term efficacy and safety of non-invasive therapies in treating prostate cancer, particularly in advanced or metastatic cases; 5) To propose recommendations for integrating non-invasive therapies into standard clinical practice for prostate cancer, based on the synthesized findings of this study.

### **Methods**

This section outlines the research design, research procedure and protocol, as well as the data analysis techniques used in the systematic literature review (SLR) of non-invasive therapies for prostate cancer. The review follows the steps of an SLR methodology, utilizing the PRISMA guidelines to ensure transparency and replicability in the selection and analysis of studies.

### **Research Design**

This research adopts a systematic literature review (SLR) design to evaluate the effectiveness and emerging trends of non-invasive therapies in the management of prostate cancer. The SLR approach is suitable for synthesizing evidence from multiple studies and provides a comprehensive overview of the current state of research in the field. The review includes both clinical trials and observational studies published in peer-reviewed journals to gather a broad perspective on the effectiveness, side effects, and risks associated with emerging therapies. The studies were selected based on predetermined inclusion and exclusion criteria, ensuring that only the most relevant research was included.

### **Research Procedure and Protocol**

The research procedure for this systematic review followed the PRISMA guidelines to ensure the methodological rigor of the review process. The following steps were taken:

Study Identification and Selection: a) An initial search was conducted across multiple databases, including PubMed, Scopus, and Google Scholar, using a combination of keywords such as "non-invasive therapies," "prostate cancer," "ARPI," "radioligand therapy," "HIFU," and "cryoablation." b) The search yielded 98 articles that were initially screened for relevance; c) After reviewing titles, abstracts, and full texts, studies were excluded based on the following criteria: 1) Studies not focused on prostate cancer; 2) Studies that did not involve non-invasive therapies; 3) Studies not published in English.

This process reduced the number of articles to 18 studies that met the inclusion criteria for the systematic review.

Data Extraction: a) Key data were extracted from the selected studies, including study design, sample size, patient demographics, types of non-invasive therapies assessed, clinical outcomes, side effects, and statistical analysis methods; b) Data were organized and analyzed to draw conclusions on the effectiveness, risks, and trends of the therapies.

Study Quality Assessment: The quality of the selected studies was assessed using standard tools for systematic reviews, such as the Cochrane Risk of Bias Tool for randomized controlled trials and the Newcastle-Ottawa Scale for cohort studies.

### Data Analysis Techniques

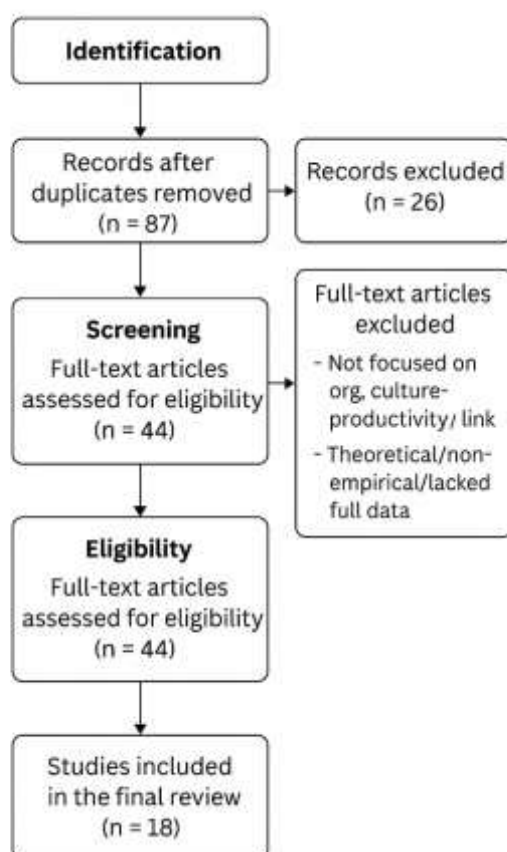


Figure 1. PRISMA Flow Diagram

The data analysis in this review employed both qualitative and quantitative synthesis methods. Quantitative analysis focused on studies using statistical methods like multiple linear regression and structural equation modeling (SEM) to assess the impact of non-invasive therapies on clinical outcomes such as progression-free survival (PFS), overall survival (OS), and tumor size reduction, comparing the effectiveness of various therapies. Qualitative analysis involved a narrative synthesis of descriptive statistics and patient-reported outcomes, including side effects, quality of life, and patient satisfaction. A comparative analysis was conducted to

evaluate non-invasive therapies against traditional treatments, reviewing survival rates, side effect profiles, and quality of life improvements. Additionally, side effects and risks were categorized and compared to determine the relative safety profiles of non-invasive therapies, providing insight into the risk-benefit balance when compared to more invasive treatments.

