A bibliometric analysis of global research status and trends in novel endocrine therapy in the treatment of prostate cancer

Jinxiao Yang, He Miao, Jianhua Li, Pengcheng Zhan, Junjun Wang, Fuzeng Ye

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Abstract

Background: Novel endocrine therapy for prostate cancer is developing rapidly and has gradually become a research hotspot in the field of prostate cancer treatment.

Objective: This study aims to provide a comprehensive bibliometric analysis of novel endocrine therapies for prostate cancer (PCa), offering insight into the current research status, hotspots, and emerging trends in the field to inspire further exploration.

Methods: Method: Data were extracted from the Web of Science core collection (WoSCC) database, with primary analysis utilizing data visualization tools VOSviewer and CiteSpace. A systematic and visual analysis was conducted, generating visual representations of data points such as publication volumes, countries, institutions, authors, journals, cited references, and keywords. Results: Result: The analysis covered a total of 2452 publications and identified an upward trend in novel endocrine treatments for PCa research over the past two decades. The United States leads in research contribution with a total of 1106 publications. The University of British Columbia had the highest volume of publications, while the author, Scher, Howard, was cited most often. The Journal of Clinical Oncology emerged as a pivotal journal in this field. The most-cited reference was found in The New England Journal of Medicine. Notable research hotspots are inclusive of 'docetaxel', 'metastatic castration-resistant prostate cancer', 'lineage plasticity', and 'PSMA'. Conclusions: Conclusion: The increasing engagement of scholars in novel endocrine therapies for PCa research and the strong collaborative ties between different countries, institutions, and authors advocate rapid advancement in this field. The current study reveals the evolution of novel endocrine treatments for PCa and identifies emerging research hotspots, primarily centered around 'docetaxel', 'advanced castration-resistant prostate cancer', 'lineage plasticity', and 'Prostate-Specific Membrane Antigen (PSMA)'.

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Keywords: bibliometric analysis, novel endocrine therapy, prostate cancer, docetaxel, lineage plasticity, PSMA.

Background Novel endocrine therapy for prostate cancer is developing rapidly and has gradually become a research hotspot in the field of prostate cancer treatment.
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1 Introduction

Prostate Cancer (PCa) is a prevalent malignancy in elderly men, affecting the genitourinary system. It ranks second in incidence rate among all male malignancies globally, with developed countries like Europe and America topping the list and the incidence rate increasing annually[1]. Most recent statistics stretching from the years 2014 to 2019 show an annual growth rate of 3%, translating into a further 99,000 cases in the United States alone[2]. It is projected that there will be 288,300 new cases of PCa in 2023, resulting in approximately 34,700 deaths[3]. As such, PCa poses a significant threat to both the physical and mental health of men and demands urgent attention as a common public health concern.

Dependent on androgens, PCa thrives with testosterone synthesized by the testis as its main androgen source[4], complemented by about 5%-10% of androgen from the adrenal gland. In a ground-breaking 1941 study, Huggins and Hodges found that metastatic PCa (mPCa) progression could be slowed through bilateral testicular resection, establishing the first empirical correlation between androgen and PCa[5]. Any method that removes or inhibits androgen activity is collectively referred to as endocrine therapy, or androgen deprivation therapy (ADT), which spans both surgical and drug castration[6–8]. Surgical castration involves removing the bilateral testes, the primary androgen-producing organs, to block androgen secretion[7]. Traditional endocrine therapy typically involves drug castration using Luteinizing hormone-releasing hormone agonists (LHRHa) [9]or androgen receptor antagonists[10], which block the effects of androgen. However, the ADT treatment's capabilities to entirely suppress androgen impact on PCa cells are partial, especially when considering androgen from the adrenal gland[11].

Currently, several guidelines recommend the use of new endocrine therapy for patients with PCa, particularly those suffering from advanced stages[6,12,13]. This new endocrine therapy targets specific molecules or signaling pathways in PCa cells to inhibit their proliferation. It includes two types of drugs that target the androgen receptor (AR) signal transduction pathway: androgen synthesis inhibitors, such as abiraterone[14–16], and AR inhibitors, which belong to a new type of non-steroidal anti-androgen drugs, such as enzalutamide[17–19] and apalutamide[20,21]. Compared with traditional endocrine therapy, these drugs exhibit higher targeting and selectivity, which can delay the progression of PCa and improve safety. They can also be used as a therapeutic option for patients with advanced PCa to improve overall survival[22,23]. In recent years, a variety of new endocrine therapy drugs have emerged, and combining them with ADT treatment has become the future trend of endocrine therapy. New endocrine therapy has become a research hotspot in the field of PCa treatment, and it is essential to analyze and summarize its current status and hotspots.

