Systematic Review and Meta-Analysis

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Metastatic castration-resistant prostate cancer: Academic insights and perspectives through bibliometric analysis

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Abstract

Background: In recent years, metastatic castration-resistant prostate cancer (MCRPC) and studies related to MCRPC have drawn global attention. The main objective of this bibliometric study was to provide an overview of MCRPC, explore clusters and trends in research and investigate the future direction of MCRPC research.

Methods: A total of 4089 publications published between 1979 and 2018 were retrieved from the Web of Science (WoS) Core Collection database. Different aspects of MCRPC research, including the countries/territories, institutions, journals, authors, research areas, funding agencies and author keywords, were analyzed.

Results: The number of annual MCRPC publications increased rapidly after 2010. American researchers played a vital role in this increase, as they published the most publications. The most productive institution was Memorial Sloan Kettering Cancer Center. De Bono, JS (the United Kingdom [UK]) and Scher, HI (the United States of America [USA]) were the two most productive authors. The National Institutes of Health (NIH) funded the largest number of published papers. Analyses of keywords suggested that therapies (abiraterone, enzalutamide, etc.) would attract global attention after US Food and Drug Administration (FDA) approval.

Conclusions: Developed countries, especially the USA, were the leading nations for MCRPC research because of their abundant funding and frequent international collaborations. Therapy was one of the most vital aspects of MCRPC research. Therapies targeting DNA repair or the androgen receptor (AR) signing pathway and new therapies especially prostate-specific membrane antigen (PSMA)-based radioligand therapy (RLT) would be the next focus of MCRPC research.

Abbreviations: AA/P = abiraterone acetate plus prednisone, ACCP = average citations per paper, AR = androgen receptor, CTC = circulating tumor cells, DDA = Derwent Data Analyzer, FDA = Food and Drug Administration, MCRPC = metastatic castration-resistant prostate cancer, nCC = number of cooperative countries or regions, OS = overall survival, PSMA = prostate-specific membrane antigen, RLT = radioligand therapy, SP = Share of publications, TC = total citations, TP = total paper, TPR% = the percentage of articles of journals in total publications, WoS = Web of Science.

Keywords: bibliometric analysis, bone metastases, drug resistance, metastatic castration-resistant prostate cancer (MCRPC), prostate-specific membrane antigen (PSMA), therapy

1. Introduction

Prostate cancer (PCa) is one of the most prevalent malignancies in the world[1–3] and the third most common cause of male cancer-related death in the United States of America (USA).[1] The majority of men with newly diagnosed PCa present with localized disease and undergo radical prostatectomy and/or radiological therapy, followed by androgen deprivation therapy (ADT).[4,5] Depending on the grade of the cancer, a variable percentage of these patients experience progression to castration-resistant prostate cancer (CRPC) within 10 years.[6,7] CRPC was previously named "hormone-refractory prostate cancer" and

Editor: Giandomenico Roviello.

This work is financially supported by the Natural Science Foundation of Zhejiang Province (No. LY18H160063) and the Zhejiang Medical Science and Technology Project (No. 2019RC241).

The authors have no conflicts of interest to disclose.

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How to cite this article: He L, Fang H, Chen C, Wu Y, Wang Y, Ge H, Wang L, Wan Y, He H. Metastatic castration-resistant prostate cancer: Academic insights and perspectives through bibliometric analysis. Medicine 2020;99:15(e19760).

Received: 16 August 2019 / Received in final form: 28 December 2019 / Accepted: 3 January 2020

http://dx.doi.org/10.1097/MD.0000000000019760

"androgen-independent prostate cancer".[8,9] However, because castration treatments including ADT were ineffective, these cancers still showed reliance upon hormones for androgen receptor (AR) activation.[10] Thus, "hormone-refractory prostate cancer" and "androgen-independent prostate cancer" were replaced by the term "castration-resistant prostate cancer (CRPC)".[11] Although metastatic castration-resistant prostate cancer (MCRPC) patients currently benefit from a wealth of effective treatment options, MCRPC remains incurable, and the prognosis of these patients is quite poor. For men with CRPC, the median survival ranges from 9 to 30 months, and for those with MCRPC, this survival is reduced to 9–13 months.[12]

Currently, cytotoxic chemotherapy agents, AR blocking agents, immunotherapies, and radiopharmaceuticals represent effective therapeutic strategies for MCRPC treatment.[7,13] Taxane chemotherapy (docetaxel and cabazitaxel) is the standard for MCRPC treatment.[7,14,15] Abiraterone and enzalutamide represent significant breakthroughs in the treatment of MCRPC and bestow significant survival benefits.[16–23] Sipuleucel-T, a novel active cellular immunotherapy, can prolong the overall survival (OS) of men with MCRPC.[13,24–27] Radium-223 (Ra 223) dichloride targets bone metastases with high-energy, short-range a-particles, improves OS, and is a good treatment option for patients with CRPC and symptomatic bone metastases.[28–30] Denosumab, a human anti-RANKL monoclonal antibody, can delay bone metastasis in men with PCa.[31,32] According to recent guidelines, the first-line treatments for MCRPC include abiraterone acetate plus prednisone (AA/P), enzalutamide, radium 223, docetaxel, and sipuleucel-T. Cabazitaxel, AA/P, enzalutamide, and radium have been approved as second-line treatments for CRPC following docetaxel treatment.[6,7,13,28,33–35]