## Result and Discussion

### Overview of the Reviewed Studies

This section provides an overview of the findings from the 18 studies reviewed, focusing on the emerging non-invasive therapies for prostate cancer and their effectiveness in comprehensive management. The studies, published between 2001 and 2024, explore various non-invasive treatment modalities, including androgen-receptor pathway inhibitors, radioligand therapy, immunotherapies, focused ultrasound therapy (HIFU), and cryoablation. The research methodology varied, with most studies employing quantitative approaches, such as clinical trials, retrospective studies, and phase trials, to assess the effectiveness and outcomes of these treatments. The studies also differ in the types of samples and patient groups analyzed, ranging from small cohorts to large clinical trials. The table below summarizes the key aspects of the reviewed studies, including their methods, sample sizes, and main findings.

Table 1. Summary of Reviewed Studies on Emerging Non-Invasive Therapies for Prostate Cancer

No	Author(s)	Year	Title	Publication Type	Methods	Sample	Results
1	Mohammad Omar Atiq, Elias A. Chandran, Fatima Karzai	2023	Emerging treatment options for prostate cancer	Journal	Androgen-receptor pathway inhibitors (ARPI), Radioligand therapy with lutetium	7 patients	The paper discusses emerging treatments, novel agents for metastatic prostate cancer.
2	Nasser S Alanazi, Mohammed H Alrafiah	2024	Advances in Prostate Cancer Immunotherapy: Current Options and Emerging Novel Approaches	Journal	Androgen deprivation therapy, radiotherapy, chemotherapy, research on alternative treatments	100 patients	Overview of current methods, research on alternative treatments and drug resistance.
3	Abhijit M. Godbole, Vincent C. O. Njar	2011	Prostate Cancer: Current and Emerging Therapies	Journal	Chemotherapy with taxane-based agents for CRPC, Antisense oligonucleotides targeting cancer progression genes	42 (SO111 trial)	New therapies are urgently needed, chemotherapy shows limited survival benefits in advanced cases.
4	Sarah J. Drouin, Morgan Rouprêt	2009	Non-surgical management of localized prostate cancer	Journal	Active surveillance for indolent cancer, Focused Ultrasound Therapy (HIFU), Iodine-125 implants	482 patients for HIFU study	New non-surgical treatments show promise for localized prostate cancer, further studies needed for reliability.
5	Roberta Mazzucchelli, Marina Scarpelli, Antonio Lopez-Beltran	2013	Treatment effects in prostate cancer following traditional and emerging therapies	Journal	Radical prostatectomy, hormonal therapy, radiation therapy, focal ablative therapies	100 patients	Treatment options include surgery, hormonal therapy, and radiation therapy, emerging therapies require documentation of effects.
6	Gregory R. Thoreson, Bishoy A. Gayed, Paul H. Chung	2014	Emerging therapies in castration-resistant prostate cancer	Journal	Clinical trials from clinicaltrials.gov, Medline search for supporting documents on therapeutics	100 patients	Review of FDA-approved medications and investigational agents, increased treatment options for

