Submitted: 14 April, 2024 Accepted: 19 June, 2024 Published: 30 November, 2024 DOI:10.22514/jomh.2024.181

REVIEW

JOMH Journal of Men's Health

Current state of prostate cancer treatment and future strategies

Yeonhee Pyo[1], Ki Han Kwon[2,*]

[1]Department of Beauty Cosmetics, College of Biomedical and Health Science, Konkuk University, 27478 Chungju, Republic of Korea
[2]College of General Education, Kookmin University, 02707 Seoul, Republic of Korea

***Correspondence**
kihan.kwon@kookmin.ac.kr
(Ki Han Kwon)

Abstract

Prostate cancer (PCa) is the most common malignancy in men. It forms heterogeneous PCa masses with lining epithelial cells that require androgen signaling, and heterogeneous PCa masses can metastasize to lymph nodes and bone, making early diagnosis and treatment critical. PCa treatments include chemical castration, surgical resection, chemotherapy, hormonal changes, and androgen deprivation therapy. Diagnosis begins with a digital rectal exam (DRE) or prostate-specific antigen, and is often associated with a negative prognosis and pain. Furthermore, malignancy metastasizes or recurs to the bone. It is vital to develop personalized treatment based on the understanding of cancer pathophysiology. PCa is an aggressive multifactorial disease being focused in men's health research. PCa handling is crucial in men's survival. It is constantly studied for diagnosis, prevention and treatment. This article reviews it from therapeutic perspective. It thus summarizes current and emerging therapeutic strategies and biomarkers for PCa.

Keywords

Prostate cancer; Treatment strategies; Target agent; Biomarker; Men's health

1. Introduction

Prostate cancer (PCa) is the most prevalent malignant tumor in men worldwide [1–3]. Prostate has two layers, *i.e.*, basal and luminal epithelial cells with different characteristics. The luminal epithelial cells require androgen signaling for androgen receptor expression and survival, while basal ones are androgen negative and do not need specific orchiectomy. Heterogeneous PCa masses occur in a small number of cases, but they do not give rise to cancer stem cells. However, these cancer cells can metastasize to the lymph nodes and bones. This gives rise to cancer stem cells which metastasize toward the lymph and bone [4, 5]. Genetics account for ~58% PCa cases whereas poor lifestyle increases the PCa risk [6].

Smoking, alcohol, increasing age, black ethnicity, certain gene mutations, family history of insulin-like growth factor (IGF) or malignancy, obesity, diabetes, and radiation exposure contribute to the PCa development [7–9]. PCa can be localized, progressive, or metastatic. The 10-year PCa-specific survival rate is ~95% for localized disease. The 5-year survival rate for metastasis is ~35% which makes it dangerous for men [10]. It is brought by the androgenic male hormones. Early diagnosis and treatment are vital as it can invade bones if metastasized through the bloodstream, not the lymphatic system [11, 12]. PCa accounts for large proportion of cancer-related deaths. It involves both immutable and modifiable risk factors. Age, race, family history and germline variation are the non-modifiable, while metabolic syndrome, obesity and smoking are the known modifiable risk factors [13]. Resultantly, there are several diagnostic and treatment choices for early PCa detection.

Early detection of metastatic or high-risk prostate cancer is crucial. It includes physical examination, magnetic resonance imaging (MRI), prostate-specific antigen (PSA) test, and biopsy. Most cases of prostate cancer are not aggressive and can be managed with active surveillance [14–16]. Monitoring is recommended for early diagnosis because of its asymptomatic nature, long latency period, and potential aggressiveness [17–20]. The approach to treatment is usually through hormones. Hormone replacement therapy interferes with the production of male hormones, *i.e.*, androgen and testosterone. It combines radiation therapy with chemotherapy [14]. If PCa becomes severe, there are therapies to remove testicles for reducing testosterone levels or to replace hormone that kills invasive cancer cells [21]. PCa prognosis is still not conducive despite implementing various diagnostic and therapeutic approaches. Moreover, problems like erectile dysfunction, low libido, obesity and decreased bone mass also arise [22]. Mortality and PCa incidence have been related with human development indices and influenced by the regional differences in epidemiologic characteristics [23]. Epidemiologic reviews, diagnosis, treatment, and prevention need to be systematically organized. This review thus aims to summarize epidemiologic review of PCa, PCa diagnosis at early, intermediate and late stages, and PCa treatment and prevention strategies including surgical and chemotherapeutic. This can predict potential future treatments for PCa and define currently available diagnostic, treatment and prevention methods. Few papers are

published on PCa which use multiple modalities for strategic diagnosis, modeling, and analysis of clinical settings. PCa being the leading cause of death in men has many challenges to be addressed.

2. Methods

The content was systematically searched from online databases including PubMed, Science Direct, Scopus and Google Scholar using keywords, "prostate cancer treatment", "PCa", "PCA" and "prostate cancer" in the period from 2019 to 2024. Articles were screened based on predefined inclusion and exclusion criteria. Inclusion criteria covered clinical case studies, randomized controlled trials, experiments and longitudinal, epidemiologic and bioactivity studies related to research topic. Exclusion criteria filtered out the non-essential articles including reviews, case analyses, theses, letters, editorials, articles with no full text access, and those having clinical concerns. Literature search yielded total of 1890 articles with 924 from PubMed, 92 from ScienceDirect, 51 from Scopus and 823 from Google Scholar. The duplicates and articles without full-text access were removed. A primary review was conducted to scrutinize the abstracts and full texts for their relevance. This reduced the pool to 1247 articles.

A secondary review was conducted to further refine the selection which resulted in 17 articles. The selected articles were comprehensively evaluated for their adherence to inclusion criteria. The study subjects, methods and results were examined to ensure the robustness and reliability of gathered literature (Fig. 1).

3. PCa diagnosis

PCa is categorized as androgen-sensitive or androgen-insensitive. This indicates testosterone stimulation and assists in choosing the treatment strategy. PCa treatment is divided into active surveillance, chemotherapy, radiation therapy, ablative surgery, hormonal therapy, and cryotherapy based on androgen response-based diagnosis. The patient's tumor level is subdivided according to PSA level, recurrence and metastasis likelihood, and prostatectomy presence [24–26]. PSA testing is effective for the early detection of PCa, but it does not reliably predict prognosis. Therefore, there is a need to identify new prognostic biomarkers. PCa is diagnosed through PSA testing, rectal examination, tissue biopsy, and standard biochemical testing. However, these diagnostic methods are not suitable for the very early stages of prostate cancer, highlighting the need for the discovery of new biomarkers. PSA levels can be elevated in PCa as well as other conditions such as benign prostatic hyperplasia and prostatitis. The PSA test becomes unreliable in prostate cancer patients with values below 4 ng/mL. Therefore, PSA testing is often performed in conjunction with a rectal examination or biopsy [27].