Although men with MCRPC benefit from all of these new therapies, a significant proportion of patients exhibit primary resistance to these agents, and virtually all patients develop secondary resistance.[36,37] The resistance mechanisms of tumors to AR blocking agents, including AR protein overexpression, AR gene amplification, AR gene mutations, and AR variants (AR-Vs), are directly related to the activation of AR-dependent pathways[38,39] and processes independent of the AR signaling pathway. The reported mechanisms of resistance to taxanes are related to several contributing factors, such as tubulin alterations, multidrug-resistance (MDR) kinesin overexpression, signaling pathways and cytokines related to epithelial-mesenchymal transition (EMT), ETS fusion gene family members, and AR splice variants (AR-SVs).[40] Putative predictive biomarkers, including AR-SVs, homologous recombination (HR) repair defects including BRCA2 loss, mismatch repair (MMR) defects, and phosphatase and tensin homolog (PTEN) loss, would also benefit the treatment of the disease.[41] Comprehensive and integrative genomic analysis of MCRPC could make individualized targeted therapies possible and help to develop new drugs.[42] Olaparib was the first poly(adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitor to be tested in men with PCa and could prolong OS in patients with PARP mutations.[43–45] Other PARP inhibitors (rucaparib and niraparib) are still being tested in clinical trials.[46,47] Pembrolizumab, an anti-PD 1 antibody, might be useful in advanced PD-L1-positive PCa.[48–51] The results of clinical trials treating MCRPC with another anti-PD 1 antibody, atezolizumab, were reported recently.[52–55] Radioligand therapy (RLT) with [Lu-177] Lu-PSMA-617 (Lu-PSMA) is a novel targeted therapy that seems to be safe, and this therapy prolong overall survival in men with MCRPC.[56–60] Ipatasertib (an AKT inhibitor) in combination with abiraterone acetate might be active against tumors with PIK3CA mutations or PTEN loss in men with MCRPC.[61] There are other therapies (veliparib and ipilimumab) for MCRPC in clinical trials not mentioned above.[62–65]Thus, sequencing-based tumor analyses could identify specific genomic aberrations and guide individualized therapy.[41] To implement precision cancer medicine effectively, more predictive or prognostic biomarkers (such as circulating tumor cells [CTC][66] or AR-V7[67]) are being developed to predict the therapeutic efficiency or resistance to therapy as well as patient prognosis.[68,69]

Bibliometric analysis is an effective method for analyzing scientific publications and identifying the trends of present or future studies. This approach has been widely used in the area of medicine.[70–72] MCRPC remains incurable and is a hot topic in the field of urology. An increasing number of articles and reviews related to the therapies, cellular mechanisms, and other aspects of MCRPC have been published, but a quantitative description of the publications on MCRPC is lacking. A comprehensive bibliometric study was conducted on this subject. This study aimed to provide an overview of MCRPC from 1979 to 2018, explore clusters and trends in research, and investigate the future direction of MCRPC research.

2. Method and data

This bibliometric study analyzed the papers related to "metastatic castration-resistant prostate cancer" obtained from the Science Citation Index-Expanded (SCI-E) that were published during the period from 1979 to 2018 (the year 1979 was chosen as a starting point when the first paper was published[73]). The data were acquired through the Web of Science (WoS) Core Collection database by searching the "topic" field, which included the title, abstract, and keyword fields, on 4 November 2018. The search strategy for the WoS database was (TS =("castrat* resistant" or "hormone refractory" or "hormone independent" or "hormone resistant" or "hormone insensitive" or "androgen independent" or "androgen insensitive" or "androgen refractory" or "castration recurrent" or "androgen resistant" or "castration refractory") and metastatic and ("prostat* Neoplasm*" or "prostat* Tumor*" or "prostat* Cancer*" or "prostat* carcinoma*" or "prostat* adenocarcinoma*") or "MCRPC" or "metastatic CRPC" or "metastatic neuroendocrine prostate cancer" OR "metastatic NEPC"). The papers originating from England, Scotland, Northern Ireland, and Wales were classified as belonging to the United Kingdom (UK), while those from Macao, Taiwan, and Hong Kong were not grouped under the China heading.

A total of 6304 publications, including 118 SCI-E highly cited articles and 4 SCI-E hot articles, matched the choice criteria listed above across 13 document types. The 13 document types were article (3304), meeting abstract (1883), review (785), editorial material (201), proceedings paper (123), letter (82), correction (29), news item (10), note (9), data paper (5), book chapter (4), retracted publication (3), and retraction (1). Of the 6304 publications, a total of 6124 (97.145%) were published in English. The other eight languages were German (83; 1.317%), French (65; 1.031%), Spanish (25; 0.397%), Hungarian (3; 0.048%), Korean (1; 0.016%), Polish (1; 0.016%), Welsh (1; 0.016%), and Turkish (1; 0.04%). Thus, English was the predominant language of the academic publications on MCRPC

research. Only articles and reviews were further analyzed because they not only comprised the majority of the publications but also were peer-reviewed. Meeting abstracts were not evaluated because they tend to reflect organizational logistics rather than editorial decisions.[74] The impact factors (IFs) of the WoS journals were determined from the 2017 Journal Citation Reports (JCR). Derwent Data Analyzer (DDA) software was used to assess the data and analyze journals, keywords, and international cooperation.

3. Results and discussion

3.1. The performance of related publications and countries

Seventy-six countries contributed 6304 publications to the MCRPC research field between 1979 and 2018, indicating that MCRPC is a global health problem that attracts worldwide attention. During the first year, there was only one published study within the WoS, and annual publication numbers grew slowly in the first 20 years (Fig. 1). During the next 10 years, the number of annual publications increased from 66 (2000) to 187 (2009). In the last 9 years (2010–2018), the annual publication number has increased rapidly, rising from 189 (2010) to 606 (2018). Thus, MCRPC has attracted increasing attention and has become one of the hottest research fields in cancer research.

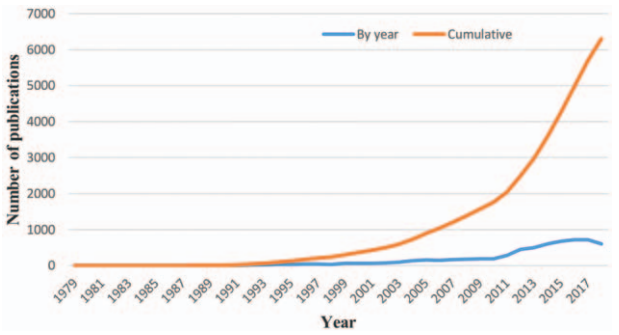

Figure 1. Trends in the number of publications related to MCRPC by year.

3.2. Cooperation of countries/territories

Publications on MCRPC between 1979 and 2018 came from 76 countries. The top 20 most productive countries/territories in the MCRPC research field are shown in Table 1. The USA headed the list, with a publication share of 35.96% and the highest h-index (155). The UK ranked second, followed by Canada, France, Italy and Germany. The Netherlands, mainland China, Japan, and Spain were ranked in positions 6–10. The remaining 20 most productive countries/territories were mostly in Europe. Economic development seemed to not only increase the incidence of PCa[75,76] but also contribute to high scientific and academic investments, as nearly all of the 20 most productive countries/territories were economically prosperous. In Western countries, the incidence of PCa was higher than that in developing countries. The first reason for this difference was that the men in Western countries had more access to medical care, including screening and early detection.[77] The second reason was that the incidence of PCa was related to environmental, dietary, and genetic factors.[78–80]

DDA software was used to draw a network diagram from a cooccurrence matrix.[81] Each node represented a different country, and node size corresponded to the number of publications. Similarly, the lines connecting the countries represented their cooperation, and the line thickness indicated the frequencies of that collaboration. The academic collaboration network of the top 20 most productive countries/territories is shown in Figure 2. The USA was the center of this collaboration network and the leader of MCRPC research in cooperation with the other 53 countries/territories. Asian countries/territories such

Table 1

Contribution and impact of the top 20 most productive countries/territories in MCRPC research.