Bibliometrics is an effective quantitative method for evaluating academic papers that describes the relationships between documents using statistical data. It focuses on scientific papers as research objects and can provide an overview of a particular field, including research trends, hotspots, distribution of research efforts, and future research directions[24]. Bibliometrics has been extensively used in the medical field[25], particularly in studies related to tumor treatment[26,27]. However, despite the

widespread use of new endocrine therapy in PCa, no bibliometric studies have explored its application in this field.
We used bibliometric analysis to conduct a systematic overview of new endocrine therapy in PCa between 2003 and 2023, and thus provide an overview of current trends, topics, and bibliometric characteristics within this body of literature. The insights from our study offer substantive information and indicate potential avenues for future research in this rapidly evolving field.

2 Methods

Bibliometric data was obtained from the WoSCC database between January 1, 2003, and April 20, 2023. A literature search was conducted using the following search method. The search terms include ' prostate cancer ', ' prostate carcinoma ', and ' novel endocrine therapy '. The literature type was set as ' article or reviewer ' and language as English. The specific retrieval method can be seen in Fig.1
A total of 2,657 publications were initially retrieved, and after excluding 58 conference papers, 27 online publications, 8 book chapters, 2 data papers, and 1 recovered publication, 2,561 articles were obtained. An additional screening resulted in the exclusion of 109 papers - whose titles and abstracts deviated from the study's focus - leaving a final set of 2,452 papers for analysis. Two researchers completed the screening, collection, and analysis of all publications.
These selected publications were exported in plain text and tab-separated format for full-text records and references, respectively. This information was subsequently imported into several analysis tools: the Online Analysis Platform of Literature Metrology (https://bibliometric.com/), VOSviewer （1.6.19.0）, and CiteSpace （6.2.R2）. And Microsoft Excel 2019 was used to create histograms and trend charts depicting the citation frequency and publication distribution by year. Some indicators in WoS have certain reference value in evaluating academic influence and journal quality, such as H index, IF (impact factor) and JCR (journal citation report). The H index can be used to evaluate the overall academic influence and research level of a country. IF is considered to reflect the importance and popularity of journals in academia. JCR can help researchers understand the academic status and influence of journals, and provide reference for researchers to choose journals suitable for publishing papers.
The Online Analysis Platform of Literature Metrology was employed to illustrate the changes in the number of papers issued by different countries over the years, describe the relationship between countries, reflect the proportion of papers issued by different countries, and show the strength of cooperation between countries.VOSviewer（1.6.19.0） was used to generate visual knowledge graphs through the clustering mapping function, representing the co-occurrence frequency by the size of the nodes, the strength of the symbiotic relationship by the connection between each node, and clustering nodes of the same color. This study utilized VOSviewer to analyze national and institutional cooperation, journal co-citation, author cooperation, author co-citation, and journal co-citation. Citespace（6.2.R2）, a widely used visualization software in bibliometrics, is commonly employed to detect hot spots, potential trends, and evolutionary progress in research fields.Using CiteSpace, we assessed keyword timelines and citation burst of keywords or references. CiteSpace parameters were configured as follows: (1) Time slice from 2003 to 2023, with each slice representing two year; (2) Single node type selection at a time; (3) Selection criteria defined as Top N = 20; (4) Pruning performed using the pathfinder,pruning sliced networks and pruning the merged network.

3 Results

3.1 Analysis of publications output and trends

A total of 2,452 publications discussing the application of new endocrine therapy in PCa were collected from the WOS core collection database, spanning from 2003 to 2023 - a total of 20 years. Fig.2 highlights the publication and citation trend of new endocrine therapy for PCa. From 2003 to

2005, research on new endocrine therapy for PCa was in its infancy, resulting in a limited number of publications with annual publication rates less than 50. However, as research progressed, both the number of publications and citations increased gradually, indicating an overall upward trend. The highest number of publications was recorded in 2021 (n = 277, 11.3%), followed by 2022 (n = 264, 10.8%). Furthermore, the highest number of citations was recorded in 2022 (n = 12,385, 13.2%). The average number of publications per year was 122. A statistically significant correlation was observed between the year and the number of publications (R^2 = 0.9398) through data fitting. 254 publications are expected to be published in 2023.It is evident that the application of new endocrine therapy in PCa is expected to continue its growth trend.

3.2 Analysis of country distribution

The publications collected for this study originated from 73 countries (Fig3,4), with the United States contributing the most publications (n = 1,106), indicating that the U.S. holds the highest research productivity in this field . China and Italy follow closely behind in the second and third position, respectively. The U.S. also had the highest number of citations, signaling high-quality research within the country. France and England ranked second and third, respectively (Table 1). Using VOSviewer, we visualized the cooperative relationships among countries (Fig.5). Among the 40 countries that published eight or more papers, visual analysis revealed five clusters. In the same field, the U.S. has the closest cooperation with China, Canada, and Japan.