Tumor, node and metastasis (TNM) classification system considers tumor size, lymph node involvement, and distant metastases to assess tumor staging [28]. This accurately determines the tumor characteristics of PCa. Low-grade PCa have smaller and slow-growing tumors with fewer symptoms. PCa of intermediate malignancy is relatively fast-growing which may invade surrounding tissues. Highly malignant PCa grows rapidly and spreads to surrounding tissues and lymphatic vessels [29]. TNM classification and tumor malignancy influence treatment choices. For instance, low-malignancy PCa may be considered for conservative treatment like surveillance or radiation therapy, while high-grade tumors may require more curative approach, *e.g.*, surgery, chemotherapy and radiation therapy. Clear, and easy-to-understand communication between patient and doctor helps in understanding TNM classification and tumor malignancy [30]. Treatment strategies for PCa are thus individualized by considering tumor pathological characteristics and patient's overall health status. A conservative treatment is considered for tumors of low- or intermediate-risk [31, 32]. PCa is graded based on the TNM staging system and Gleason score. Monitoring is recommended for early diagnosis because of its asymptomatic nature, long latency period, and potential aggressiveness [33]. This minimizes side effects and maintains patient's life quality by considering tumor growth and managing treatment accordingly. An intense treatment may be needed for high-risk PCa which includes surgery, radiation therapy, chemotherapy, hormone therapy, and other radical treatments [34]. These treatments remove or control the tumor, prevent recurrence, and improve patient survival. It is important to consider tumor risk and patient's overall situation for determining appropriate treatment. A non-radical treatment emphasizes on tumor growth and conducted when necessary [35].

Early diagnosis and prompt treatments are crucial for PCa management. Biopsy being a key diagnostic test for PCa requires anesthesia. Anesthesia involves a blend regarding pain management, skin consideration, and muscle relaxation with the intensity depending on approach toward perineal and rectal biopsy. Proper anesthesia is essential for completing the histologic examination [36]. Anesthesia includes postoperative analgesia as the local anesthesia. It also involves neurological, pulmonary, cardiovascular, and hematologic evaluations. Regional anesthesia is safe, however there can be the risks of failure and low incidence of local anesthetic systemic toxicity (LAST), nerve damage, falls, or complications like hematomas, infections and allergic reactions. Therapeutic guidelines, especially for antipsychotic medications, are being followed in the regional anesthesia administration [37].

NOD-like receptor family, pyrin domain containing 1 (*NLRP1*) and NOD-like receptor family, CARD domain containing 4 (*NLRC4*) gene expressions are increased in prostate cancer patients, as observed in the clinical diagnosis of PCa by immunohistochemical staining. NLRP1 expression is linearly correlated with interleukin-1β (IL-1β) and IL-18. NLRP1 and NLRC4 are highly expressed in the plasma membrane of PCa patients, which promote the maturation and release of inflammatory cytokines, *i.e.*, IL-1β and IL-18, and promote tumorigenesis. Significant changes are observed in PSA levels, *i.e.*, from 25 to 33 at 29 months and 16 to 24 at 20 months after using metformin. These clinical values have important role in tumor progression, PCa risk assessment, and prognosis [38]. Disease diagnosis via AI (artificial intelligence) is based on data sets' utilization, which are taken from diagnostic methods such as magnetic resonance

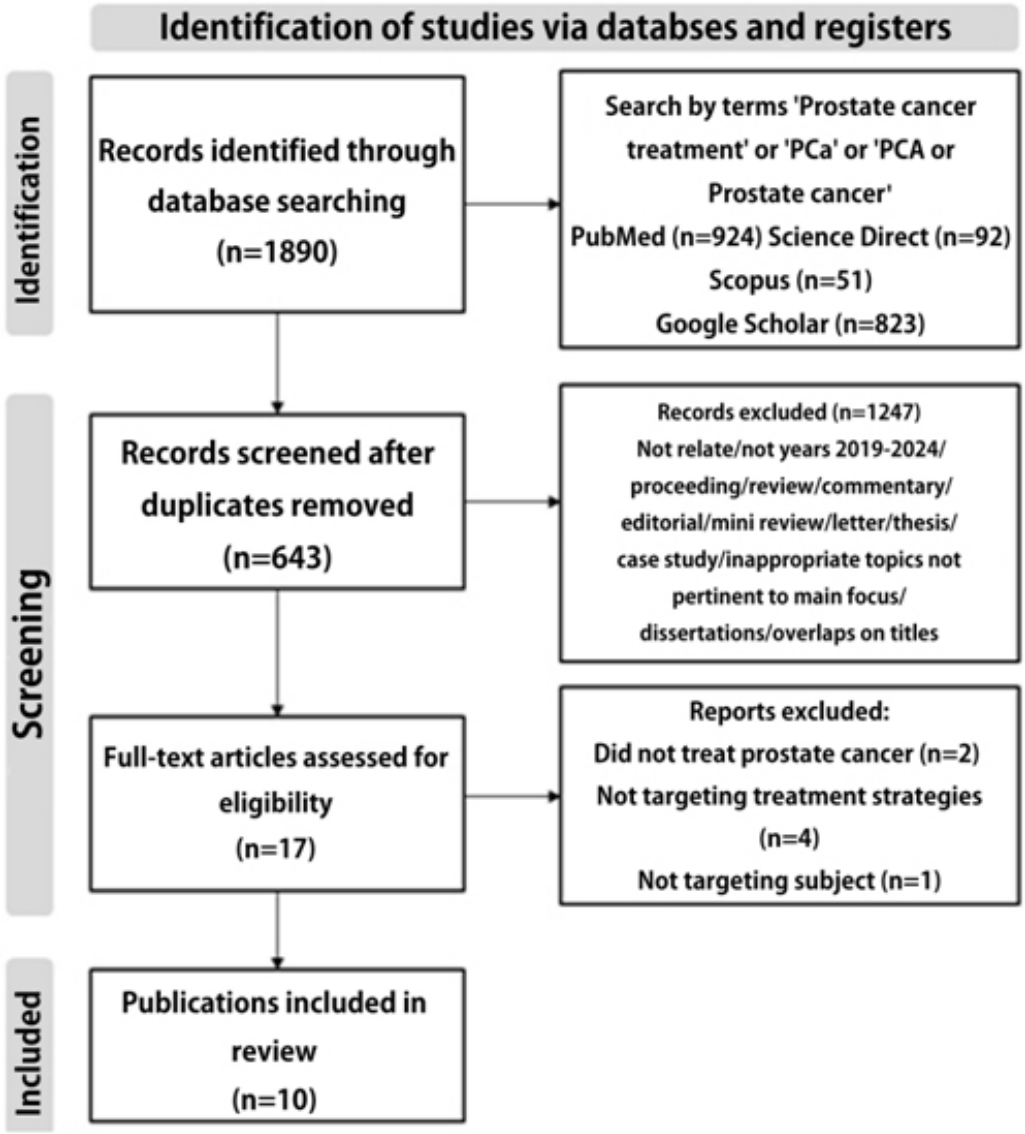

FIGURE 1. Flowchart of the articles' selection process. PCa: Prostate cancer.

scans, computed tomography scans, ultrasound diagnostics, X-rays, or electronic health records, and integrated into new AI models [39]. For instance, there is an online tool (web application) that employs smart AI for rapid PCa diagnosis. It learns deeply and acts as a multi-model for enhanced PCa diagnosis [40]. These treatments separately address localized and metastatic PCa. The methods used to diagnose tumor for localized PCa include PSA testing, digital rectal exam, and biopsy [41]. Non-invasive treatments such as medication or radiation therapy are considered for the early stages. However, a surgical approach may be required to remove tumor in high-risk patients. Metastatic PCa has different treatment strategy as the tumor spreads to bones or intestine [42, 43]. Radical treatments like chemotherapy, hormone therapy, radiation therapy, and colony-targeted therapy are thus considered. Treatments are adjusted based on the patient's condition and tumor nature [44].