Rank	Country/territory	TP	TPR%	h-index	ACCP	TC	SP (%)	nCC
1	Usa	2267	35.96	155	53.97	122361	31.58	53
2	Uk	413	6.55	72	80.62	33296	63.68	45
3	Canada	383	6.08	69	72.51	27772	67.62	40
4	France	343	5.44	61	71.15	24404	56.56	42
5	Italy	343	5.44	49	47.41	16252	42.86	40
5	Germany	341	5.41	57	46.79	15954	48.97	43
7	The Netherlands	230	3.65	55	79.67	18323	73.91	41
8	Peoples R China	196	3.11	29	16.81	3294	45.92	19
9	Japan	185	2.93	32	26.09	4827	30.27	30
10	Spain	162	2.57	31	42.1	6820	56.79	39
11	Australia	146	2.32	40	85.81	12528	57.53	36
12	Belgium	132	2.09	34	73.98	9766	84.85	40
13	Sweden	102	1.62	28	78.55	8012	57.84	34
14	Switzerland	88	1.40	33	55.08	4847	78.41	25
15	Taiwan	55	0.87	15	12.13	667	61.82	14
15	Denmark	54	0.86	22	83.93	4532	72.22	33
17	South Korea	52	0.82	12	29.23	1520	44.23	27
18	Austria	51	0.81	23	58.67	2992	70.59	25
19	Finland	44	0.698	23	55.55	2444	77.27	22
20	Greece	43	0.682	19	54.3	2335	62.79	31

ACCP = average citations per paper, nCC = number of cooperative countries or regions, SP = Share of publications, TC = total citations, TP = total paper, TPR% = the percentage of articles of journals in total publications.

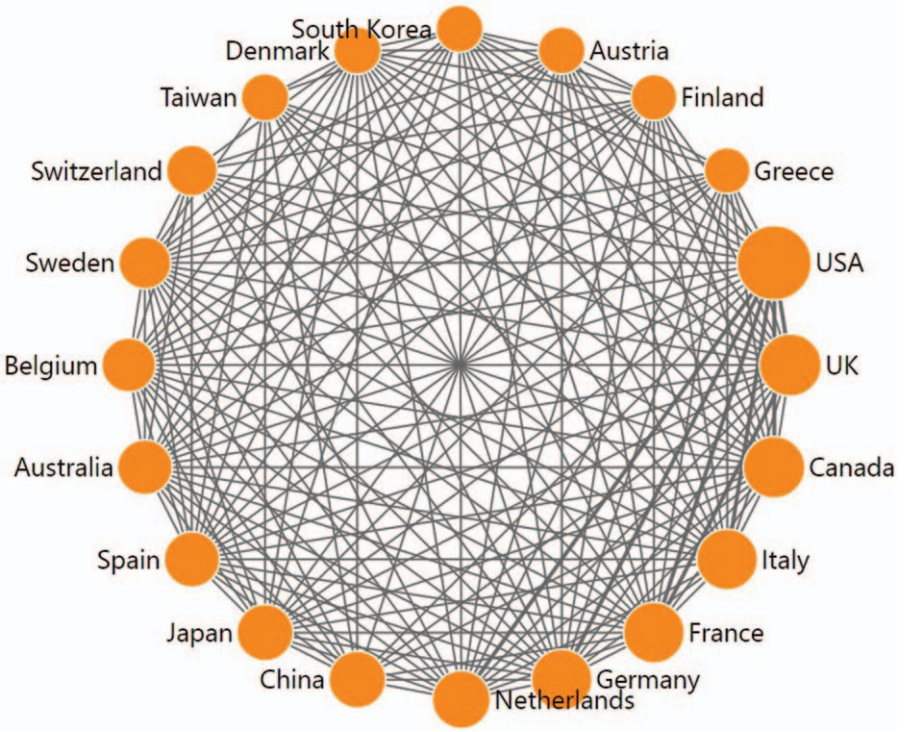

Figure 2. Collaborative relationships among the top 20 most productive countries/territories.

as mainland China, Japan, South Korea, and Taiwan had smaller collaboration networks than European countries and North American countries, might explain why Asian countries/territories had smaller h-indexes, TCs, and ACCPs.[82] This network might also suggest that collaborations benefit the number, impact, and quality of the papers.[83,84]

3.3. Institute contributions to publications

The top 20 most productive institutes from 1979 to 2018 are listed in Table 2: three of these institutes are based in the UK, two are in Canada, and the rest are in the USA. This distribution reiterated the predominance of the USA in the research field of MCRPC. As the most historical and largest private cancer center in the world,

Table 2

The top 20 most productive institutions of publication, citations, and h-index.

Rank	Institution	TP	TPR%	TC	ACCP	h-index	Country
1	Memorial Sloan Kettering Cancer Center	208	5.087	22064	106.08	64	USA
2	University of California San Francisco	181	4.427	17523	96.81	49	USA
3	University of Washington	178	4.353	19564	109.91	53	USA
4	University of Michigan	145	3.546	16401	113.11	54	USA
5	National Cancer Institute	143	3.497	7501	52.45	45	USA
5	Johns Hopkins University	136	3.326	15333	112.74	47	USA
7	Institute of Cancer Research	130	3.179	15708	120.83	46	UK
8	Duke University	126	3.081	8680	68.89	39	USA
9	Dana-Farber Cancer Institute	119	2.910	10797	90.73	36	USA
10	Harvard University	104	2.543	10615	102.07	39	USA
11	Oregon Health & Science University	91	2.225	6510	71.54	27	USA
12	University of Texas MD Anderson Cancer Center	91	2.225	7760	85.27	31	USA
13	University of British Columbia	79	1.932	2652	33.57	29	Canada
14	Royal Marsden NHS Foundation Trust	77	1.883	5916	76.83	31	UK
15	University of California Los Angeles	75	1.834	5459	72.79	31	USA
15	Weill Cornell Medical College	75	1.834	8744	116.59	33	USA
17	Fred Hutchinson Cancer Research Center	70	1.712	3946	56.37	26	USA
18	Baylor College of Medicine	66	1.614	5658	85.73	29	USA
19	University of Toronto	63	1.541	6489	103	28	Canada
20	The Royal Marsden Hospital	62	1.516	11383	183.6	32	UK

ACCP = average citations per paper, SP = Share of publications, TC = total citations, TP = total paper, TPR% = the percentage of articles of journals in total publications.