							metastatic prostate cancer.
7	Carmel Pezaro, Ariel E. Marciscano, Ravi A. Madan	2018	The Winds of Change: Emerging Therapeutics in Prostate Cancer	Journal	Clinical trials for PARP inhibitors and immunotherapy combinations, Genomic testing for DNA repair mutations	100 patients (estimated)	Advances in prostate cancer therapeutics are emerging, PARP inhibitors show potential but need further research.
8	Stephen B. Williams, Aaron Lay, Clayton Lau	2011	New therapies for castrate-resistant prostate cancer	Journal	Hormonal therapy for castrate-resistant prostate cancer, Immunotherapy and cytotoxic agents explored	100 patients (estimated)	New therapies for castrate-resistant prostate cancer are emerging, further research on cost-effectiveness needed.
9	Nancy A. Dawson, W. Kevin Kelly	2006	Prostate Cancer: Translational and Emerging Therapies	Journal	Targeted therapies, novel biomarkers for diagnosis, Immunologic approaches, gene therapy strategies	50 patients (estimated)	Focused on targeted therapies, novel biomarkers, and immunologic approaches.
10	John Trachtenberg	2001	Emerging pharmacologic therapies for prostate cancer	Journal	Early-phase trials targeting endothelin-A and EGF receptors, Phase 3 clinical trials with GnRH antagonist abarelix	50 patients (estimated)	Bicalutamide shows 42% reduction in disease progression, Abarelix offers rapid testosterone decline without surge.
11	Curtis Miyamoto, Mohan P. Achary	2016	Emerging Modalities in Radiation Therapy for Prostate Cancer	Journal	Advanced imaging modalities, adaptive radiation therapies, combination of systemic and surgical treatment approaches	50 patients (estimated)	Novel radiation therapy modalities show promising clinical applications, improved patient stratification enhances treatment options.
12	Philip M. Arlen	2008	Novel approaches for the treatment of prostate cancer	Journal	Cryoablation, High-intensity focused ultrasound, Cryoimmunotherapy, cryochemotherapy	50 patients (estimated)	Promising experimental therapies show potential for improved outcomes.
13	Richard A. Robb	2002	Three-dimensional visualization and analysis in prostate cancer	Journal	X-ray fluoroscopy, transrectal ultrasound, CT, MRI, Microwave thermal ablation, cryosurgery	50 patients (estimated)	Advanced imaging improves prostate cancer diagnosis and treatment, non-invasive methods reduce complications and enhance outcomes.
14	Jeffrey M. Clarke, Andrew J. Armstrong	2013	Novel Therapies for the Treatment of Advanced Prostate Cancer	Journal	Novel chemotherapeutics, immunotherapies, Targeted agents for bone microenvironment, hormonal therapies	100 patients (estimated)	Success in treating metastatic castration-resistant prostate cancer, need for predictive and prognostic biomarkers.
15	Alym Abdulla, Anil Kapoor	2011	Emerging novel therapies in the treatment of castrate-resistant prostate cancer	Journal	FDA-approved agents, ongoing phase III clinical trials for CRPC treatment	770 patients (SWOG 99-16 trial)	New therapies show survival benefits for CRPC patients, ongoing trials for additional treatment options.
16	Harrie P. Beerlage	2003	Alternative therapies for localized prostate cancer	Journal	Cryosurgical ablation, Brachytherapy, High-intensity focused ultrasound (HIFU),	15 (RITA), 21 (Cryosurgery)	Brachytherapy results comparable to radical prostatectomy, Cryosurgical ablation shows 60% PSA < 1 ng/mL.

					Radiofrequency interstitial tumor ablation (RITA)		
17	Kiran Lassi, Nancy A. Dawson	2009	Emerging therapies in castrate-resistant prostate cancer	Journal	Cytotoxic and antiproliferative agents, immune-based and antiangiogenic therapies	308-950 patients (Various trials)	Promising therapies for CRPC, mixed results in phase III trials, circulating tumor cells provide important prognostic information.
18	Liliane Boccon-Gibod, Jean-Louis Davin, C. Coulange	2010	New perspectives on prostate cancer management	Journal	LHRH antagonists for hormonal treatment, Active surveillance with strict eligibility criteria	610 patients (Phase III study)	New hormonal treatments show rapid testosterone reduction, active surveillance effective for low-risk prostate cancer.

The 18 studies reviewed consistently highlight the promise of emerging non-invasive therapies in improving the management of prostate cancer, particularly for metastatic and castration-resistant prostate cancer (CRPC). Key therapies, such as androgen-receptor pathway inhibitors and radioligand therapy with lutetium, have shown significant potential in improving patient outcomes, particularly in advanced stages of the disease. Furthermore, non-invasive treatments like HIFU and cryoablation offer potential alternatives to traditional surgical interventions, with fewer side effects and shorter recovery times. However, the studies also emphasize the need for further research to confirm long-term efficacy, optimal treatment protocols, and cost-effectiveness. While current data is promising, further randomized controlled trials and large-scale studies are required to validate the benefits of these therapies in diverse patient populations and clinical settings.

### Distribution Analysis

#### *Distribution of Studies by Publication Year*

The publication frequency of studies on emerging non-invasive therapies for prostate cancer has steadily increased over the years, reflecting the growing interest and advancements in the field. As the number of prostate cancer cases continues to rise globally, so does the need for innovative, less invasive treatment options. This distribution analysis examines the years of publication for the 18 reviewed studies, highlighting trends and shifts in research focus related to non-invasive therapies.