4. Chemotherapy for PCa

Androgen deprivation therapy (ADT) has long been used as chemotherapy regimen to treat PCa which keeps testosterone levels below 50 ng/dL. Medical castration to stop androgens production from testes is accomplished by using agonists or antagonists of gonadotropin-releasing hormone. The study is divided into experimental and control groups for evaluating the tamsulosin impact on bladder function. The experimental group takes 0.4 g tamsulosin daily for 6 months at the start of external beam radiation therapy (EBRT). Control group is used to evaluate the urine amount after urination which remains in bladder after EBRT [45]. Fixed oral dose of dexamethasone (8 mg) is given for the successful treatment [46]. The metformin efficacy as chemotherapeutic agent for PCa has been shown, especially in hormone sensitive prostate cancer (HSPC). It is safe and inexpensive drug to prevent locally advanced or metastatic PCa. This is demonstrated in 124-patient randomized controlled trial (RCT) that depicts improvements in castration-resistant prostate cancer-free survival (CRPC-FS)

with no adverse effects on PSA response. Diarrhea is noticed with metformin grade II which confirms the usage of lower doses. In 64-patient study, the modified shenqi dihuang decoction (MSDD) group has lower castration resistance (28.12% *vs.* 71.87%), new metastases (18.75% *vs.* 40.63%, $p < 0.05$), and higher physical status score (79.87 *vs.* 70.45, $p < 0.05$) compared to the control group. There is no difference in pain scores or adverse events [47].

In the case of chemotherapy in combination with radiation therapy for PCa patients, a 70-patient clinical trial confirms that chemotherapy improves life quality, increases treatment adherence, and reduces side effects in PCa patients undergoing radiation therapy. In a trial comparing expanded prostate cancer index composite (EPIC) score with the incidence of chemoradiotherapy, the incidence of proctitis and cystitis is lower and EPIC score is higher in the nursing intervention group compared to chemotherapy-treated experimental group or the control group receiving routine care. Dex 0.4 mg is thus effective in mitigating hemodynamic responses and reducing postoperative analgesic requirements [48]. The α-blockers for PCa are the chemical components having prophylactic role in radiation therapy of lower urinary tract. The α-blockers efficacy in preventing acute urinary retention (AUR) in EBRT patients is demonstrated through 108 PCa patients' clinical trial. The change in international prostate symptom score (IPSS) after 3 months of treatment is correlated with α-blocker alone, and the drug-induced side effects are mild which indicate α-blocker efficacy [49]. Furthermore, steroids are an incomplete regimen in chemotherapeutic armamentarium of PCa treatment, and docetaxel is suggested as an alternative. A 60 PCa patients' clinical trial demonstrates its impact with fixed dose of 8 mg. This is effective in patients missing steroid premedication with no hypersensitivity reactions or dermatotoxicity [50].

Chemotherapy for PCa is employed as an adjuvant treatment to control negative prognosis after resection surgery. Hormones expressed after castration may negatively impact the bone metastasis. MSDD is used to treat this. RCT of 76 patients with bone metastasis hormone-sensitive PCa exhibits that it improves patients' quality of life (QoL) scores and memory T cell (TCM) symptom scores. This is confirmed in a comparison with treatment control of maximal androgen blockade (MAB), which suggests that MSDD improves life quality of PCa patients by improving the serum markers and reducing the bone metastatic pain [51]. Chemotherapy is also used to relieve pain after PCa surgery. It is revealed that low-dose usage of dexmedetomidine (DM) combined with hydromorphone (HM) as postoperative analgesia improves serum IL-6 and C-reactive protein (CRP) levels in PCa patients. The combination is thus safe, acts as an effective chemotherapy for postoperative analgesia, and inhibits the expression of inflammatory factors [52]. The clinical case studies have been summarized in Table 1.

5. Hormone replacement therapy for PCa

The outcomes of research and clinical trials over past decade have depicted that androgen receptor and pathway inhibitors such as enzalutamide, abiraterone and apalutamide are the current care standard for hormone-sensitive and treatment-resistant PCa [53, 54]. The hormone replacement therapy and testosterone replacement therapy (TRT) can prevent prostate side effects. TRT is a pharmacological treatment for PCa, acute urinary retention, invasive prostate procedures, and hypo-dose-resistant lower urinary tract symptoms in men. RCT of 5204 men shows that PSA concentrations are higher with TRT compared to placebo [55]. A 6-month trial of TRT treatment reveals that it improves pain and life quality in late-onset hypogonadal (LOH) men having chronic pain from PCa. This is according to the Japanese RCT that compares TRT in 31 experimental and 29 control subjects. It is found that TRT contributes to body pain, mental health and sleep disturbance [56]. TRT is exogenous and often used to treat hypotestosteronism and erectile dysfunction, and associated with 65% improvement in sexual function. Nguyen *et al*. [57] (2021) depict that 85% patients receiving stereotactic body radiation therapy (SOLAR-P) for low alpha-beta resistant bone metastases get pain relief. However, TRT can have side effects. Andriole *et al*. [58] (2023) exhibit that TRT leads to 50% decrease in sperm production with increased infertility risk. This study analyzes the impact of 18F-fluciclovine positron emission tomography/computed tomography (PET/CT) on androgen blockade therapy in biochemical recurrent PCa patients [58]. TRT discontinuation is often linked with the medication discomfort, followed by concerns about cost or side effects, lack of efficacy, and return of symptoms. Mean TRT duration is 15.4 ± 7.6 months. Usage of phosphodiesterase-5 (PDE5) inhibitors has been effective treatment [59].

6. Radiation and surgical treatments of PCa

A biochemical response tracking clinical trial of stereotactic body radiation therapy (SBRT) in combination with ADT in men of 70 years and older confirms the safety and curative efficacy of SBRT. SBRT dosage is 35–40 Gy given in five doses. SBRT is a well-tolerated treatment that provides biochemical disease control in older patients with median PSA level of 0.5 ng/mL. Androgen blockade levels possess high prognostic value in localized PCa patients receiving high-dose radiation therapy and ADT [60]. SBRT relieves pain and treats bone metastases. It is more efficient to radiate disease from primary malignancies with low alpha-beta ratios, especially for the pain relief. It relieves pain as shown in a 40-patient clinical trial. It improves patient's life quality and provides direction for future research regarding its impact on painful bone metastases [61].

Chemotherapy is also associated with PCa recurrence. Biochemical recurrence (BCR) is common, and 18F-fluciclovine PET/CT is used in 317 patients to determine the higher efficacy than ADT. This cures and delays the ADT associated diseases [62]. MRI-guided focal therapy for PCa combines targeted focusing with ultrasound to attain safety and early oncologic and functional outcomes. This can be seen during the monitoring of periprocedural complications. A clinical trial of 44 PCa patients shows no adverse events. Moreover, 41 out of 44 post-ablation patients depict no treatment-related side effects [63].

TABLE 1. Summary of clinical chemotherapeutic studies for PCa.