Table 3

Contribution of the top 15 authors in MCRPC research.

Rank	Name	TP	TPR%	TC	ACCP	h-index	Institution	Country
1	de Bono, JS	132	2.745	16423	124.42	49	Institute of Cancer Research	UK
2	Scher, HI	115	2.391	17978	156.33	53	Memorial Sloan Kettering Cancer Center	USA
3	Small, EJ	103	2.142	13628	132.31	40	University of California San Francisco	USA
4	Fizazi,K	97	2.017	11239	115.87	40	University of Paris Saclay	France
5	Saad,F	92	1.913	11884	129.17	33	University of Montreal	Canada
6	Higano, CS	80	1.664	12150	151.88	39	University of Washington Seattle	USA
7	Armstrong,AJ	75	1.560	5989	79.85	28	Duke University	USA
8	Ryan,CJ	75	1.560	5903	78.71	26	University of California San Francisco	USA
9	Chi,KN	73	1.518	11050	151.37	32	British Columbia Cancer Agency	Canada
10	Carducci,MA	72	1.497	6167	85.65	34	Johns Hopkins University	USA
11	Kantoff,PW	71	1.476	7182	101.15	29	Memorial Sloan Kettering Cancer Center	USA
12	Beer,TM	69	1.435	5537	80.25	26	Oregon Health & Science University	USA
13	Antonarakis,ES	63	1.310	2599	41.25	22	Johns Hopkins Oncology Center	USA
14	Sartor,O	62	1.289	3796	61.23	23	Tulane University	USA
15	Sonpavde,G	61	1.268	1197	19.62	19	Dana-Farber Cancer Institute	USA

ACCP = average citations per paper, SP = Share of publications, TC = total citations, TP = total paper, TPR% = the percentage of articles of journals in total publications.

Memorial Sloan Kettering Cancer Center contributed 208 publications, more than any other institution, accounting for 5.087% of the world's publications in this field, and these publications were accompanied by 22,064 citations. The University of California San Francisco was second in productivity, with 181 publications and a total of 17,523 citations. The University of Washington and the University of Michigan ranked third and fourth, respectively. Regarding the h-index, Memorial Sloan Kettering Cancer Center also ranked first, followed by the University of Michigan and University of Washington. The institutions with high h-indexes were mainly from the USA, the UK and Canada, indicating that these countries had outstanding academic institutions and capabilities in this field of MCRPC.

3.4. Contributions of leading authors

Many scientists from a wide range of origins have researched MCRPC and published their findings in the WoS. The top 15 authors in MCRPC research are listed in Table 3. The most prolific author on the topic was de Bono, JS, who published 132 scientific articles and had a total of 16,423 citations. In addition, the author with the highest number of citations and the most citations per article published was Scher, HI, who had 115 articles and 17,978 citations. In the top 15 authors, de Bono, JS was the only author from the UK; Fizazi, K was from France; Saad, F and Chi, KN were from Canada; Scher, HI and the other top 10 scientists were American. These institutions where these scientists worked were generally among the top 20 most productive institutions. For example, de Bono, JS worked at the Institute of Cancer Research, and Scher, HI worked at Memorial Sloan Kettering Cancer Center. In addition to these top scientists, there were more than 16,000 scientists in the world researching MCRPC.

3.5. Contributions in leading research areas and journals

A total of 4089 articles were published in the MCRPC research field, and these articles involved 52 research areas. The distribution of the top 20 research areas in MCRPC research is listed in Table 4. "Oncology" was undoubtedly the dominant research area, with 2120 articles, followed by "urology nephrology," "pharmacology pharmacy," "endocrinology metabolism," "cell biology," and "biochemistry molecular biology." There were 2120 publications in the area of "oncology," comprising 51.85% of the total publications, and "oncology" had the highest h-index (134). This analysis illustrated that research hotspots were correlated with the prevention, diagnosis, and treatment of cancer. "Pharmacology pharmacy" ranked third, indicating that therapy was an essential area of MCRPC research. All indicated the importance of treatments such as chemotherapy, new hormone therapy, immunotherapy, radiotherapy, and targeted therapy in the MCRPC research field.

A total of 4089 articles were published in 595 journals, with 257 journals publishing only one article and 111 journals publishing only two articles. There are 20 journals identified in Table 5, and their MCRPC publication numbers, total citations, average citations per item, h-indexes, and impact factors (impact factors were obtained from JCR 2017) are also listed. The journal *Prostate* headed the list with a total number of 184 publications, followed by the journal *Clinical Cancer Research* (153), the journal *European Urology* (123), and the journal *Clinical Genitourinary Cancer* (116). The sixth place journal *Oncotarget* was excluded from the WoS in 2017; thus, its IF was unknown.

A bubble chart was also used to show the trend in the publications.[85] The trend of the top 20 productive journals by year is displayed in Figure 3. There were quite a few articles published in the top 20 productive journals from 1981 to 2000. During 2001–2010, the publications in these journals increased steadily, similar to the pattern for total publication numbers shown in Figure 1. Since 2010, the annual number of articles in most journals, such as *Prostate, Clinical Cancer Research*, *European Urology,* and *Clinical Genitourinary Cancer,* has increased rapidly, as shown in Figure 3. Annual papers of partial journals remained relatively steady, such as the journal *Cancer Research*, the journal *Cancer*, and the *Journal of Clinical Oncology*.

3.6. Contributions of funding agencies

Scientific productivity is related to research and development expenditures.[86–88] The distribution of the top 20 most

Table 4

Contribution of the top 20 research areas in MCRPC research.