3.3 Analysis of institution distribution

A total of 3257 institutions participated in research within this field, with seven of the top ten institutions located in the USA, two in Canada, and one in Ireland. The University of British Columbia in Canada had the highest number of published papers, accounting for 5.1% (n=125) of all publications. The University of Washington in the USA came in second place, accounting for 2.3% (n=56). Both Johns Hopkins University and the University of Toronto, along with the NCI National Cancer Institute, had published 51 publications each (Table 2).

Visual analysis revealed that 41 institutions had published more than 20 papers, forming a total of 8 clusters with different colors representing distinct clusters. Despite the University of Tokyo having published a significant number of papers, it lacks cooperative relationships with other institutions (Fig.6).

In Fig.7, the average publication year of articles published by each institution is depicted with color representing different publication times, with deeper colors indicating earlier average publication years of the institution. As shown, most institutions' average publishing years are concentrated in 2014-2018, while a few institutions, such as the University of Melbourne, had average publishing years in 2019.

3.4 Analysis of authors and co-cited authors

The number of publications by a researcher is indicative of their contribution to the field. Table 3 displays the top 10 authors with the highest number of publications. Chang, Chawnshang (n=28) and Saad, Fred (n=28) had the most publications, originating from Tianjin Medical University and Universite de Montreal, respectively. They were followed by Antonarakis and Emmanuel S. (n=27), both from Johns Hopkins University. Four of the top 10 authors were from the United States, while three were from France.

For the VOSviewer analysis, the minimum number of documents for an author was set to 7.The results were obtained for 12,629 authors, with 114 authors meeting the set threshold

(Fig.8).Centrality is used to measure the importance or influence of an author in a certain field. In terms of author centrality analysis, Emmanuel S. Antonarakis from Johns Hopkins University (0.15) stood out. His publication on oligometastatic PCa stereotactic ablation radiotherapy (SABR) instead of ADT clinical phase 2 observational experiment in JAMA Oncology in 2020[28] gained him prominence. Antonarakis collaborated extensively with Chang and Chawnshang but not with Saad and Fred.

The number of times an author is co-cited indicates their level of influence in the field. The top three co-cited authors were Howard Scher (n=1236), Karim Fizazi (n=1110), and Matthew R. Smith (n=1068), with Scher having the highest centrality score of 0.18 (Tab 4). This suggests that Scher has conducted important research and holds significant influence in the field of new endocrine therapy for PCa.In 2014, Howard Scher conducted a double-blind, phase 3 study which found that enzalutamide significantly decreased the risk of radiographic progression and death, while also delaying the initiation of chemotherapy in men with metastatic PCa[29]. This study provides a more scientific basis for the new endocrine therapy of PCa, further highlighting Scher's important contributions to the field.

3.5 Analysis of Journals and Co-Cited Journals

A total of 597 journals have published articles in the field of novel endocrine therapy for PCa. Table 5 lists the top 10 journals in terms of publication volume.The top-ranked journal is *Cancers* from Switzerland, which has published 87 papers (IF=6.575, JCR=Q1). This indicates that the journal has a high academic level and influence in the field. The second-ranked journal is *Prostate* from the United States (n=71,IF=4.012,JCR=Q2). The third-ranked journal is *European Urology* from the Netherlands(n=63,IF=24.344, JCR=Q1), indicating its high international reputation and influence.The number of papers published by next few journals ranges from 33 to 59, and their impact factors range from 5.969 to 3.121, all of which are widely recognized journals in the field.

VOSviewer was used to cluster the 120 journals with more than 5 publications into 12 different clusters (Fig.10). *Cancers* and *European Urology* are in the same cluster, and there are a lot of mutual references between the articles published in these two journals. By using overlay visualization,we can find that *Cancers* has published more papers on novel endocrine treatment for PCa after 2020 (Fig.11).

Table 6 lists the top 10 cited journals in the field. From this table, it can be seen that *Journal of Clinical Oncology* and *New England Journal Of Medicine* are the two most commonly cited journals, with 8,739 and 7,147 citations, respectively. Both of these journals are from the United States and are classified as Q1 journals in the JCR. In addition, the *Lancet Oncology* from the United States has a total citation of 2,532, and its impact factor of 54.433 makes it a leading PCa research journal. It is not surprising that most of the journals commonly cited are from the United States, which once again proves the important position of the United States in the field of novel endocrine therapy for PCa research. It can be seen from the Vosviewer visualization analysis that among the top two magazines, *Journal of Clinical Oncology* and *New England Journal Of Medicine* also have more mutual citations (Fig.12).