Study	Subject	Method	Materials	Findings
Alghandour *et al*. [42]	124 PCa patients (62 experimental, 62 control)	RCT	PSA response testing after metformin usage (29 months, 95% CI 25–33 *vs.* 20 months, 95% CI 16–24; $p = 0.01$)	Metformin and ADT adjunct therapy has enhanced outcomes in locally advanced or metastatic PCa
Li *et al*. [27]	70 PCa patients (35 intervention, 35 control)	RCT	Comparative analysis of EPIC scores and treatment responses between the groups receiving comprehensive nursing interventions *vs.* standard care applications	Comprehensive nursing interventions encompassing health education, psychotherapy, radiotherapy, chemotherapy and complication management show amelioration of life quality and reduction in adverse events among PCa patients undergoing chemoradiotherapy
Tsirkas *et al*. [45]	108 localized PCa patients (54 experimental, 54 control)	RCT	Experimental arm: tamsulosin 0.4 mg for 6 months at EBRT start Control group: post-void volume (Vres) assessment after radical EBRT	Aromatase overexpression is not imperative for clinical or biochemical hyperadrenocorticism, and the aromatase promoter utilization in adrenal cortex is feasible. AUR incidence is diminished in the experimental cohort which suggests potential prophylactic benefits of selective α-blocker usage in EBRT-treated patients
Hsu *et al*. [46]	60 eligible patients (Breast: 70%, Gastrointestinal: 12%, Prostate: 12%, Lung: 7%) (30 experimental, 30 control)	RCT	Administration of oral docetaxel 8 mg to patients with missed steroid premedication	Successful management with docetaxel adjunctive therapy supplemented by standardized dose of oral dexamethasone 8 mg
Gu *et al*. [47]	76 hormone-sensitive PCa patients with bone metastases (randomized to MSDD and control groups, 64 in total)	RCT	Control group: MAB treatment MSDD group: MAB + MSDD treatment	MSDD treatment is effective for bone and visceral metastases, post-treatment serum alkaline phosphatase levels, frequent bruising, appetite loss, fatigue, back pain, weight loss and pain relief
Yang *et al*. [48]	102 PCa patients (51 experimental, 51 control)	RCT	Experimental: HM Control group: low dose DM + HM	The experimental group exhibits reduced adverse events compared to controls at the postoperative intervals of 4, 12, 24 and 48 hours. Low dose dexmedetomidine with hydromorphone adjunct therapy demonstrates safety and efficacy in postoperative analgesia for PCa patients, which induce inhibitory effects on inflammatory mediator expression

PCa, prostate cancer; RCT, randomized controlled trial; PSA, prostate-specific antigen; CI, confidence interval; ADT, androgen deprivation therapy; EPIC, expanded prostate cancer index composite; EBRT, external beam radiotherapy; AUR, acute urinary retention; MAB, maximal androgen blockade; MSDD, modified shenqi dihuang decoction; HM, hydromorphone; DM, dexmedetomidine.

ADT usage as a general PCa treatment remains controversial. ADT combination with high-dose radiation therapy (HRT) has been effective as shown in the clinical trial of 355 patients with high-risk PCa. The 4-month ADT (lepidlene 11.25 mg, infused every 12 weeks) with HRT (78 Gy/39 fractions) arm do not show lesion metastases, and have reduced biochemical disease-free survival (bDFS) compared to control arm [64]. PET and multiparametric MRI (mpMRI) of prostate membrane specific antigen (PSMA) accurately identify lesions recurring after definitive PCa diagnosis. It employs 18F-PSMA PET/CT and mpMRI for lesion characterization and personalized treatment strategies in patients of biochemical prostatectomy having undergone post-operative radiotherapy (PORT) [65].

Surgery is an alternative PCa treatment. Robotic-assisted laparoscopic prostatecyomy (RALP) is a trending PCa surgical procedure. Patients' screening after RALP has demonstrated its safety. It is preferred oncologically and functionally regarding preoperative PSA and biopsy results, blood transfusion rates, operative time, and length of hospital stay [66]. However, positive surgical margins (PSMs) are associated with the higher risk of biochemical failure (BCF). In a follow-up of 462 patients undergone robotic-assisted radical prostatectomy (RARP), 13.2% patients have PSMs and 31.7% experience BCF. Patients with PSMs after RARP must receive early treatment interventions such as salvage radiotherapy and ADT [67]. Nonetheless, the prognosis of surgical treatment can reduce mortality. Clinical cases of radiation and surgical treatments are given in Table 2.

7. Prediction of targeted therapies and the biomarker effects

The recent approvals of (poly adenosine diphosphate-ribose polymerase) (PARP) inhibitors have provided new treatments for PCa patients. PARP inhibitors inhibit tumor growth by enhancing the repair of DNA damage. These therapies are important in managing and treating PCa. They are useful for the patients with genetic mutations [68]. PARP inhibitors include olaparib, riparoximab and veliparib. These drugs are effective against tumor cells with genetic or damaged DNA. They are employed in treating variety of tumor types like PCa [69]. The neuroendocrine prostate cancer (NEPC) is a rare but aggressive subtype of PCa. It is resistant to traditional ADT as the cancer cells have acquired neuroendocrine cell characteristics which make them insensitive to androgens [70]. NEPC has poor prognosis and limited treatments.

TABLE 2. Summary of the studies on clinical radiation and surgical treatments of PCa.

Study	Subject	Method	Materials	Findings
Nguyen *et al.* [57]	40 patients (prostate, breast, renal cell carcinoma and melanoma)	Clinical trail	Primary assessment: pain inventory; Secondary evaluation: pain response, toxicity, life quality, local control, and salvage surgery at 6 months	SBRT reduces pain from spinal lesions and demonstrates favorable toxicity and life quality outcomes
Andriole *et al.* [58]	146 patients undergoing 18F-fluciclovine PET/CT	RCT	ADT monotherapy 60 combined with other therapies 86 pre-scan	18F-fluciclovine-PET/CT impacts the management plans for most patients with pre-scan plans of ADT. Potential to exempt/delay the DT-related disease
Zapatero *et al.* [60]	355 patients with intermediate- and high-risk PCa	RCT	Stratified into three subgroups based on ADT + HRT treatment, and testosterone levels: minimum 20 ng/dL, median 20–49 ng/dL, and maximum ≥50 ng/dL	Achieving serum testosterone levels below 20 ng/dL is associated with improved clinical outcomes compared to 20–49 ng/dL. Neither ADT nor HRT impacts post-treatment testosterone recovery time
Hamdy *et al.* [64]	2664 men of 50–69 years age diagnosed with localized PCa	RCT	545 men in the active surveillance group, 553 in prostatectomy group, and 545 in radiation therapy group Primary outcome measures of mortality, and secondary outcomes of ADT treatment compared between groups at median follow-up of 15 years	Death: active surveillance group (3.1%) > radiotherapy group (2.9%) > prostatectomy group (2.2%) PCa metastasis: active surveillance group (9.4%) > radiation therapy group (5%) > prostatectomy group (4.7%) PCa mortality is low regardless of treatment, however, prostatectomy has the lowest mortality and the fewest metastases

SBRT, stereotactic body radiation therapy; RCT, randomized controlled trial; PET/CT, positron emission tomography/computed tomography; ADT, androgen deprivation therapy; DT, definitive therapy; PCa, prostate cancer; HRT, high-dose radiotherapy.

Its clinical management is thus critical. Prostate cells show neuroendocrine differentiation in response to the therapeutic interventions like ADT and chemotherapy. This adaptive mechanism promotes tumor progression [71]. Understanding NEPCs and treatment-induced neuroendocrine differentiation is crucial for managing androgen-insensitive PCa. They are the fundamentals in developing targeted therapies based on molecular mechanisms of neuroendocrine differentiation [72, 73].