Rank	Research area	TP	TPR%	TC	h-index	ACCP
1	Oncology	2120	51.846%	83120	134	39.21
2	Urology Nephrology	1158	28.320%	26221	72	22.64
3	Pharmacology Pharmacy	342	8.364%	4556	33	13.32
4	Endocrinology Metabolism	297	7.263%	8621	49	29.03
5	Cell Biology	237	5.796%	7599	40	32.06
5	Biochemistry Molecular Biology	210	5.136%	8180	45	38.95
7	Radiology Nuclear Medicine Medical Imaging	172	4.206%	3971	36	23.09
8	Research Experimental Medicine	138	3.375%	5008	36	36.29
9	Science Technology Other Topics	129	3.155%	9078	34	70.37
10	General Internal Medicine	86	2.103%	21524	21	250.28
11	Biotechnology Applied Microbiology	75	1.834%	2054	21	27.39
12	Pathology	66	1.614%	3589	27	54.38
13	Immunology	64	1.565%	1581	21	24.7
14	Genetics Heredity	62	1.516%	2646	26	42.68
15	Health Care Sciences Services	55	1.345%	577	12	10.49
15	Chemistry	40	0.978%	418	10	10.45
17	Hematology	35	0.856%	375	13	10.71
18	Toxicology	27	0.660%	255	11	9.44
19	Geriatrics Gerontology	20	0.489%	262	9	13.1
20	Biophysics	19	0.465%	580	13	30.53

ACCP = average citations per paper, TC = total citations, TP = total paper, TPR% = the percentage of share publications.

productive funding agencies for MCRPC research is displayed in Table 6. The National Institutes of Health (NIH) topped the list with 809 funded articles and the highest h-index (111). The pharmaceutical company Johnson & Johnson ranked second with 166 funded articles. The Prostate Cancer Foundation (PCF) ranked third with 161 funded articles. Pfizer (157) and Astellas (155) followed the Department of Defense (DOD), which funded 161 articles. The National Natural Science Foundation of China (NNSFC) ranked 11th with 77 funded articles and an h-index of 15. Twelve of these 20 funding agencies were global pharmaceutical companies, and the remaining 8 were state-funded institutions or charitable foundations. The NIH was the world's largest funder of biomedical research and invested approximately $30 billion per year in biomedical research.[89] The PCF was the world's leading philanthropic organization funding and accelerating PCa research, and it raised more than $765 million and funded more than 2000 research programs at nearly 210 cancer centers and universities.[90] The NNSFC, the largest natural science foundation in China, invested nearly $1.1 billion in biomedical research in 2018.[91] Compared with the

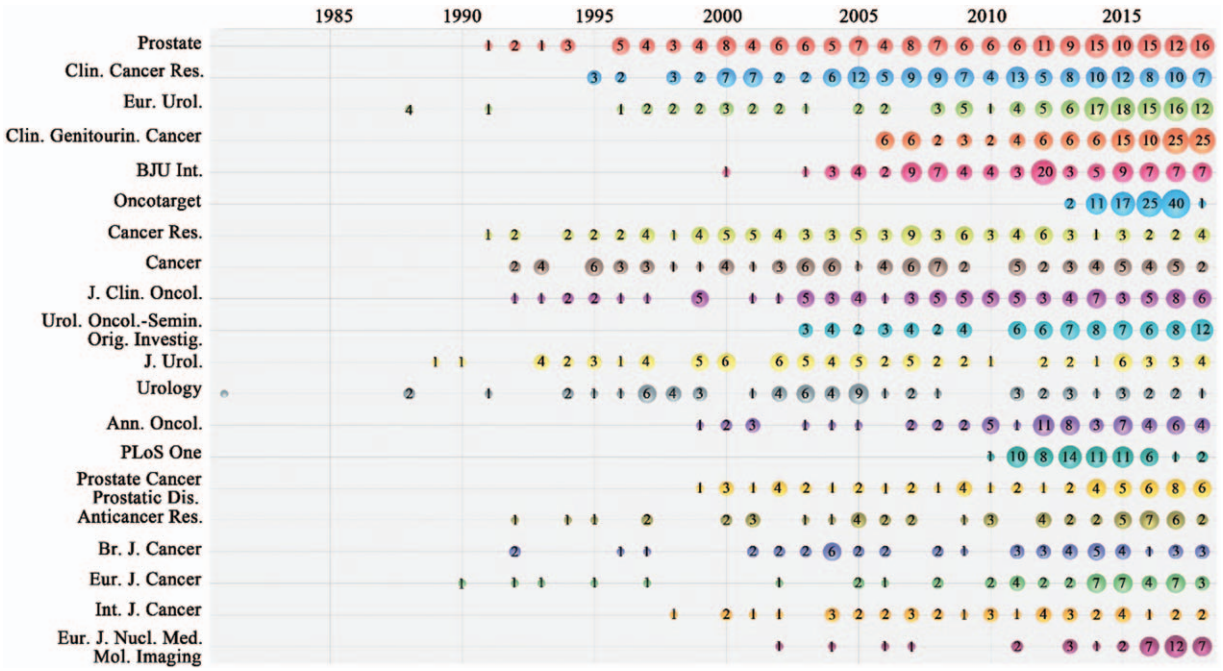

Figure 3. Bubble chart of the top 20 productive journals by year.

NIH and PCF, the NNSFC needs to expend more efforts to not only increase research sponsorship funds but also improve the quality of academic outputs.

The influence of commercial interests on medical science was worldwide and essential.[92] The discovery of new medications, devices, and techniques was always funded primarily by for-profit companies.[93] For example, abiraterone acetate was first reported in the 1990s,[94] and until 2009, the rights for the commercialization of abiraterone acetate were held by Johnson & Johnson, which conducted ongoing clinical trials to expand the clinical uses of abiraterone acetate. With the efforts of Johnson & Johnson, abiraterone acetate became a standard treatment for CRPC and MCRPC. The commercialization of other drugs followed similar patterns. However, biomedical research funded by for-profit companies can be influenced in important ways.[95] The sponsorship of drug or device studies by the manufacturing company led to more favorable efficacy results and conclusions than sponsorship by other sources.[96–98] Even the professional medical associations (PMAs) playing an essential role in defining and advancing health care standards could be influenced by pharmaceutical and device companies.[99] Sometimes irregularities at those companies, such as refusing to provide all the research data to the study team,[100] reporting partial data as the primary outcome, incomplete reporting of some adverse events,[101–103] or concealing some clinical trial data showing harm,[104] were reported. In addition, the worst breach of trust was that clinical trial manuscripts authored by sponsor employees attributed first authorship to investigators who did not always disclose their industry-based financial support.[105] This issue was also the reason that authors were required to detail their competing interests.