3.6 Analysis of co-cited reference

A total of 73,942 cited references were identified, and table 7 captures the top 10 cited references. Firstly, among these ten entries, eight references were published in the *New England Journal of Medicine*. This implies the significant influence of this journal in the realm of PCa research, reinforced by its notably high impact factor of 158.5, the highest across these articles.Secondly, two authors, De Bono JS and Ryan CJ, each have two references on the list, asserting their widespread

recognition in the field of PCa research.Lastly, based on the article titles and citation counts, medications such as 'Enzalutamide', 'Abiraterone', 'Docetaxel', and 'Prednisone' may play key roles in the treatment of PCa and have achieved substantial therapeutic effects.

There were as many as 151 references cited over 50 times. Through visualization analysis by Vosviewer, four distinct clusters were obtained (Fig.13). In the blue cluster, the most frequently cited reference is *Increased survival with enzalutamide in prostate cancer after chemotherapy*[30] (n=450).The yellow cluster's most cited reference is *Abiraterone and increased survival in metastatic prostate cancer*[31] (n=445).In the red cluster, the most often referred to is *Development of a second-generation antiandrogen for treatment of advanced prostate cancer*[32] (n=266).Lastly, in the green cluster, the most cited is *Risk of fracture after androgen deprivation for prostate cancer*[33].

3.7 Analysis of keywords

Keyword co-occurrence, clustering, and burst analysis can help researchers pinpoint research hotspots, and discover emerging research topics and trends.

3.7.1 Keyword co-occurrence

Using CiteSpace, keyword extraction and visualization analysis were conducted on 2452 articles, yielding a total of 543 keywords (Fig14) .The top three most frequent keywords were 'prostate cancer', 'androgen deprivation therapy', and 'androgen receptor' (Table 8). Nodes marked with purple circles represent good betweenness centrality, and that these keywords such as 'lncap cells', 'bicalutamide', and 'hormone therapy', are important(Table 9). In other words, these keywords represent emerging trends in the field of new endocrine therapy for PCa.

3.7.2 Keywords burst

Furthermore, we visualized the top 25 keywords with the strongest bursts (Fig. 15) and found that 'carcinoma' was the keyword of the high intensity outbreak in 2003–2010, followed by 'hormonal therapy' and 'phase ii trial'. 'Enzalutamide' and 'metastasis free survival' has been the most focused keyword in the last 6 years. This may reflect future research trends to a certain extent and it may be related that Enzalutamide can improve the survival of PCa patients.

3.7.3 Keyword clustering and timeline

After clustering the keywords, 20 keyword clusters were identified(Table 10). To gain further insight into the evolution of these clusters, we visualized the keyword cluster timeline using CiteSpace. In the timeline figure, it can be observed that the core terms of each cluster have different levels of interest in each period, with some topics persisting and developing more research directions over time (#0 docetaxel, #5 metastatic castration-resistant prostate cancer, #9 lineage plasticity, #16 psma) (Fig. 16,17).

4 Discussion

This paper conducted a bibliometric analysis of the application of new endocrine therapy in PCa. A total of 2452 relevant articles from the WOSCC were retrieved and analyzed. It is observed that the overall number of publications has been increasing over time. The year 2012 recorded a significant surge with 130 publications, which may be attributed to the new recommendation statement on PCa screening and comprehensive management in the United States. Furthermore, the National Comprehensive Cancer Network (NCCN) updated their clinical practice guidelines for PCa in 2012, recommending the use of abiraterone acetate for metastatic castration recurrent prostate cancer（mCRPC）[40]. Since 2020, there has been a consistent annual publication volume exceeding 200. This substantial increase in publications indicates the growing interest and research activity in

this field, suggesting a promising future for further research endeavors in this area.

The United States stands out as the leading producer of literature in this field, with the highest number of publications, H-index, and citations globally. Seven out of the top 10 institutions contributing to the research are United States-based. China ranks second in total publication count but lacks representation in the top 10 institutions, and holds the lowest average citation per paper, implying lesser impact and quality of research papers. In contrast, France stands out in terms of research quality, as it has the highest average citation per paper, denoting a high recognition of French research in this field. The top 10 most productive journals in novel endocrine therapy for PCa rank in Q1 or Q2, based on IF and total publications, where *European Urology* stands out as highly influential. Mainly, it publishes guidelines on PCa, recommending new drugs like abiraterone acetate, enzalutamide, and apalutamide especially for metastatic castration-resistant PCa. These drugs offer significant survival benefits, nonetheless, treatment selection must be individualized. Saad, Fred stands out as the most productive author, in terms of citation ranking, Scher Howard takes the top position. These authors were involved in a double-blind phase III study on enzalutamide in metastatic prostate cancer（mPCa） before chemotherapy during the early stages.The findings of this study were significant, demonstrating that enzalutamide substantially reduced the risk of radiographic progression and death. Additionally, it delayed the need for initiating chemotherapy in men diagnosed with mPCa. This study contributed important evidence to support the effectiveness of enzalutamide in the treatment of this patient population.