PCa is a common genitourinary malignancy in older men. The common treatments include surgery and radiation followed by chemotherapy and androgen deprivation. PCa patients are immune-sensitive and require combination treatment and immunotherapeutic prevention [74]. Current PCa treatments include medical castration with gonadotropin-releasing hormone (GnRH), physical castration with resection, and ADT depending on the progression mechanism of castration-resistant PCa [75, 76]. ADT treatment is androgen receptor (AR) dependent [77, 78], where testosterone is injected into the cell by diffusion and converted to dihydrotestosterone (DHT) by 5-alpha-reductase. AR is then phosphorylated, dimerized and nuclearized where it binds to androgen response elements in host DNA to transcribe genes involved in survival [79].

Lambertianic acid (LA) is a diterpene bioactive compound purified from Pinus species. It is a natural optical isomer. It serves as potential targeted therapy to treat PCa malignancy. LA shows anticancer characteristics by targeting the key signaling components including protein kinase B (AKT), adenosine monophosphate-activated protein kinase (AMPK), nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB), cyclooxygenase-2 (COX-2), signal transducer, activator of transcription 3 (STAT3), *etc.*, to inhibit cancer cell proliferation and induce apoptosis [80]. AKT pathway is a signaling pathway associated with obesity and diabetes and known as the targeted therapeutic pathway for obesity [81]. AMPK, NFκB and COX are the signaling pathways with anti-inflammatory and anticancer therapeutic effects [82]. STAT3 is one of the STAT proteins transducing signals from cytokines and growth factors and their receptors inhibit the progression of malignant tumors and shape up the anticancer metabolic process [83]. Prostate cancer stem cells (CSCs) maintain stem-like state and provide microenvironment to the stem cells for responding to any situation in homeostasis and regulate regeneration and balance [84, 85]. CSC microenvironment protects and resists drug-induced apoptosis, and is involved in tumor metastasis and development. The monoclonal antibody bevacizumab targets vascular endothelial growth factor (VEGF) which disrupts CSC microenvironment by reducing angiogenesis. Bevacizumab is a targeted therapy similar to ADT. Patients receiving bevacizumab benefit from change in baseline PSA at maximum tolerated dose (MTD) in 5 of 16 subjects included in immune response evaluation trial. ADT and bevacizumab combination has median survival of 14.5 months, however, excluding bevacizumab decreases survival to 14.3 months [86]. Chimeric antigen receptor (CAR) T cell therapies are also the promising treatments. They proliferate CAR T cells (CARTs) with anti-cancer activity and sustain immune responses for long time. They are involved in immunosurveillance activities to prevent tumor recurrence and attach to prostate stem cell antigen (PSCA), PSMA and epithelial cells as the targets to show preclinical effects in PCa [87–89]. Harnessing the antitumor immune response of gut microbiome as potential therapeutic agent, and administering gut microbiome prevotella stercorea, are identified as the efficient combination therapy for overcoming endocrine resistance [90, 91]. RNA interference (RNAi) has been investigated for its potential in identifying biomarkers and therapeutic targets for prostate cancer based on gene expression. RNAi technology reduces the tumor's ability to initiate and metastasize in prostate cancer, playing a critical role in targeting cancer stem cell-like properties [92]. The tumor microenvironment (TME) is linked to carcinogenesis, invasion, and drug resistance. The current preclinical research is focused on immune-based therapies. Understanding the complex TME system in PCa can develop new therapies, design combination treatments, and overcome resistance to existing therapies for improving the lives of PCa patients [93, 94]. Immune checkpoint blockade (ICB) therapies, TME as immunotherapeutic strategy to target immunosuppressive cells in cancer development, progression, and metastasis, and pembrolizumab and ipilimumab are being employed in preclinical studies. The resistance to ICB therapy is conducive for more treatments and combinations when compared to other cancer models. Future targeted therapeutics and biomarker approaches may utilize immunosuppressive cells in TME, microbiota, autophagy, and epigenetic factors which can be extended to RCTs to overcome PCa [95, 96].

8. Conclusions

PCa being a major disease affects only men. Most PCa treatments are based on surgical physical castration, chemical hormonal castration, combinations of chemotherapy, or ADT. PCa can have negative prognosis accompanied by recurrence and pain. The importance of new treatments is thus emphasized. It is vital to choose appropriate treatment for PCa by considering the prognosis and recurrence risk. Early PCa diagnosis is effective, however, it can be difficult because of no symptoms. It is thus important to find and apply appropriate and personalize treatments for preventing side effects and metastasis. Chemotherapeutic and hormonal therapies are used in combination with surgical treatment, radiotherapy, or targeted therapy to improve the survival rates of PCa patients. Today's emerging usage of stem cells, gut microbiome, autophagy, and acquired genes suggest that they can be safe anticancer, anti-inflammatory, and immunotherapeutic agents. The therapeutic paradigm shifts are expanding pertaining to the microorganisms, genes, and biomarkers in addition to new drugs' development. It is thus imperative to widen the scope of clinical cases involving animal and human experiments.

ABBREVIATIONS

ADT, androgen deprivation therapy; AKT, protein kinase B; AMPK, adenosine monophosphate-activated protein kinase; BCF, biochemical failure; BCR, biochemical recurrence; bDFS, biochemical disease-free survival; CAR, Chimeric antigen receptor; CART, CarT cell; COX-2,

cyclooxygenase-2; CRP, C-reactive protein; CRPC-FS, castration-resistant prostate cancer-free survival; CSC, cancer stem cells; DHT, dihydrotestosterone; DM, dexmedetomidine; EPIC, expanded prostate cancer index composite; EBRT, external beam radiotherapy; AUR, acute urinary retention; GnRH, gonadotropin-releasing hormone; HRT, high-dose radiotherapy; HSPC, hormone sensitive prostate cancer; ICB, immune checkpoint blockade; IL, interleukin; IPSS, international prostate symptom score; LA, lambertianic acid; LOH, late-onset hypogonadal; MAB, maximal androgen blockade; HM, hydromorphone; mpMRI, multiparametric magnetic resonance imaging; PORT, post-prostatectomy radiation therapy; MSDD, modified Shenqi Dihuang decoction; MTD, maximum tolerated dose; PCa, prostate cancer; PDE5, phosphodiesterase-5; PET, positron emission tomography; CT, computed tomography; PSA, prostate-specific antigen; PSMA, prostate membrane specific antigen; PSMs, positive surgical margins; QoL, quality of life; RALP, robotic-assisted laparoscopic prostatecyomy; RARP, robotic-assisted radical prostatecyomy; RCT, randomized controlled trail; RNAi, RNA interference; SBRT, stereotactic body radiation therapy; STAT3, signal transducer and activator of transcription 3; TCM, memory T cell; TME, tumor microenvironment; TNM, tumor, nodes and metastasis; TRT, testosterone replacement therapy; VEGF, vascular endothelial growth factor.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

AUTHOR CONTRIBUTIONS

YP and KHK—conceptualization; validation; writing-review. YP—methodology, software; formal analysis, investigation, resources, data curation, writing-original draft preparation; editing, visualization. KHK—supervision. All authors have read and agreed to the published version of the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

ACKNOWLEDGMENT

Not applicable.

FUNDING

This research received no external funding.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

[1] Sun DQ, Lei L, Cai Y, Li H, Cao MM, He SY, *et al*. Research advances in the relationship of dietary factors and prostate cancer risk. Chinese Journal of Oncology. 2021; 43: 443–448. (In Chinese)

[2] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, *et al*. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians. 2021; 71: 209–249.

[3] Rawla P. Epidemiology of prostate cancer. World Journal of Clinical Oncology. 2019; 10: 63–89.

[4] Wong YN, Ferraldeschi R, Attard G, de Bono J. Evolution of androgen receptor targeted therapy for advanced prostate cancer. Nature Reviews Clinical Oncology. 2014; 11: 365–376.