3.6.1. Analysis of keywords. Keyword analysis offers information on how authors conceptualize their own research, and keywords have been vital for monitoring the development of science.[85,106–108] However, our keyword analysis also had a limitation: papers without author keywords were excluded from the analysis. Keywords appearing in the MCRPC articles from 1979 to 2018 were analyzed and ranked. The top 30 author keywords by year are displayed in Figure 4. Apart from the most frequently used searching keywords "prostate cancer" and "castration-resistant prostate cancer," the other keywords that frequently appeared at the same time were "docetaxel" (330, ranking 3rd), "abiraterone" (321, ranking 4th), "castration-resistant" (321, ranking 5th), "metastatic castration-resistant prostate cancer" (275, ranking 6th), "metastasis" (274, ranking 7th), "chemotherapy" (263, ranking 8th), "androgen receptor" (ranking 9th) and "enzalutamide" (ranking 10th). Obviously, some author keywords were related to MCRPC therapy, such as "docetaxel," "abiraterone," and "cabazitamide." Docetaxel and

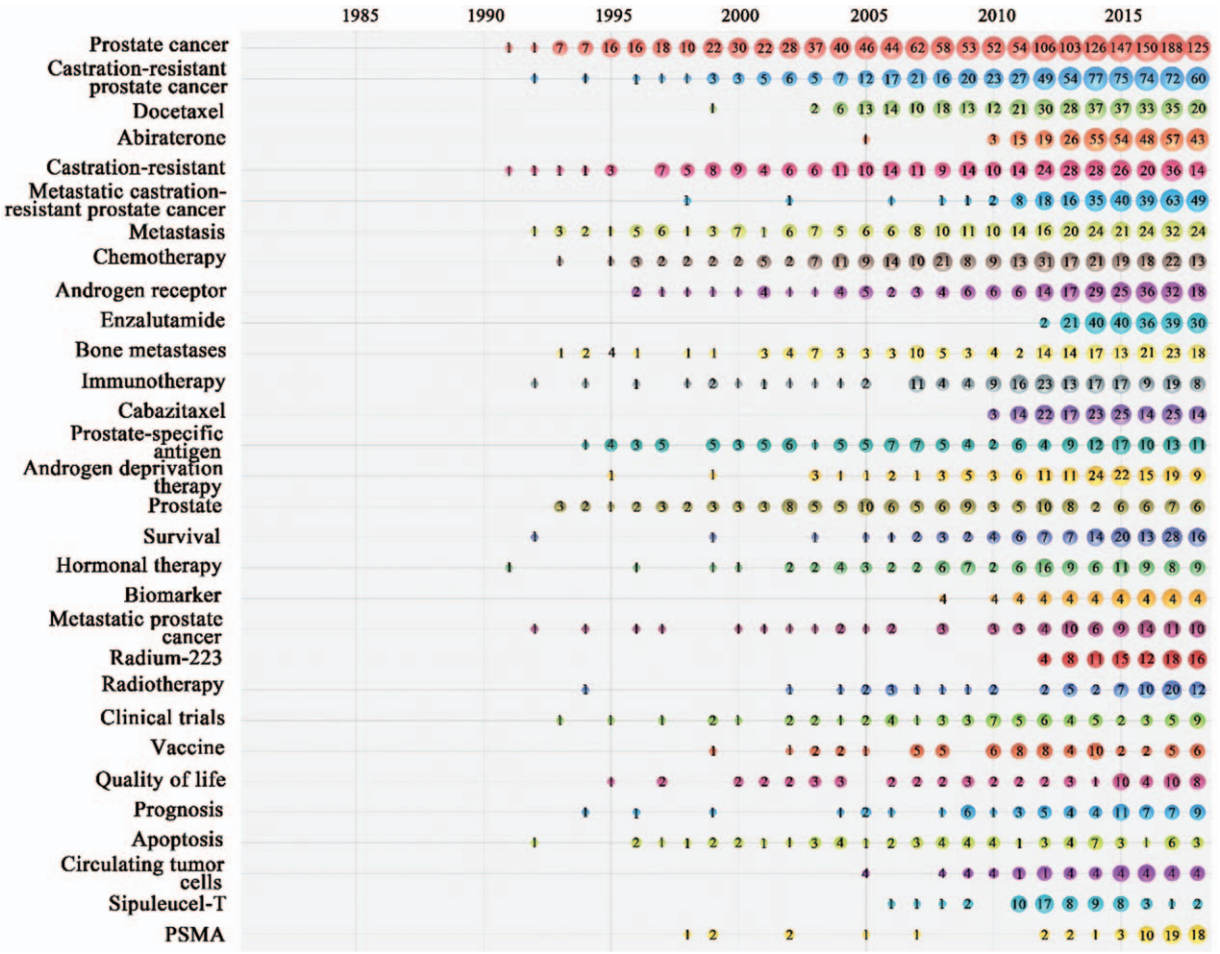

Figure 4. Bubble chart of top 30 author keywords by year.

Table 5

Contribution of the top 20 most productive Journals in MCRPC research.

Journal name	TP	TPR%	TC	h-index	ACCP	PCP%	IF
Prostate	184	4.500	6171	39	33.54	92.391	3.347
Clinical Cancer Research	153	3.742	12841	61	83.93	96.732	10.199
European Urology	123	3.008	5973	41	48.56	100.000	17.581
Clinical Genitourinary Cancer	116	2.837	942	18	8.12	79.310	2.539
BJU International	96	2.348	2103	26	21.91	95.833	4.688
Oncotarget	96	2.348	1089	19	11.34	90.625	
Cancer Research	92	2.250	13922	60	151.33	96.739	9.13
Cancer	90	2.201	3974	33	44.16	97.778	6.537
Journal of Clinical Oncology	87	2.128	12626	56	145.13	100.000	26.36
Urologic Oncology Seminars And Original Investigations	82	2.005	1167	20	14.23	80.488	3.397
Journal of Urology	80	1.956	3248	31	40.6	96.250	5.381
Urology	66	1.614	2442	26	37	98.485	2.3
Annals of Oncology	64	1.565	3156	33	49.31	98.438	13.93
PloS One	64	1.565	1409	20	22.02	96.875	2.766
Prostate Cancer And Prostatic Diseases	61	1.492	861	18	14.11	91.803	4.099
Anticancer Research	52	1.272	578	14	11.12	92.308	1.865
British Journal of Cancer	49	1.198	1478	23	30.16	95.918	5.922
European Journal of Cancer	49	1.198	1430	22	29.18	100.000	7.191
International Journal of Cancer	40	0.978	1359	22	33.98	97.500	7.36
European Journal of Nuclear Medicine And Molecular Imaging	38	0.929	927	17	24.39	100.000	7.704

ACCP = average citations per paper, IF = impact factor, TC = total citations, TP = total paper, TPR% = the percentage of articles of journals in total publications.