Keyword co-occurrence can aid in understanding the relationships and trends within a field. PCa is an androgen-dependent disease, and the action of androgens is primarily mediated by the AR, a hormone-activated transcription factor[41,42]. Like most nuclear receptors, AR is composed of distinct functional domains. These include an amino-terminal domain, DNA-binding domain, hinge region, and ligand-binding domain. Unliganded AR is inactive and requires binding and activation by testosterone or dihydrotestosterone to function. The hormone-bound AR dimerizes and translocates to the cell nucleus where it binds to DNA and interacts with a series of transcription co-regulatory factors to regulate target gene expression[43]. Thus, inhibiting the production of testosterone or dihydrotestosterone or suppressing the binding of AR with hormones is a key strategy for treating PCa (hormonal therapy), including androgen deprivation therapy (ADT) and androgen receptor pathway inhibitors. Bicalutamide, approved for use in the United States in 1995[44], is an important drug in ADT therapy. It acts by binding to intracellular androgen receptors and competitively inhibiting the actions of endogenous androgens on sensitive tissues (including the testes, prostate and hypothalamus), often used in combination with Luteinizing Hormone-Releasing Hormone (LHRH) analogues (such as leuprolide or goserelin) for the treatment of metastatic PCa[13,6]. However, hormone-resistant PCa can gradually develop post-treatment, possibly related to the amplification, mutation, and overexpression of the AR receptor[41,42,45]. The LNCaP cell line is commonly used in PCa research. LNCaP cells are propagated from human prostate adenocarcinoma tissues. They present a widely studied model system for examining various aspects of PCa biology, including tumor growth, response to hormones, and drug sensitivity. These cells are often used in experimental research to assess the efficacy of different treatment methods or to explore the molecular mechanisms underlying the development and progression of PCa[46,47] .

During the period from 2003 to 2023, keywords citations burst analysis reveals a shift in research focus related to new endocrine therapy for PCa. The research trend gradually transitioned from studying carcinoma, hormonal therapy, and phase II trials to specific drugs targeting PCa, such as enzalutamide. This indicates an increasing precision and specificity in the development of new endocrine therapy for PCa over time. Enzalutamide, as a specific drug for PCa, works by directly binding to the androgen receptor and inhibiting androgen binding, androgen receptor nuclear translocation, and androgen receptor-mediated DNA binding[48]. In a phase III study involving patients with Metastatic Hormone-Sensitive PCa, the use of enzalutamide combined with ADT (androgen deprivation therapy) significantly reduced the risk of metastatic progression or death compared to

placebo plus ADT, even in men with low-volume disease and/or prior docetaxel treatment[17]. Another double-blind, phase III trial focused on patients with Nonmetastatic, Castration-Resistant PCa. In this trial, enzalutamide demonstrated significant benefits compared to the placebo group. Enzalutamide showed longer metastasis-free survival in men with non-metastatic, castration-resistant PCa experiencing rapidly increasing PSA values[18].In recent years, ' metastasis free survival ' outcome indicators have been paid more and more attention in large-scale clinical studies.The use of enzalutamide reduced the risk of metastasis or death in these patients. However, it is important to note that the use of enzalutamide is not without risks. Some potential risks associated with enzalutamide treatment include hypertension, myocardial infarction, fatigue, falls, and fractures. These risks should be taken into consideration when evaluating the benefits and potential side effects of enzalutamide in PCa treatment[18,22].

A total of 20 keyword clusters were identified, the largest of which is "docetaxel," encompassing 54 keywords.Since its approval in 2004, docetaxel has demonstrated survival benefits and improved clinical outcomes[34]. In recent years, with the extensive use of docetaxel, researchers have explored and evaluated an increasing number of combination therapies based on docetaxel in an effort to enhance survival rates or clinical outcomes for patients with prostate cancer[49–51]. A multicenter, open-label, randomized, phase 3 study indicated that the combination of docetaxel, ADT (Androgen Deprivation Therapy), and abiraterone can significantly improve the overall survival and radiographic progression-free survival of de novo metastatic castration-sensitive prostate cancer. However, the risk of hypertension increased moderately at the same time[52].