[5] Skvortsov S, Skvortsova II, Tang DG, Dubrovska A. Concise review: prostate cancer stem cells: current understanding. Stem Cells. 2018; 36: 1457–1474.

[6] Plym A, Zhang Y, Stopsack KH, Delcoigne B, Wiklund F, Haiman C, *et al*. A healthy lifestyle in men at increased genetic risk for prostate cancer. European Urology. 2023; 83: 343–351.

[7] Berenguer CV, Pereira F, Câmara JS, Pereira JAM. Underlying features of prostate cancer—statistics, risk factors, and emerging methods for its diagnosis. Current Oncology. 2023; 30: 2300–2321.

[8] Culp MB, Soerjomataram I, Efstathiou JA, Bray F, Jemal A. Recent global patterns in prostate cancer incidence and mortality rates. European Urology. 2020; 77: 38–52.

[9] Barsouk A, Padala SA, Vakiti A, Mohammed A, Saginala K, Thandra KC, *et al*. Epidemiology, staging and management of prostate cancer. Medical Sciences. 2020; 8: 28.

[10] Pinsky PF, Parnes H. Screening for prostate cancer. New England Journal of Medicine. 2023; 388: 1405–1414.

[11] Chen S. Huang V, Xu X, Livingstone J, Soares F, Jeon J, *et al*. Widespread and functional RNA circularization in localized prostate cancer. Cell. 2019; 176: 831–843.e22.

[12] Mei W, Lin X, Kapoor A, Gu Y, Zhao K, Tang D. The contributions of prostate cancer stem cells in prostate cancer initiation and metastasis. Cancers. 2019; 11: 434.

[13] Blanc-Lapierre A, Spence A, Karakiewicz PI, Aprikian A, Saad F, Parent MÉ. Metabolic syndrome and prostate cancer risk in a population-based case-control study in Montreal, Canada. BMC Public Health. 2015; 15: 913.

[14] Bax C, Taverna G, Eusebio L, Sironi S, Grizzi F, Guazzoni G, *et al*. Innovative diagnostic methods for early prostate cancer detection through urine analysis: a review. Cancers. 2018; 10: 123.

[15] Kasivisvanathan V, Rannikko A, Borghi M, Panebianco V, Mynderse LA, Vaarala MH, *et al*. MRI-targeted or standard biopsy for prostate-cancer diagnosis. The New England Journal of Medicine. 2018; 378: 1767–1777.

[16] Barani M, Sabir F, Rahdar A, Arshad R, Kyzas GZ. Nanotreatment and nanodiagnosis of prostate cancer: recent updates. Nanomaterials. 2020; 10: 1696.

[17] McGuigan A, Kelly P, Turkington RC, Jones C, Coleman HG, McCain RS. Pancreatic cancer: a review of clinical diagnosis, epidemiology, treatment and outcomes. World Journal of Gastroenterology. 2018; 24: 4846–4861.

[18] Wang L, Lu B, He M, Wang Y, Wang Z, Du L. Prostate cancer incidence and mortality: global status and temporal trends in 89 countries from 2000 to 2019. Frontiers in Public Health. 2022; 10: 811044.

[19] Siegel RL, Miller DM, Wagle NS, Jemal A. Cancer statistics, 2023. CA: A Cancer Journal for Clinicians. 2023; 73: 17–48.

[20] Lowrance W, Dreicer R, Jarrard DF, Scarpato KR, Kim SK, Kirkby E, *et al*. Updates to advanced prostate cancer: AUA/SUO guideline (2023). Journal of Urology. 2023; 209: 1082–1090.

[21] Selvi I, Basar H. Subcapsular orchiectomy versus total orchiectomy and LHRH analogue in the treatment of hormone-sensitive metastatic prostate cancer: a different perspective in evaluation of the psychosocial effects. Supportive Care in Cancer. 2020; 28: 4313–4326.

[22] Velonas VM, Woo HH, dos Remedios CG, Assinder SJ. Current status of biomarkers for prostate cancer. International Journal of Molecular Sciences. 2013; 14: 11034–11060.

[23] Zhu Y, Mo M, Wei Y, Wu J, Pan J, Freedland SJ, *et al*. Epidemiology

and genomics of prostate cancer in Asian men. Nature Reviews Urology. 2021; 18: 282–301.

[24] Lomas DJ, Ahmed HU. All change in the prostate cancer diagnostic pathway. Nature Reviews Clinical Oncology. 2020; 17: 372–381.

[25] Tan X, Ding XF. Research progress of anesthesia methods in prostate biopsy. Chinese Journal of Surgery. 2022; 60: 504–508. (In Chinese)

[26] Liang K, Tang CY, Ke ZJ, Zhang XJ, Huang JH. Expressions of NLRP1 and NLRC4 inflammasomes in prostate cancer and their clinical value. National Journal of Andrology. 2023; 29: 31–37. (In Chinese)

[27] Li J, Cao DH, Wei Q, Liu LR. Advances in the genetic diagnosis and treatment of prostate cancer. National Journal of Andrology. 2022; 28: 715–721. (In Chinese)

[28] Rosen RD, Sapra A. TNM classification. StatPearls Publishing: Treasure Island (FL). 2024.

[29] Das S, Dey MK, Devireddy R, Gartia MR. Biomarkers in cancer detection, diagnosis, and prognosis. Sensors. 2024; 24: 37.

[30] Sekhoacha M, Riet K, Motloung P, Gumenku L, Adegoke A, Mashele S. Prostate cancer review: genetics, diagnosis, treatment options, and alternative approaches. Molecules. 2022; 27: 5730.

[31] Blas L, Shiota M, Eto M. Active surveillance in intermediate-risk prostate cancer: a review of the current data. Cancers. 2022; 14: 4161.

[32] Clinckaert A, Devos G, Roussel E, Joniau S. Risk stratification tools in prostate cancer, where do we stand? Translational Andrology and Urology. 2021; 10: 12–18.

[33] Tonry C, Finn S, Armstrong J, Pennington SR. Clinical proteomics for prostate cancer: understanding prostate cancer pathology and protein biomarkers for improved disease management. Clinical Proteomics. 2020; 17: 41.

[34] Taylor JM, Chen VE, Miller RC, Greenberger BA. The impact of prostate cancer treatment on quality of life: a narrative review with a focus on randomized data. Research and Reports in Urology. 2020; 12: 533–546.

[35] Zarrabi A, Perrin D, Kavoosi M, Sommer M, Sezen S, Mehrbod P, *et al*. Rhabdomyosarcoma: current therapy, challenges, and future approaches to treatment strategies. Cancers. 2023; 15: 5269.

[36] Debela DT, Muzazu SG, Heraro KD, Ndalama MT, Mesele BW, Haile DC, *et al*. New approaches and procedures for cancer treatment: current perspectives. SAGE Open Medicine. 202; 9: 20503121211034366.

[37] Liu YP, Zheng CC, Huang YN, He ML, Xu WW, Li B. Molecular mechanisms of chemo- and radiotherapy resistance and the potential implications for cancer treatment. MedComm. 2021; 2: 315–340.

[38] Anand U, Dey A, Chandel AKS, Sanyal R, Mishra A, Pandey DK, *et al*. Cancer chemotherapy and beyond: current status, drug candidates, associated risks and progress in targeted therapeutics. Genes & Diseases. 2022; 10: 1367–1401.