cabazitaxel are taxane chemotherapy agents. Abiraterone and enzalutamide are ADT agents. The articles related to "docetaxel," "abiraterone," "chemotherapy," "enzalutamide," "immunotherapy," "cabazitaxel," or "radium-223" sharply increased after 2010. This increase illustrated that the new therapies became topics of interest once they were approved by the US Food and Drug Administration (FDA); however, the increase in docetaxel publications did not match this trend since docetaxel was approved by the FDA in 2004.[109]

3.6.2. Research trends and future hotspots. Given the results in Figure 4, new therapies appear to become areas of interest once they are reported. Therapies that target critical cellular mechanisms of drug resistance are considered to be the most promising approaches for MCRPC therapy.[11] Many new drugs (such as darolutamide[110] and apalutamide[111]) targeting androgen signaling are being tested in clinical trials and will hopefully be effective in abiraterone- or enzalutamide-resistant patients. Emergence Indicators in DDA8 software have been proved useful to spotlight "hot" research topics within the domain.[112,113] The scores are calculated from four criteria—Novelty, Persistence, Growth and Community[114]—and represent the accuracy of predicting the research trends in the next few years. The emergence scores of 15 author keywords are displayed in Table 7. "Prostate-specific membrane antigen (PSMA)" achieved the second highest emergence score of 10.504, followed

Table 6

Contribution of the top 20 most productive funding agencies in MCRPC research.

Rank	Funding agencies	TP	TC	ACCP	h-index	Country
1	National Institutes of Health	809	49261	60.89	111	USA
2	Johnson & Johnson	166	11194	67.43	35	USA
3	Prostate Cancer Foundation	161	13497	83.83	49	USA
4	Department of Defense	161	9151	56.84	42	USA
5	Pfizer	157	10389	66.17	35	USA
5	Astellas	155	9361	60.39	32	Japan
7	Sanofi Aventis	119	10524	88.44	35	France
8	Sanofi	107	2847	26.61	23	France
9	Bayer	89	6862	77.1	21	German
10	Novartis	83	7726	93.08	29	Switzerland
11	National Natural Science Foundation of China	77	680	8.83	15	China
12	Cancer Research UK	74	4162	56.24	31	UK
13	Dendreon	71	9648	135.89	26	USA
14	Bristol Myers Squibb	65	9184	141.29	29	USA
15	Astrazeneca	47	7293	155.17	25	UK and Sweden
15	National Institute For Health Research	45	5497	122.16	26	UK
17	Medical Research Council	41	5114	124.73	25	UK
18	Amgen	41	6544	159.61	20	USA
19	American Cancer Society	40	3105	77.63	22	USA
20	Takeda	34	4153	122.15	15	Japan

Table 7

The emergence scores in MCRPC field.

Rank	Records	Term	Score
1	275	Metastatic castration-resistant prostate cancer	23.172
2	62	PSMA	10.504
3	71	Radiotherapy	5.862
4	84	Radium-223	5.04
5	14	Liquid biopsy	4.907
6	173	Bone metastases	4.613
7	12	Ra-223	3.829
8	10	DNA repair	3.729
9	9	circulating tumour cells	3.454
10	10	Lu-177	3.287
11	8	PD-L1	2.543
12	7	neuroendocrine prostate cancer	2.463
13	14	therapy	2.27
14	8	MDV 3100	2.18
15	7	PARP inhibitor	2.18

by "Radiotherapy" (5.862), "Radium-223" (5.04), "Liquid biopsy" (4.907) and "Bone metastases" (4.613).

PSMA is frequently overexpressed and strongly upregulated in PCa, making PSMA-based RLT a promising treatment for MCRPC.[115–118] RLT with [Lu-177] Lu-PSMA-617 (Lu-PSMA) was first reported in 2015[57] and attracted the most scholarly attention due to its low toxicity profile and respectable response rates.[57,59,119,120] Liquid biopsy is widely applied to cancer research and will play a vital role in predicting the therapeutic efficiency or resistance to therapy.[121–123] "DNA repair" ranked 8th with an emergence score of 3.729. DNA repair defects might present another promising treatment opportunity for patients with MCRPC,[124] treatments that might include PARP inhibition[43] and platinum chemotherapy.[125] Research on bone metastasis has also attracted considerable attention, and radium 223 is the most promising treatment for patients with bone metastases. AR and the AR signaling pathway remain the principal drivers of the development and progression of MCRPC, making AR and its signaling pathway the main targets of principal therapeutic approaches.[126] The drug resistance or cross-resistance of therapies might affect drug sequence choices in MCRPC,[127] making drug sequences a promising hotspot in the future.

3.7. An Analysis of the most cited papers

Although multiple indicators were used to evaluate the impact of scientific publications, citation counts are still an important measurement of influence in this research field.[120,121] The top 20 most cited publications in the MCRPC research field during 1981–2018 are presented in Table 8. The most highly cited paper was "Sipuleucel-T Immunotherapy for Castration-Resistant Prostate Cancer." This article was published in the New England Journal of Medicine in 2010 by Kantoff, PW and headed the lists of total citations (2715) and annual citations (339.36). "Abiraterone and Increased Survival in Metastatic Prostate Cancer," authored by de Bono, JS et al, took second place, with 2045 total citations and 292.14 annual citations. "Increased Survival with Enzalutamide in Prostate Cancer after Chemotherapy," authored by Scher, HI et al, ranked third with 1857 total citations and 309.5 annual citations.

Among these top 20 papers, 7 were published in the *New England Journal of Medicine*; 2 were published in *Lancet*; 2 were published in the *Journal of Clinical Oncology*; 2 were published in *European Urology*;2 were published in *Clinical Cancer Research*; and *Nature*, *Science*, *Cell*, *Lancet Oncology* and *Cancer Research* each published 1 of the top articles. Eight papers had only American authors, and the remaining 12 papers had authors from more than 2 countries, meaning they were papers that resulted from international cooperation. Fifteen of the top scientists, such as de Bono, JS and Scher, HI, participated in 14 papers in a cooperative manner. This finding illustrated that the top scientists played a key role in the development of the entire field and that collaborations benefited the number, impact and quality of papers. Most of the top 20 papers were related to therapies for MCRPC, demonstrating that therapy was the most critical area of MCRPC research.