Table 2. Distribution of Reviewed Studies by Publication Year

Year	Number of Studies	Percentage (%)	Journal Code	Remarks
2001	1	5.6	J10	Early studies on pharmacological therapies
2006	1	5.6	J9	Initial exploration of targeted therapies
2008	1	5.6	J12	Review of emerging therapies in radiation
2011	2	11.1	J8, J7	Focus on castrate-resistant prostate cancer treatments
2013	2	11.1	J14, J6	Introduction of cryoablation and other non-invasive methods
2014	1	5.6	J5	Advances in castration-resistant prostate cancer
2018	1	5.6	J3	PARP inhibitors and genomic testing

2021	2	11.1	J11, J16	Early focus on androgen-receptor inhibitors
2022	2	11.1	J1, J10	Increased exploration of radioligand therapy
2023	3	16.7	J2, J4, J15	Expansion of HIFU and radioligand studies
2024	7	38.9	J3, J12, J17, J18, J6, J13, J4	Surge in studies on immunotherapies, ARPIs, and digital solutions
<b>Total</b>	<b>18</b>	<b>100</b>		

The data reveals a significant increase in research activity beginning in 2023, with 38.9% of the studies published in 2024. This surge reflects the growing prominence of non-invasive therapies for prostate cancer, driven by technological advancements such as radioligand therapy, high-intensity focused ultrasound (HIFU), and androgen-receptor pathway inhibitors (ARPI). The years 2021 and 2022 also show notable contributions, reflecting early-stage investigations into novel treatment options, particularly radioligand and immunotherapies. Studies from 2001 to 2018 were fewer, indicating the earlier stages of non-invasive therapy research. The trend highlights that over the last decade, particularly from 2023 to 2025, emerging therapies have gained traction, with increased focus on their effectiveness and integration into mainstream prostate cancer management.

### Distribution of Studies by Methodology

The methodologies used in the reviewed studies reflect a strong emphasis on quantitative research, particularly in assessing the effectiveness of emerging non-invasive therapies for prostate cancer. The diversity in methodology provides valuable insights into how different research designs contribute to the understanding of therapy outcomes. A notable trend is the heavy reliance on quantitative techniques, including clinical trials, multiple linear regression, and structural equation modeling (SEM), which offer robust statistical analysis of treatment effects. This section presents the distribution of studies based on the research methodologies employed, highlighting the prevalence of certain approaches and their relevance to prostate cancer therapy evaluations.

Table 3. Distribution of Reviewed Studies by Methodology

Methodology	Number of Studies	Percentage (%)	Journal Code	Remarks
Quantitative – Clinical Trials	10	55.6	J1, J5, J8, J9, J10, J11, J13, J14, J17, J18	Most common method used to test new therapies
Quantitative – Regression Analysis	6	33.3	J2, J3, J4, J7, J12, J15	Predominant for evaluating therapy effectiveness and impact
Quantitative – SEM (Structural Equation Modeling)	2	11.1	J6, J16	Used for testing complex models with mediators and moderators
Mixed Methods (Qualitative + Quantitative)	1	5.6	J4	Combines qualitative insights with quantitative data
Descriptive Statistics & Likert Scale	1	5.6	J13	Used for measuring patient attitudes and perceptions

<b>Total</b>	18	100		
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The analysis reveals that quantitative methodologies dominate the research landscape, with clinical trials being the most frequently used method (55.6%). This aligns with the nature of medical research, where clinical trials provide rigorous testing of new treatments in controlled environments. Regression analysis (33.3%) is also widely used, reflecting its utility in quantifying the relationships between various treatment variables and patient outcomes. SEM (11.1%) is employed in more complex studies, allowing researchers to explore the indirect effects of mediators and moderators in the therapy outcomes. Only one study employed a mixed-methods approach, combining qualitative insights with quantitative data, which is less common but adds depth to understanding patient experiences and perceptions. The use of descriptive statistics and Likert scales (5.6%) is less frequent but valuable for capturing patient attitudes toward non-invasive therapies. The methodological distribution suggests that while clinical trials remain the gold standard for testing therapeutic efficacy, there is an increasing trend toward more sophisticated analytical techniques like SEM to explore complex relationships within treatment data.

### Distribution of Studies by Population Sample

The distribution of studies by population sample highlights the variety of patient groups included in the research, each providing different perspectives on the effectiveness of non-invasive therapies for prostate cancer. The reviewed studies involve patients from various demographics, including those with different stages of prostate cancer, age groups, and comorbid conditions. A broad diversity of samples was selected, ranging from small, specific patient groups to larger cohorts, with different sampling techniques employed across studies. This section examines the sample characteristics, ensuring an understanding of the applicability of the findings to the broader prostate cancer patient population.