[39] Topol EJ. High-performance medicine: the convergence of human and artificial intelligence. Nature Medicine. 2019; 25: 44–56.

[40] Litjens G, Kooi T, Bejnordi BE, Setio AAA, Ciompi F, Ghafoorian M, *et al*. A survey on deep learning in medical image analysis. Medical Image Analysis. 2017; 42: 60–88.

[41] Kamel I, Ahmed MF, Sethi A. Regional anesthesia for orthopedic procedures: what orthopedic surgeons need to know. World Journal of Orthopedics. 2022; 13: 11–35.

[42] Alghandour R, Ebrahim MA, Elshal AM, Ghobrial F, Elzaafarany M, ELbaiomy MA. Repurposing metformin as anticancer drug: randomized controlled trial in advanced prostate cancer (MANSMED). Urologic Oncology. 2021; 39: 831.e1–831.e10.

[43] Milosevic M, Jin Q, Singh A, Amal S. Applications of AI in multi-modal imaging for cardiovascular disease. Frontiers in Radiology. 2024; 3: 1294068.

[44] Singh A, Randive S, Breggia A, Ahmad B, Christman R, Amal S. Enhancing prostate cancer diagnosis with a novel artificial intelligence-based web application: synergizing deep learning models, multimodal data, and insights from usability study with pathologists. Cancers. 2023; 15: 5659.

[45] Tsirkas K, Zygogianni A, Kougioumtzopoulou A, Kouloulias V, Liakouli Z, Papatsoris A, *et al*. A-blockers for the management of lower urinary tract symptoms in patients with prostate cancer treated with external beam radiotherapy: a randomized controlled study. World Journal of Urology. 2021; 39: 1805–1813.

[46] Hsu T, Fergusson D, Stober C, Daigle K, Moledina N, Vandermeer L, *et al*.; REaCT investigators. A randomized clinical trial comparing physician-directed or fixed-dose steroid replacement strategies for incomplete dexamethasone dosing prior to docetaxel chemotherapy. Supportive Care in Cancer. 2021; 29: 3113–3120.

[47] Gu JY, Tan MY, Ge MY, Zhai XY, Guo DD, Xu DL. Modified Shenqi Dihuang Decoction for bone metastasis of hormone-sensitive prostate cancer after castration. National Journal of Andrology. 2021; 27: 161–166. (In Chinese)

[48] Yang ZH, Xia XQ, Gao X, Yu YB, Gong RJ, Li YH. Effects of low-dose dexmedetomidine combined with hydromorphone in postoperative analgesia and on the serum IL-6 and CRP levels of prostate cancer patients. National Journal of Andrology. 2021; 27: 713–717. (In Chinese)

[49] Bhasin S, Travison TG, Pencina KM, O'Leary M, Cunningham GR, Lincoff AM, *et al*. Prostate safety events during testosterone replacement therapy in men with hypogonadism: a randomized clinical trial. JAMA Network Open. 2023; 6: e2348692.

[50] Kato Y, Shigehara K, Kawaguchi S, Izumi K, Kadono Y, Mizokami A. Efficacy of testosterone replacement therapy on pain in hypogonadal men with chronic pain syndrome: a subanalysis of a prospective randomised controlled study in Japan (EARTH study). Andrologia. 2020; 52: e13768.

[51] Yang HJ, Kim KH, Kim DS, Lee CH, Jeon YS, Shim SR, *et al*. The effect of testosterone replacement on sexual function in the elderly: a systematic review and meta-analysis. World Journal of Men's Health. 2023; 41: 861–873.

[52] Diaz P, Reddy R, Blachman-Braun R, Zucker I, Dullea A, Gonzalez DC, *et al*. Comparison of intratesticular testosterone between men receiving nasal, intramuscular, and subcutaneous pellet testosterone therapy: evaluation of data from two single-center randomized clinical trials. World Journal of Men's Health. 2023; 41: 390–395.

[53] Mir N, Burke O, Yates S, Rajasekaran T, Chan J, Szmulewitz R, *et al*. Androgen receptor pathway inhibitors, prostate cancer, and older adults: a global young international society of geriatric oncology drug review. Therapeutic Advances in Medical Oncology. 2023; 15: 17588359221149887.

[54] Ong S, O'Brien J, Medhurst E, Lawrentschuk N, Murphy D, Azad A. Current treatment options for newly diagnosed metastatic hormone-sensitive prostate cancer-a narrative review. Translational Andrology and Urology. 2021; 10: 3918–3930.

[55] Bhasin S, Travison TG, Pencina KM, O'Leary M, Cunningham GR, Lincoff AM, *et al*. JAMA Netw Open. 2023; 6: e2348692.

[56] Gregucci F, Carbonara R, Surgo A, Ciliberti MP, Curci D, Ciocia A, *et al*. Extreme hypofractionated stereotactic radiotherapy for elderly prostate cancer patients: side effects preliminary analysis of a phase II trial. Radiologia Medica. 2023; 128: 501–508.

[57] Nguyen EK, Quan K, Parpia S, Tran S, Swaminath A. Stereotactic body radiotherapy for osseous low alpha-beta resistant metastases for pain relief-SOLAR-P. Radiation Oncology. 2021; 16: 170.

[58] Andriole GL, Scarsbrook AF, Savir-Baruch B. LOCATE/FALCON study groups. impact of 18F-fluciclovine PET/CT on plans for androgen deprivation therapy in patients with biochemical recurrence of prostate cancer: data analysis from two prospective clinical trials. Urologic Oncology. 2023; 41: 293.e1–293.e7.

[59] Ghai S, Finelli A, Corr K, Chan R, Jokhu S, Li X, *et al*. MRI-guided focused ultrasound ablation for localized intermediate-risk prostate cancer: early results of a phase II trial. Radiology. 2021; 298: 695–703.

[60] Zapatero A, Álvarez A, Guerrero A, Maldonado X, González San Segundo C, Cabeza MA, *et al*. Prognostic value of testosterone castration levels following androgen deprivation and high-dose radiotherapy in localized prostate cancer: results from a phase III trial. Radiotherapy and Oncology. 2021; 160: 115–119.

[61] Rowe LS, Harmon S, Horn A, Shankavaram U, Roy S, Ning H, *et al*. Pattern of failure in prostate cancer previously treated with radical prostatectomy and post-operative radiotherapy: a secondary analysis of two prospective studies using novel molecular imaging techniques. Radiotherapy and Oncology. 2021; 16: 32.

[62] Cetin T, Yalcin MY, Karaca E, Ozbilen MH, Ergani B, Koc G, *et al*. Laparoscopic surgery experience does not influence oncological and functional results of robotic-assisted laparoscopic prostatectomy. Urologia. 2022; 89: 240–243.