4. Conclusions

In this paper, a bibliometric analysis was performed to evaluate the trends in MCRPC research during 1979–2018. The results showed that the publications in MCRPC research increased significantly after 2010, possibly due to new therapies, such as abiraterone and enzalutamide. The findings illustrated that the USA dominated the MCRPC research in the areas of total publications, top institutions, top scientists and most cited papers. Some information could be obtained from this study:

(1) MCRPC has attracted increasing attention and has become a worldwide health issue.
(2) Compared with the USA, Asian countries, especially mainland China, are required to exert more effort in the areas of research funding and international collaboration to improve the impact and quality of their publications.
(3) When facing drug resistance, combined therapies might improve quality of life and extend survival. Understanding the cellular mechanisms would help the development of new drugs that overcome existing resistance. Liquid biopsy will play a vital role in predicting the therapeutic efficiency or resistance to therapy.
(4) Therapies that target critical cellular mechanisms of drug resistance, especially PSMA-based RLT and new therapies

Table 8

The top 20 most cited publications in MCRPC research field during 1979-2018.

No	Authors	Title	Total citations	Citation/year	Journal/IF2017	Publication year	Country (authors from)
1	Kantoff, PW[1*]; Higano, CS; et al	Sipuleucel-T Immunotherapy for Castration-Resistant Prostate Cancer.	2715	339.36	New England Journal Of Medicine /79.258	2010	USA
2	de Bono, JS[1*]; Fizazi, K;Chi, KN; Saad, F; Ryan, CJ; Scher, HI; et al	Abiraterone and Increased Survival in Metastatic Prostate Cancer.	2045	292.14	New England Journal Of Medicine /79.258	2011	UK, USA, France, Canada, Australia, Italy
3	Scher, HI[1*]; Fizazi, K,; Saad, F,; Chi, KN,; Armstrong, AJ; de Bono, JS; et al	Increased Survival with Enzalutamide in Prostate Cancer after Chemotherapy.	1857	309.5	New England Journal Of Medicine /79.258	2012	USA, France, Canada, Italy, Germany, The Netherlands, UK, Australia
4	de Bono, JS[1*]; Sartor,O;et al	Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial	1615	201.86	Lancet /53.254	2010	UK, USA, France, Turkey, Denmark, Belgium, Czech Republic, Hungary
5	Topalian, SL[*]; Brahmer, JR[1];et al	Phase I Study of Single-Agent Anti-Programmed Death-1 (MDX-1106) in Refractory Solid Tumors: Safety, Clinical Activity, Pharmacodynamics, and Immunologic Correlates	1368	171	Journal Of Clinical Oncology /26.303	2010	USA
6	Ryan, CJ[1*];de Bono, JS; Fizazi, K; Small, EJ; Saad, F; Higano, CS; Scher, HI; et al	Abiraterone in Metastatic Prostate Cancer without Previous Chemotherapy	1237	247.4	New England Journal Of Medicine /79.258	2013	USA, UK, Australia, France, Spain, The Netherlands, Canada, Belgium, Germany, Greece
7	de Bono, JS[1*]; Scher, HI; et al	Circulating Tumor Cells Predict Survival Benefit from Treatment in Metastatic Castration-Resistant Prostate Cancer.	1099	109.9	Clinical Cancer Research /10.199	2008	UK, USA
8	Parker, C[1*]; Sartor, O; et al	Alpha Emitter Radium-223 and Survival in Metastatic Prostate Cancer	1099	219.8	New England Journal Of Medicine /79.258	2013	UK, Sweden, Norway, Czech Republic, Poland, Slovakia, Germany, Brazil, USA
9	Jung, ME[*]; Tran, C[1]; Higano, CS; Beer, TM,; Scher, HI; et al	Development of a Second-Generation Antiandrogen for Treatment of Advanced Prostate Cancer	1103	122.56	Science /41.058	2009	USA
10	Pienta, KJ[*];Grasso, CS[1]; et al	The mutational landscape of lethal castration-resistant prostate cancer	979	163.17	Nature /41.577	2012	USA
11	Beer, TM[1*]; Armstrong, AJ; Higano, CS; de Bono, JS; Fizazi, K; Saad, F; Scher, HI; et al	Enzalutamide in Metastatic Prostate Cancer before Chemotherapy	941	235.25	New England Journal Of Medicine /79.258	2014	USA, France, Italy, Denmark, Spain, UK, Australia, Canada, South Korea, Japan, Germany, Belgium
12	Antonarakis, ES[1*]; Carducci, MA; et al	AR-V7 and Resistance to Enzalutamide and Abiraterone in Prostate Cancer.	928	232	New England Journal Of Medicine /79.258	2014	USA
13	Taube, JM[1*]; et al	Association of PD-1, PD-1 Ligands, and Other Features of the Tumor Immune Microenvironment with Response to Anti-PD-1 Therapy	907	226.75	Clinical Cancer Research /10.199	2014	USA
14	Heidenreich, A[1*];et al	EAU guidelines on prostate cancer.	870	87	European Urology /17.581	2008	Germany,Sweden, France, Belgium, Russia, Switzerland, Italy
15	Nelson,PS[*];Montgomery, RB[1]; Higano, CS; et al	Maintenance of intratumoral androgens in metastatic prostate cancer: A mechanism for castration-resistant tumor growth	797	79.7	Cancer Research /9.13	2008	USA
16	Sawyers,CL[*];Robinson, D[1]; Scher, HI; Kantoff, PW; de Bono, JS; et al	Integrative Clinical Genomics of Advanced Prostate Cancer	772	257.33	Cell /31.398	2015	USA,UK, Italy
17	Scher, HI[1*]; Beer, TM; Higano, CS;et al.	Antitumor activity of MDV3100 in castration-resistant prostate cancer: a phase 1–2 study	667	83.38	Lancet /53.254	2010	USA
18	Heidenreich, A[1*]; et al	EAU Guidelines on Prostate Cancer. Part II: Treatment of Advanced, Relapsing, and Castration-Resistant Prostate Cancer	673	168.25	European Urology /17.581	2014	Germany, Spain,Sweden, France, Belgium, The Netherlands,UK, Russia, Italy
19	Tannock, IF[*]; Berthold, DR[1]; et al	Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer: Updated survival in the TAX 327 study	662	66.2	Journal Of Clinical Oncology /26.303	2008	Canada, The Netherlands, USA
20	Fizazi, K[1*]; Scher, HI; Chi, KN; Saad, F; de Bono, JS;et al	Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study	622	103.67	Lancet Oncology /36.418	2012	France, USA, Canada, Scotland, Canada, Australia, Italy

[1]: first author; *: corresponding author; Total Citation/Year: Total Citation/(2018-Publication Year).

targeting DNA repair or the AR signing pathway, could be the next hotpot.

(5) Research on bone metastasis has also attracted considerable attention, and radium 223 is the most promising treatment for patients with bone metastases.

This study will help researchers understand the global overview of MCRPC, find potential collaborators in Western countries and grasp the promising attractive areas of MCRPC research.

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