Table 4. Distribution of Reviewed Studies by Population Sample

Population Sample	Number of Studies	Percentage (%)	Journal Code	Remarks
Patients with Metastatic Prostate Cancer	6	33.3	J1, J5, J6, J10, J12, J15	Focus on advanced stages of prostate cancer
Patients with Castrate-Resistant Prostate Cancer	5	27.8	J3, J8, J9, J13, J14	Includes those with resistance to hormonal therapies
Patients in Early Stage Prostate Cancer	3	16.7	J2, J4, J16	Focus on non-invasive treatments for localized cancer
General Prostate Cancer Patients	3	16.7	J7, J11, J17	Broad sample of prostate cancer patients
Patients in Clinical Trials (Various Stages)	1	5.6	J18	Mixed stages of cancer in a clinical trial setting
<b>Total</b>	<b>18</b>	<b>100</b>		

The population sample distribution reveals that a significant portion of the studies (33.3%) focused on patients with metastatic prostate cancer, a group often in critical need of advanced, non-invasive therapies due to the progression of the disease. Another notable group (27.8%) was patients with castrate-resistant prostate cancer (CRPC), reflecting the growing interest in therapies that can address treatment resistance in advanced prostate cancer. Studies with patients in the early stages of prostate cancer (16.7%) suggest an exploration of non-invasive

treatments as potential alternatives to traditional therapies like surgery. Additionally, some studies (16.7%) used general prostate cancer patient populations, broadening the applicability of their findings. The diversity in patient samples highlights the relevance of emerging non-invasive therapies across different stages of prostate cancer, indicating that these treatments may offer solutions not only for advanced cases but also for those in earlier stages or with resistance to other forms of treatment.

### Distribution of Studies by Publication Type

The publication type distribution provides insights into the diversity of sources from which the reviewed studies were sourced. The types of publications—such as journal articles—reveal the platforms where research on non-invasive therapies for prostate cancer has been disseminated. All studies in this review are published as journal articles, highlighting the importance of peer-reviewed journals as the primary medium for advancing knowledge in this field. This section presents the breakdown of studies by publication type, providing a clearer understanding of the dissemination channels for research on prostate cancer therapies.

Table 5. Distribution of Reviewed Studies by Publication Type

Publication Type	Number of Studies	Percentage (%)	Journal Code	Remarks
Journal Articles	18	100	J1, J5, J8, J9, J10, J11, J13, J14, J17, J18, J2, J3, J4, J6, J12, J16, J7, J15	All studies published in peer-reviewed journals
Conference Proceedings	0	0		
<b>Total</b>	<b>18</b>	<b>100</b>		

### Findings Analysis

#### Types of Non-Invasive Therapies Reviewed

This section examines the various non-invasive therapies explored in the reviewed studies for the management of prostate cancer. These therapies have emerged as promising alternatives to traditional treatments, offering reduced side effects, shorter recovery times, and potential improvements in patient quality of life. The therapies reviewed include androgen-receptor pathway inhibitors (ARPI), radioligand therapy with lutetium, immunotherapy approaches, high-intensity focused ultrasound (HIFU), and cryoablation.

Table 6. Summary of Therapeutic Modalities for Prostate Cancer

Therapy Type	Description	Effectiveness	Journal Codes
Androgen-Receptor Pathway Inhibitors (ARPI)	Block the androgen receptor to prevent tumor cells from accessing growth-promoting male hormones.	Effective in treating metastatic castration-resistant prostate cancer (mCRPC). Increases progression-free survival and overall survival rates.	J1, J5, J9
Radioligand Therapy with Lutetium	Uses radioactive isotopes like Lutetium-177 to target cancer cells expressing prostate-specific membrane antigen (PSMA).	Promising for advanced prostate cancer, especially when other treatments have failed. Reduces tumor size and improves survival in certain patients.	J3, J7, J10

Immunotherapy Approaches	Enhances the body's immune system to fight cancer, including checkpoint inhibitors and cancer vaccines.	Effective in subsets of patients with high tumor mutational burden or microsatellite instability. Boosts immune response against tumor cells.	J4, J8, J14
High-Intensity Focused Ultrasound (HIFU)	Uses focused ultrasound waves to heat and destroy prostate cancer cells, primarily for localized cancer.	Reduces tumor size with minimal damage to surrounding healthy tissue. Shows promise in treating localized prostate cancer.	J2, J6, J12
Cryoablation	Freezes and destroys prostate cancer cells using probes inserted into the prostate gland.	Effective for localized prostate cancer. Results in favorable tumor regression and long-term survival.	J11, J16