[63] Su SH, Chang YH, Huang LK, Chu YC, Kan HC, Liu CY, *et al*. Clinical

predictors for biochemical failure in patients with positive surgical margin after robotic-assisted radical prostatectomy. Tumori. 2022; 108: 270–277.
[64] Hamdy FC, Donovan JL, Lane JA, Metcalfe C, Davis M, Turner EL, *et al*. Fifteen-year outcomes after monitoring, surgery, or radiotherapy for prostate cancer. New England Journal of Medicine. 2023; 388: 1547–1558.
[65] Liu J, Li WP, Yang SJ. Updated studies on the immunotherapy of prostate cancer. National Journal of Andrology. 2022; 28: 349–355. (In Chinese)
[66] Cornford P, van den Bergh RCN, Briers E, Van den Broeck T, Cumberbatch MG, De Santis M, *et al*. EAU-EANM-ESTRO-ESUR-SIOG guidelines on prostate cancer. Part II-2020 update: treatment of relapsing and metastatic prostate cancer. European Urology. 2021; 79: 263–282.
[67] van Leenders G, van der Kwast TH, Grignon DJ, Evans AJ, Kristiansen G, Kweldam CF, *et al*. The 2019 international society of urological pathology (ISUP) consensus conference on grading of prostatic carcinoma. The American Journal of Surgical Pathology. 2020; 44: e87–e99.
[68] Tisseverasinghe S, Bahoric B, Anidjar M, Probst S, Niazi T. Advances in PARP inhibitors for prostate cancer. Cancers. 2023; 15: 1849.
[69] Nambiar DK, Mishra D, Singh RP. Targeting DNA repair for cancer treatment: lessons from PARP inhibitor trials. Oncology Research. 2023; 31: 405–421.
[70] Yamada Y, Beltran H. Clinical and biological features of neuroendocrine prostate cancer. Current Oncology Reports. 2021; 23: 15.
[71] Wang Y, Wang Y, Ci X, Choi SYC, Crea F, Lin D, *et al*. Molecular events in neuroendocrine prostate cancer development. Nature Reviews Urology. 2021; 18: 581–596.
[72] Xie Y, Ning S, Hu J. Molecular mechanisms of neuroendocrine differentiation in prostate cancer progression. Journal of Cancer Research and Clinical Oncology. 2022; 148: 1813–1823.
[73] Zamora I, Freeman MR, Encío IJ, Rotinen M. Targeting key players of neuroendocrine differentiation in prostate cancer. International Journal of Molecular Sciences. 2023; 24: 13673.
[74] Harris WP, Mostaghel EA, Nelson PS, Montgomery B. Androgen deprivation therapy: progress in understanding mechanisms of resistance and optimizing androgen depletion. Nature Clinical Practice Urology. 2009; 6: 76–85.
[75] Debes JD, Tindall DJ. Mechanisms of androgen-refractory prostate cancer. The New England Journal of Medicine. 2004; 351: 1488–1490.
[76] Shahinozzaman M, Islam M, Basak B, Sultana A, Emran R, Ashrafizadeh M, *et al*. A review on chemistry, source and therapeutic potential of lambertianic acid. A Journal of Biosciences. 2021; 76: 347–356.
[77] Savova MS, Mihaylova LV, Tews D, Wabitsch M, Georgiev MI. Targeting PI3K/AKT signaling pathway in obesity. Biomedicine & Pharmacotherapy. 2023; 159: 114244.
[78] Pérez-Cremades D, Bueno-Betí C, García-Giménez JL, Ibañez-Cabellos JS, Pallardó FV, Hermenegildo C, *et al*. Extracellular histones trigger oxidative stress-dependent induction of the NF-κB/CAM pathway via TLR4 in endothelial cells. Journal of Physiology and Biochemistry. 2023; 79: 251–260.
[79] Li YJ, Zhang C, Martincuks A, Herrmann A, Yu H. STAT proteins in cancer: orchestration of metabolism. Nature Reviews Cancer. 2023; 23: 115–134.
[80] Masoumi J, Jafarzadeh A, Abdolalizadeh J, Khan H, Philippe J, Mirzaei H, *et al*. Cancer stem cell-targeted chimeric antigen receptor (CAR)-T cell therapy: challenges and prospects. Acta Pharmaceutica Sinica B. 2021; 11: 1721–1739.
[81] Yang J, Aljitawi O, Van Veldhuizen P. Prostate cancer stem cells: the role of CD133. Cancers. 2022; 14: 5448.
[82] Gogola S, Rejzer M, Bahmad HF, Alloush F, Omarzai Y, Poppiti R. Anti-cancer stem-cell-targeted therapies in prostate cancer. Cancers. 2023; 15: 1621.
[83] Davenport AJ, Jenkins MR, Cross RS, Yong CS, Prince HM, Ritchie DS, *et al*. CAR-T cells inflict sequential killing of multiple tumor target cells. Cancer Immunology Research. 2015; 3: 483–494.
[84] Wolf P, Alzubi J, Gratzke C, Cathomen T. The potential of CAR T cell therapy for prostate cancer. Nature Reviews Urology. 2021; 18: 556–571.
[85] Junghans RP, Ma Q, Rathore R, Gomes EM, Bais AJ, Lo ASY, *et al*. Phase I trial of anti-PSMA designer CAR-T cells in prostate cancer: possible role for interacting interleukin 2-T cell pharmacodynamics as a determinant of clinical response. Prostate. 2016; 76: 1257–1270.
[86] Cimadamore A, Santoni M, Massari F, Gasparrini S, Cheng L, Lopez-Beltran A. Microbiome and cancers, with focus on genitourinary tumors. Frontiers in Oncology. 2019; 9: 178.
[87] Kloss CC, Lee J, Zhang A, Chen F, Melenhorst JJ, Lacey SF, *et al*. Dominant-Negative TGF-β receptor enhances PSMA-targeted human CAR T cell proliferation and augments prostate cancer eradication. Molecular Therapy. 2018; 26: 1855–1866.
[88] Alzubi J, Dettmer-Monaco V, Kuehle J, Thorausch N, Seidl M, Taromi S, *et al*. PSMA-directed CAR T cells combined with low-dose docetaxel treatment induce tumor regression in a prostate cancer xenograft model. Molecular Therapy Oncology. 2020; 18: 226–235.
[89] Lin M, Sun X, Lv L. New insights and options into the mechanisms and effects of combined targeted therapy and immunotherapy in prostate cancer. Molecular Therapy Oncology. 2023; 29: 91–106.
[90] Gabrielli G, Shouval R, Ghilardi G, van den Brink M, Ruella M. Harnessing the gut microbiota to potentiate the efficacy of CAR T cell therapy. Hemasphere. 2023; 7: e950.
[91] Fu C, Yang Z, Yu J, Wei M. The interaction between gut microbiome and anti-tumor drug therapy. American Journal of Cancer Research. 2021; 11: 5812–5832.
[92] Riscado M, Baptista B, Sousa F. New RNA-based breakthroughs in Alzheimer's disease diagnosis and therapeutics. Pharmaceutics. 2021; 13: 1397.
[93] Xiao Y, Yu D. Tumor microenvironment as a therapeutic target in cancer. Pharmacology & Therapeutics. 2021; 221: 107753.
[94] Salemme V, Centonze G, Avalle L, Natalini D, Piccolantonio A, Arina P, *et al*. The role of tumor microenvironment in drug resistance: emerging technologies to unravel breast cancer heterogeneity. Frontiers in Oncology. 2023; 13: 1170264.
[95] Zhou X, Ni Y, Liang X, Lin Y, An B, He X, *et al*. Mechanisms of tumor resistance to immune checkpoint blockade and combination strategies to overcome resistance. Frontiers in Immunology. 202; 13: 915094.
[96] Li T, Liu T, Zhu W, Xie S, Zhao Z, Feng B, *et al*. Targeting MDSC for immune-checkpoint blockade in cancer immunotherapy: current progress and new prospects. Clinical Medicine Insights: Oncology. 2021; 15: 11795549211035540.

How to cite this article: Yeonhee Pyo, Ki Han Kwon. Current state of prostate cancer treatment and future strategies. Journal of Men's Health. 2024; 20(11): 9-18. doi: 10.22514/jomh.2024.181.