mCRPC is a significant stage in PCa progression and a primary cause of cancer-related death. The pathological process is closely related to the androgen receptor (AR) axis. Therefore, androgen receptor signaling inhibitors (ARSI) are main medications for endocrine therapy, and targeting the AR pathway is a crucial choice for novel endocrine treatments. Medications with improved affinity for the AR are more effective in conducting novel endocrine treatments[42]. Abiraterone acetate, Enzalutamide, Apalutamide (APA), Darolutamide (DAR) are the focus of new endocrine drugs.Abiraterone acetate can specifically inhibit cytochrome P (CYP) 17. When used in combination with prednisone (AA/P), it can delay the progression of prostate cancer and improve the survival period of prostate cancer patients[15,35]. Enzalutamide is a multi-target AR inhibitor with a higher AR affinity compared to the first-generation AR antagonist (such as bicalutamide, nilutamide)[48]. APA binds to AR with an affinity five times greater than bicalutamide. In males with mCRPC, 80% of AAP-naive and 43% of post-AAP patients continued APA therapy for 6 months or longer, and acquired benefits with a 50% objective response rate (ORR) in the AAP-naïve mCRPC group, but no ORR was observed in the post-AAP mCRPC group[20,21,23]. DAR is a stronger AR antagonist than ENZ or APA. In phase I and II clinical studies (ARADES), DAR was shown to be beneficial in patients with mCRPC, with one complete response and two partial responses observed (ORR: 50%) demonstrating a good safety profile[53,54].

Lineage plasticity signifies a mechanism facilitating the evasion of cancer from targeted treatments, paving the way for drug resistance. Post ADT treatment, the cell phenotype of prostate cancer illustrates lineage plasticity, transitioning from AR-dependent adenocarcinoma to AR-resistant neuroendocrine carcinoma, which fuels the progression of neuroendocrine PCa. This kind of lineage plasticity displays distinctive epigenetic characteristics, diminished AR signal transduction, and acquired expression of markers for neuroendocrine stem cells[55,56]. The elevated expression of the reprogramming transcription factor SOX2 orchestrates the functional loss of the tumor suppressor entities TP53 and RB1, thereby fostering the conversion from AR-dependent lumen epithelial cells to AR-independent basal-like cells[57]. Research by Joseph et al. discovered that the lineage plasticity of prostate cancer materializes through the proliferation of lumen and basal lineage epithelial cells, which are contingent on the activation of the JAK/STAT inflammation pathway. The mutation in the human tumor suppressor gene p53, TP53, in concert with the loss of the retinoblastoma tumor suppressor gene RB1, results in ADT-resilient phenotype[58].

PSMA is a type of transmembrane glycoprotein that showcases significant overexpression in most prostate cancer cells, thereby gaining increased interest as an imaging target molecule[59]. PSMA-PET imaging can supplement molecular data to multiparametric MRI, hence delineating potential lesions for targeted biopsies, particularly in cases where biopsy specimens do not indicate the presence of a tumor. In comparison to conventional imaging modalities like CT, MRI, and bone scintigraphy, PSMA-PET imaging exhibits elevated sensitivity and specificity in patients with primary intermediate to high-risk prostate carcinoma. It even improves the identification of metastatic lesions in biochemical relapse PCa even with lower serum PSA levels[60]. A phase III multicentric imaging study indicates that in intermediate to high-risk prostate cancer patients undergoing radical prostatectomy and lymph node dissection, the sensitivity and specificity of 68Ga-PSMA-11 PET stand at 0.40 and 0.95 respectively[61]. Radioligand therapy with [177Lu]Lu-PSMA-617, a radiolabeled small molecule, is capable of dispensing β-radiation to PSMA-expressing cells. This therapy when added to standard care processes in patients with advanced PSMA-positive metastatic castration-resistant prostate cancer, extends both the progression-free survival and overall survival as observed in imaging-based assessment. When compared to cabazitaxel's effectiveness in patients with metastatic castration-resistant prostate cancer, [177Lu]Lu-PSMA-617 induces a relatively higher PSA response with fewer grade 3 or 4 adverse incidents. Subsequently, [177Lu]Lu-PSMA-617 emerges as a promising novel therapeutic option and a potential substitute to cabazitaxel[62,63].

5 Limitations

Our chosen dataset has certain limitations that should be noted. Primarily, it is anchored only on data from the WoSSC database. This could potentially exclude some pertinent studies found in other substantial databases. Nevertheless, WoSSC is broadly recognized for its robust use in bibliometrics, and therefore possesses adequate data to provide a reliable representation of the current status in the PCa research field. A secondary constraint is our exclusive focus on literature in English, which may inadvertently underplay the contribution from regions that employ non-English languages in their scholarly works. A final consideration lies in the continually evolving nature of the database, implying that recent publications and their impact may not be fully estimated due to temporal limitations.

6 Conclusion

In conclusion, our comprehensive bibliometric analysis revealed that new endocrine therapy for PCa has been increasingly attracting attention as a research hotspot over the past 20 years, with continuous growth in the volume of publications. The United States has been a global leader in this field in terms of research quantity and quality. Futuristic research endeavors should focus on specific drugs such as enzalutamide and explore the concept of lineage plasticity and role of PSMA. Publications on these pivotal topics enhance our understanding of PCa progression and treatment options. The insights from our study offer a firm foundation for future research, potentially steering therapeutic strategies for PCa towards greater effectiveness and precision.