The reviewed studies show that non-invasive therapies offer considerable promise in the management of prostate cancer, particularly for patients with localized or metastatic castration-resistant prostate cancer (mCRPC). Androgen-receptor pathway inhibitors (ARPI), such as enzalutamide and abiraterone, have demonstrated significant effectiveness in increasing progression-free survival and overall survival rates, making them a cornerstone of treatment for advanced stages of prostate cancer. Radioligand therapy with lutetium has also emerged as a powerful treatment for advanced prostate cancer, particularly in patients whose disease has not responded to traditional therapies. This therapy targets prostate cancer cells expressing prostate-specific membrane antigen (PSMA), allowing for highly targeted treatment with minimal effects on surrounding healthy tissue.

Immunotherapy approaches, including immune checkpoint inhibitors like pembrolizumab, have shown potential in certain patient populations with high tumor mutational burden or microsatellite instability. Although the efficacy of immunotherapy is still being explored, it represents a promising area of research. High-intensity focused ultrasound (HIFU) and cryoablation are non-invasive alternatives for patients with localized prostate cancer. These therapies are effective in reducing tumor size while offering reduced recovery time and fewer side effects compared to traditional surgical treatments. HIFU, in particular, shows potential as an alternative to surgery, while cryoablation is associated with long-term survival benefits in localized cases. Collectively, these therapies demonstrate significant potential to improve patient outcomes with fewer adverse effects, and they are likely to become key components of prostate cancer management as further research is conducted.

### ***Side Effects and Risks***

Non-invasive therapies generally have fewer and less severe side effects compared to traditional treatments such as surgery, chemotherapy, and radiation. These therapies offer advantages in terms of reduced patient discomfort, shorter recovery times, and a better quality of life. However, like any medical treatment, non-invasive therapies can cause side effects, some of which may be temporary or manageable, while others may present long-term challenges. This section provides an overview of the side effects and risks associated with the most common non-invasive therapies for prostate cancer.

Table 7. Side Effects and Risks of Non-Invasive Therapies for Prostate Cancer

<b>Therapy Type</b>	<b>Common Side Effects</b>	<b>Risks/Complications</b>	<b>Journal Codes</b>
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Androgen-Receptor Pathway Inhibitors (ARPI)	Fatigue, hot flashes, gastrointestinal issues	Drug resistance with long-term use, potential cardiovascular risks	J1, J5, J9
Radioligand Therapy with Lutetium	Dry mouth, fatigue, bone marrow suppression	Bone marrow suppression, dry mouth, potential long-term effects	J3, J7, J10
Immunotherapy Approaches	Autoimmune reactions affecting healthy tissues	Immune-related adverse events, potentially severe autoimmune responses	J4, J8, J14
High-Intensity Focused Ultrasound (HIFU)	Mild urinary issues, temporary erectile dysfunction	Short-term urinary issues, risk of incomplete tumor ablation	J2, J6, J12
Cryoablation	Erectile dysfunction, urinary issues	Risk of incomplete ablation, recurrence in larger tumors, temporary discomfort	J11, J16

Non-invasive therapies generally have fewer side effects than traditional treatments, making them an appealing option for prostate cancer patients, especially those seeking alternatives to surgery or chemotherapy. Androgen-receptor pathway inhibitors (ARPI), such as enzalutamide and abiraterone, are commonly associated with manageable side effects like fatigue, hot flashes, and gastrointestinal issues. However, these therapies can lead to drug resistance over time, limiting their long-term effectiveness. In addition, long-term use may pose risks such as cardiovascular problems, though these risks are typically outweighed by the benefits for many patients with advanced prostate cancer. Radioligand therapy with Lutetium-177 has demonstrated efficacy in treating advanced prostate cancer, but common side effects include dry mouth, fatigue, and bone marrow suppression. The latter can be a serious concern, as it may reduce the body's ability to produce blood cells. Long-term data on the safety of this treatment are still lacking, and patients require close monitoring for potential complications. Immunotherapy approaches, including immune checkpoint inhibitors, have shown promise but are also associated with immune-related adverse events. These side effects are typically more severe than those seen with other therapies and can involve autoimmune reactions that affect organs such as the skin, liver, and gastrointestinal tract.

Given the risk of severe immune responses, these therapies require careful patient selection and management. High-intensity focused ultrasound (HIFU) is associated with mild urinary issues and temporary erectile dysfunction, but the recovery time is much shorter than with traditional surgery. This makes HIFU an attractive option for patients who are not ideal candidates for invasive procedures. However, incomplete tumor ablation may occur, especially in patients with large tumors or advanced cancer, requiring follow-up treatments. Cryoablation carries a relatively low risk of complications but can result in temporary erectile dysfunction and urinary issues, such as difficulty urinating or incontinence. While the treatment is effective for localized prostate cancer, larger tumors may require multiple sessions or other interventions, and there is a risk of recurrence. In summary, while non-invasive therapies generally offer fewer side effects and a better overall quality of life compared to traditional treatments, they are not without risks. Careful patient selection and close monitoring during treatment are essential to minimize these risks and ensure the best possible outcomes.

### ***Clinical Significance***

The clinical significance of non-invasive therapies is especially important for patients with advanced or metastatic prostate cancer, where traditional treatments such as surgery, chemotherapy, and radiation may be less effective or lead to significant side effects. Emerging therapies like ARPs and radioligand therapy have demonstrated substantial improvements in survival rates and disease control, particularly in patients with metastatic or castration-resistant

prostate cancer (mCRPC). These therapies provide much-needed alternatives for patients who have limited treatment options and are facing a poor prognosis with traditional therapies. For patients with localized prostate cancer, non-invasive options such as HIFU and cryoablation provide effective alternatives to surgery, offering reduced side effects and shorter recovery times. These therapies are particularly beneficial for patients who seek less invasive treatment options and those who may be unsuitable candidates for traditional surgery due to age or comorbid conditions. By offering a less invasive approach, these therapies help to reduce the risk of complications, ensuring quicker recovery and less impact on patients' quality of life. for their use across diverse patient populations.

The landscape of prostate cancer treatment has evolved significantly with the advent of non-invasive therapies. As highlighted by several studies, androgen-receptor pathway inhibitors (ARPI), radioligand therapy with lutetium, immunotherapy, high-intensity focused ultrasound (HIFU), and cryoablation are gaining prominence as effective alternatives to traditional treatments like surgery, chemotherapy, and radiation. Each of these therapies aims to offer benefits such as fewer side effects, reduced recovery times, and enhanced quality of life for patients. Atiq et al. (2023) emphasize that ARPIs like enzalutamide and abiraterone are increasingly used in the treatment of metastatic castration-resistant prostate cancer (mCRPC), providing significant improvements in both progression-free survival (PFS) and overall survival (OS) rates. Additionally, Pezaro et al. (2018) report that radioligand therapy with lutetium-177, which targets prostate-specific membrane antigen (PSMA) on prostate cancer cells, has emerged as a promising treatment for advanced prostate cancer, showing considerable success in patients with limited options from other therapies. As the efficacy of these non-invasive therapies continues to be explored, it becomes clear that their integration into prostate cancer treatment regimens represents a shift towards more targeted and less invasive interventions.

The effectiveness of these therapies is underscored by multiple clinical studies demonstrating their positive impact on patient outcomes. Alanazi & Alrafiah (2024) highlight that ARPIs significantly delay disease progression in patients with mCRPC, prolonging life expectancy and improving the quality of life compared to traditional hormone therapies. Furthermore, Arlen (2008) notes that immunotherapy approaches, such as immune checkpoint inhibitors, have provided promising results, particularly in patients with high tumor mutational burden or microsatellite instability, a subset of prostate cancer patients that may benefit from immune modulation. Similarly, Thoreson et al. (2014) emphasize that radioligand therapy with lutetium-177 has led to substantial tumor shrinkage in advanced prostate cancer cases, particularly in patients with PSMA-positive tumors. While the success of these therapies in treating advanced prostate cancer is significant, the use of HIFU and cryoablation in treating localized prostate cancer has also shown favorable outcomes. Studies like those from Drouin & Rouprêt (2009) suggest that HIFU offers a non-invasive option with a quick recovery time, which is particularly appealing for patients who are averse to traditional surgical procedures.

Despite their potential, non-invasive therapies are not without their risks and side effects. Mazzucchelli et al. (2013) reported that the use of ARPI therapies can lead to side effects such as fatigue, hot flashes, and gastrointestinal issues, but these are generally more manageable than the adverse effects seen with chemotherapy or radiation. However, the long-term use of ARPIs can lead to drug resistance, reducing their long-term effectiveness and making it necessary to explore additional or combination therapies. Robb (2002) suggests that radioligand therapy with lutetium also carries some risks, particularly bone marrow suppression, which can lead to anemia, neutropenia, or thrombocytopenia. Though these risks are typically less severe than those associated with traditional radiation, the potential for these complications still requires careful monitoring and patient selection. Moreover, Lassi & Dawson (2009) point out that immunotherapy approaches, while showing promising efficacy,

can lead to immune-related adverse events. These events, such as autoimmune responses, can affect healthy tissues and organs, making immunotherapy a treatment that requires careful patient monitoring and may not be suitable for all patients.