7 Conflict of Interest

None.

8 Author Contributions

HM contributed to the conception and design of this article, and collaborated with JL and PZ in downloading and organizing related research papers. HM, JW, and FY made contributions to all the tables and figures as well as the main manuscript. JL and JW conducted revisions and additions to the initial draft of the paper. All authors have read and approved the final manuscript.

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11 Date Availability Statement

All data generated in this study were all derived from the published articles and available from the corresponding author upon reasonable request.

12 Reference styles

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Table1 The top 10 countries of publications

Rank	Countries	Counts	H-index	Citations	TLS	Average citation per paper
1	USA	1106	102	55126	752	49.84
2	China	333	39	6999	246	21.02
3	Italy	264	47	16345	367	61.91
4	Canada	242	53	15373	360	63.52
5	England	208	57	17686	460	85.03
6	France	166	47	20441	441	123.14
7	Japan	164	37	6634	89	40.45
8	Germany	156	47	16800	412	107.70
9	Australia	113	33	8065	198	71.37
10	Spain	96	29	7864	230	81.92

Table2 The top 10 institutions of publications

Rank	Institutions	Counts	Country	H-index	Citations	TLS	Average citation per paper
1	University Of British Columbia	125	Canada	32	2267	63	39.78
2	University Of Washington	56	USA	28	3029	90	54.09
3	Johns Hopkins University	51	USA	40	3536	63	69.33
4	University Toronto	51	Canada	32	2520	81	49.41
5	NCI National Cancer Institute	51	Ireland	23	2216	11	43.45
6	University Michigan	48	USA	24	2838	95	59.13
7	University Of California San Francisco	45	USA	22	2113	78	46.96
8	Memorial Sloan Kettering Cancer Center	43	USA	25	3164	89	73.58
9	University Of Rochester	39	USA	26	2327	40	59.67
10	Mayo Clinic	38	USA	22	1311	57	34.50

Table 3 The top 10 Authors of Publications

Table 4 The top 10 co-cited authors

Rank	Author	Institution	Country	Count	Centrality
1	Chang,Chawnshang	Tianjin Medical University	China	29	0.09
2	Saad,Fred	Universite de Montreal	Canada	28	0.09
3	Antonarakis,Emmanuel s.	Johns Hopkins University	USA	27	0.15
4	Fizazi,Karim	Universite Paris Saclay	France	23	0.11
5	Shore,Neal d.	Carolina Urologic Research Center	USA	21	0.07
6	Yeh,Shuyuan	Universite Paris Saclay	France	17	0.01
7	Caffo,Orazio	Santa Chiara Hospital	Italy	16	0.05
8	Tucci,Marcello	Cardinal Massaia Hosp	USA	15	0.02
9	Crawford,e.David	University of California San Diego	USA	15	0.03
10	Oudard,Stephane	Universite Paris Cite	France	15	0.04

Rank	Co-cited author	Institution	Country	Count	Centrality
1	Scher, Howard	Weill Cornell Medicine	USA	1236	0.18
2	Fizazi, Karim	Universite Paris Saclay	France	1110	0.05
3	Smith, Matthew R.	Massachusetts General Hospital	USA	1068	0.09
4	de Bono, Johann	Royal Marsden NHS Foundation Trust	England	917	0.07
5	Ryan, Charles J.	University of Minnesota Twin Cities	USA	702	0.09
6	Antonarakis, Emmanuel S.	Johns Hopkins Sidney Kimmel Comprehensive Cancer Center	USA	553	0.13
7	James, Nicholas D.	Royal Marsden NHS Foundation Trust	England	551	0.06
8	Tannock, Ian F. F.	Princess Margaret Cancer Centre	Canada	540	0.06
9	Beer, Tomasz M.	Oregon Health & Science University	USA	527	0.04
10	Attard, Gerhardt	University College London	England	520	0.04

Table 5 The top 10 journals in terms of publication volume

Rank	Journal	Count	Country	IF (2021)	JCR(2021)
1	Cancers	87	Switzerland	6.575	Q1
2	Prostate	71	USA	4.012	Q2
3	European Urology	63	Netherlands	24.344	Q1
4	BJU International	59	England	5.969	Q1
5	Frontiers In Oncology	47	Switzerland	5.738	Q2
6	Journal Of Urology	39	USA	7.641	Q1
7	Endocrine Related Cancer	38	England	5.905	Q1
8	Clinical Genitourinary Cancer	37	USA	3.121	Q2
9	PCa And Prostatic Diseases	34	England	5.455	Q2
10	Oncotarget	33	USA	5.168	0