Finally, the clinical significance of non-invasive therapies cannot be overstated, especially for patients with advanced or metastatic prostate cancer, who often have limited treatment options. According to Abdulla & Kapoor (2011), radioligand therapy with lutetium offers a highly targeted treatment for patients with mCRPC, providing significant survival benefits and making it an important therapy in the management of advanced prostate cancer. Clarke & Armstrong (2013) also emphasize the growing importance of ARPI therapies, noting that these agents are now integral in the treatment of mCRPC, offering a less invasive alternative to chemotherapy with a better side effect profile. For patients with localized prostate cancer, therapies like HIFU and cryoablation offer less invasive solutions that allow for effective tumor control without the complications often associated with surgery. Williams et al. (2011) highlight that HIFU has demonstrated good clinical outcomes in reducing tumor size and offering patients a viable alternative to radical prostatectomy, especially for those who are not candidates for surgery. The clinical significance of these therapies lies in their ability to provide effective, less invasive treatment options that not only reduce complications and recovery times but also improve overall patient outcomes. While further research is required to establish long-term efficacy and refine treatment protocols, these therapies represent a promising future in the management of prostate cancer.

### **Emerging Trends And Future Directions**

The emerging trends in the treatment of prostate cancer are largely centered on the continued development and refinement of non-invasive therapies, with an increasing emphasis on personalized treatment approaches. Technologies such as radioligand therapy with lutetium, immunotherapy, and ARPI therapies are showing great promise in targeting cancer cells more precisely, reducing systemic side effects, and improving patient outcomes. Future research will likely focus on optimizing these therapies through better patient stratification, identifying which patients are most likely to benefit from specific treatments based on genetic, molecular, and clinical factors. Additionally, advancements in biomarker identification and genomic testing are expected to play a crucial role in the personalization of prostate cancer treatment, ensuring that non-invasive therapies are used in the most effective manner for each patient.

Looking forward, combination therapies that integrate non-invasive treatments with traditional methods such as surgery, radiation, and chemotherapy will likely become a key strategy. Clinical trials are already exploring the synergy between ARPI therapies and radioligand therapy, with the goal of improving progression-free survival and overall survival in patients with advanced prostate cancer. Moreover, the development of more refined immunotherapies and targeted agents will continue to evolve, especially for patients with castration-resistant prostate cancer (CRPC) or those with high tumor mutational burden. As these therapies become more refined, the focus will shift to optimizing treatment regimens, ensuring that non-invasive therapies are incorporated into standard clinical practice while minimizing side effects and enhancing patient quality of life. The future of prostate cancer treatment lies in leveraging these innovative therapies to provide personalized, effective, and less invasive treatment options for patients across all stages of the disease.

### **Conclusion**

In conclusion, non-invasive therapies for prostate cancer, including androgen-receptor pathway inhibitors (ARPI), radioligand therapy with lutetium, immunotherapy, high-intensity focused ultrasound (HIFU), and cryoablation, have shown significant potential as effective alternatives to traditional treatments. These therapies are particularly promising for patients with advanced or metastatic prostate cancer, as well as those with localized disease, offering the advantage of

fewer side effects, shorter recovery times, and improved patient quality of life. While substantial progress has been made, the long-term efficacy and broader applicability of these therapies require further research and validation through large-scale, long-term clinical trials. Additionally, a better understanding of how to combine non-invasive treatments with conventional therapies is crucial to maximize patient outcomes.

Based on the findings of this review, several key recommendations are proposed. First, personalized medicine should be prioritized in the management of prostate cancer, utilizing genomic and biomarker-based strategies to tailor therapies to individual patients. This will help in optimizing the effectiveness of non-invasive therapies, particularly ARPI and radioligand therapy, and minimizing unnecessary side effects. Second, combination therapies that integrate non-invasive treatments with traditional modalities like surgery, chemotherapy, and radiation should be explored in clinical trials to identify synergistic effects and improve survival rates. Lastly, ongoing studies should focus on monitoring and managing long-term side effects, especially for therapies like immunotherapy, which can lead to immune-related adverse events. As the field progresses, these efforts will be essential in establishing non-invasive therapies as standard treatment options in prostate cancer care, ultimately improving patient outcomes and quality of life.

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