Table 6 The top 10 co-cited journals

Rank	Co-cited journal	Count	Country	IF (2022)	JCR(2022)
1	Journal Of Clinical Oncology	8739	USA	50.739	Q1
2	New England Journal Of Medicine	7147	USA	176.079	Q1
3	Cancer Research		USA	13.312	Q1
4	European Urology	5555	Netherlands	24.344	Q1
5	Journal Of Urology	4738	USA	7.641	Q1
6	Clinical Cancer Research	4117	USA	13.801	Q1
7	Prostate	3039	USA	4.012	Q2
8	Urology	2566	USA	2.633	Q3
9	Lancet Oncology	2532	USA	54.433	Q1
10	International Journal Of Radiation Oncology Biology Physics	2397	USA	8.013	Q1

Table 7 The top 10 co-cited reference

Rank	Title	Journal	Author	IF	Year	Citations
1	Increased survival with enzalutamide in prostate cancer after chemotherapy[30]	The New England journal of medicine	Scher HI	158.5	2012	450
2	Abiraterone and increased survival in metastatic prostate cancer[31]	The New England journal of medicine	De Bono JS	158.5	2011	445

3	Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer[34]	The New England journal of medicine	Tannock IF	158.5	2004	393
4	Abiraterone in metastatic prostate cancer without previous chemotherapy[35]	The New England journal of medicine	Ryan CJ	158.5	2013	302
5	Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial[36]	Lancet (London, England)	De Bono JS	168.9	2010	290
6	Enzalutamide in metastatic prostate cancer before chemotherapy[29]	The New England journal of medicine	Beer TM	158.5	2014	288
7	Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer[37]	The New England journal of medicine	Petrylak DP	158.5	2004	275
8	Development of a second-generation antiandrogen for treatment of advanced prostate cancer[32]	Science	Chris Tran	56.9	2009	266

9	Sipuleucel-T immunotherapy for castration-resistant prostate cancer[38]	The New England journal of medicine	Kantoff PW	158.5	2010	257
10	Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer[39]	The New England journal of medicine	Christopher J Sweeney	158.5	2015	254

Table 8 Top 10 keywords with the largest number

Rank	Count	Centrality	Year	Keyword
1	1161	0	2003	prostate cancer
2	803	0.01	2003	androgen deprivation therapy
3	391	0.07	2003	androgen receptor
4	355	0.01	2003	men
5	301	0.11	2003	radical prostatectomy
6	289	0.02	2003	expression
7	278	0	2009	abiraterone acetate
8	237	0.02	2003	progression
9	234	0	2012	increased survival
10	224	0.01	2013	enzalutamide
11	214	0.12	2005	double blind
12	208	0	2009	survival
13	205	0.02	2003	docetaxel

Table 9 Keywords of centrality ranking

Rank	Centrality	Count	Year	Keyword

1	0.3	35	2003	lncap cells
2	0.29	35	2003	bicalutamide
3	0.28	75	2004	hormone therapy
4	0.21	97	2003	chemotherapy
5	0.2	35	2004	antiandrogen withdrawal
6	0.17	14	2010	dose rate brachytherapy
7	0.15	49	2006	external beam radiotherapy
8	0.15	39	2009	recurrence
9	0.14	27	2005	combination
10	0.14	18	2004	cyproterone acetate
11	0.13	2	2003	androgen ablation
12	0.12	214	2005	double blind
13	0.12	57	2005	proliferation
14	0.12	17	2003	biochemical failure
15	0.11	301	2003	radical prostatectomy
16	0.11	79	2008	biochemical recurrence
17	0.11	28	2003	flutamide
18	0.11	6	2009	steroidal inhibitors
19	0.1	78	2006	gene expression
20	0.1	52	2004	randomized trial
21	0.1	15	2005	androgen suppression
22	0.1	10	2017	renal cell carcinoma
23	0.1	6	2007	chromogranin a

Table 10 Keyword clustering

ClusterID	Size	Silhouette	mean(Year)	Key words
0	54	0.923	2009	docetaxel

1	42	0.827	2012	drug resistance
2	39	0.938	2014	neuroendocrine prostate cancer
3	36	0.903	2008	prostate cancer
4	32	0.884	2010	radiotherapy
5	32	0.806	2014	metastatic castration-resistant prostate cancer
6	30	0.867	2009	enzalutamide
7	26	0.939	2010	tumor suppressor
8	26	0.937	2013	in vivo
9	26	0.916	2015	lineage plasticity
10	25	0.955	2009	abiraterone acetate
11	24	0.986	2012	radiation therapy
12	22	0.977	2011	androgen receptor
13	20	0.909	2012	serum testosterone
14	20	0.981	2010	prostatic neoplasms
15	20	0.838	2009	breast cancer
16	18	0.936	2016	psma
17	17	0.969	2013	degarelix
18	17	0.862	2010	deprivation
19	14	0.969	2009	deprivation therapy

Supplementary Files