Proceedings of ICEGEE 2026 Symposium: AI-Based Medicine and Biological Data Analysis
DOI: 10.54254/2753-8818/2026.AU32645

Recent Advances in Early Diagnosis, Molecular Subtyping, and Precision Treatment of Prostate Cancer

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Abstract. Prostate cancer (PCa) is the second most common malignant tumor among men worldwide and is characterized by marked clinical heterogeneity. Its natural course may manifest as a long-term indolent localized lesion, or it may progress to aggressive and even fatal metastatic disease. In recent years, with the rapid development of molecular biology, genomics, and molecular imaging, important advances have been made in the early diagnosis, risk stratification, and staging evaluation of PCa, providing new technical support for the precise localization of primary and metastatic lesions. Meanwhile, the continuous refinement of molecular subtyping systems is driving the treatment model of PCa to gradually shift from traditional empirical treatment to biomarker-based individualized treatment. At present, precision treatment of PCa is characterized by being based on local treatment, implementing stratified systemic treatment, and continuously expanding novel targeted strategies. This article reviews the research progress in the early diagnosis, molecular subtyping, and precision treatment of PCa, with the aim of providing a reference for its clinical individualized management.

Keywords: prostate cancer, early diagnosis, molecular subtyping, precision treatment

1. Introduction

Prostate cancer (PCa) is increasingly becoming an important public health issue and has a significant impact on the health of Chinese men. Epidemiological data from 2020 show that, compared with European and African countries, the incidence of prostate cancer in China remains significantly lower. However, the numbers of new cases and deaths from prostate cancer in China account for 8.2% and 13.6% of the global totals, respectively. In addition, multiple studies predict that by 2030, the incidence ranking of prostate cancer in China will rise from seventh to third, with an estimated increase of 517% from 2015 to 2030 [1,2]. Against the background of an increasing disease burden, the clinical management of PCa still faces the challenge of coexistence of overdiagnosis and missed diagnosis. How to improve the early diagnostic capability for clinically significant prostate cancer and optimize risk stratification and precision treatment through molecular subtyping has become an important direction in current research and clinical practice.

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2. Early diagnosis of PCa

PCa has marked clinical heterogeneity, and its natural course may manifest as a long-term indolent localized lesion or progress to aggressive and even metastatic disease [3,4]. Clinically, manifestations such as increased nocturia, urinary frequency, urinary urgency, dysuria, urinary retention, hematuria, and erectile dysfunction may suggest the possibility of PCa, but these symptoms are also common in benign prostatic hyperplasia and prostatitis; therefore, early differential diagnosis is difficult to achieve based solely on clinical symptoms [5]. At present, the early diagnosis of PCa has gradually shifted from relying solely on symptoms or a single indicator to a comprehensive pathway integrating serological testing, imaging evaluation, risk prediction models, and pathological confirmation, with the goal of improving the detection rate of clinically significant prostate cancer (csPCa) while reducing unnecessary biopsies and overdiagnosis of indolent tumors.

2.1. Prostate-Specific Antigen (PSA) and related biomarkers

PSA remains the most commonly used biomarker in PCa screening and risk assessment [6]. PSA is secreted by prostatic epithelial cells and may be elevated in various conditions such as prostatic inflammation, hyperplasia, and tumors; therefore, it has high sensitivity but limited specificity [7,8]. In clinical practice, although elevated PSA suggests an increased risk of PCa, it cannot directly distinguish between benign and malignant lesions, nor can it accurately identify the biological aggressiveness of tumors.

To improve diagnostic efficacy, in recent years multiple complementary biomarkers based on blood or urine have been applied to pre-biopsy risk stratification. Hematologic indicators are mainly used to optimize the interpretive framework of PSA, whereas urinary biomarkers include PCA3, SelectMDx, MyProstateScore (MPS/MPS2), and ExoDX [9]. These tests do not replace PSA, but rather serve as auxiliary tools for biopsy decision-making and are used in combination with age, family history, prostate volume, and imaging findings to improve the identification of csPCa. Overall, the future direction of PCa screening is not simply to pursue universal screening with "lower thresholds," but rather to achieve more precise individualized risk assessment based on multi-parameter integration.

2.2. Multiparametric Magnetic Resonance Imaging (mpMRI)

mpMRI has become a key component of the diagnostic pathway for PCa. Standard mpMRI usually consists of T2-weighted imaging (T2WI), diffusion-weighted imaging (DWI), and dynamic contrast-enhanced imaging (DCE), and can evaluate suspicious prostate lesions from both anatomical and functional perspectives [10]. Compared with traditional transrectal ultrasound, mpMRI has clear advantages in detecting suspicious lesions, evaluating local invasion, and guiding targeted biopsy.

Over the past decade, the evaluation pathway for patients with suspected PCa has undergone important changes: mpMRI has gradually shifted from an auxiliary examination to an important tool for risk stratification before biopsy [11]. For MRI-positive patients, mpMRI can not only improve the accuracy of localization of suspicious lesions, but also provide a basis for MRI/ultrasound fusion-guided targeted biopsy, thereby improving the detection rate of csPCa; for patients who are MRI-negative and have an overall low risk, it may help reduce some unnecessary biopsies. It is worth noting that the diagnostic performance of mpMRI is highly dependent on image quality, reader experience, and standardized reporting systems. Among these, T2WI is particularly important

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in lesion spatial registration and fusion guidance and is directly related to the accuracy of targeted biopsy [12]. Therefore, image quality control and standardized interpretation are key prerequisites for the clinical application of mpMRI.

2.3. Biopsy

Although biomarkers and imaging techniques have continued to advance, the definitive diagnosis of PCa still relies on prostate biopsy and subsequent pathological evaluation. For patients with clinical suspicion of PCa, sampling strategies should be developed before biopsy by integrating PSA levels, digital rectal examination, mpMRI findings, and individual risk factors. Tissue samples obtained from biopsy should be evaluated by experienced uropathologists and should include histological diagnosis and International Society of Urological Pathology (ISUP) grading [13,14].

Traditional transrectal ultrasound-guided systematic biopsy (SBx) has long been widely used because of its convenience and low cost; however, it is essentially a template-based random sampling method, with insufficient coverage of the anterior prostate and some occult lesions, which may lead to missed diagnosis of some csPCa while also detecting some low-risk lesions of limited clinical significance. With the increasing adoption of mpMRI, the value of targeted biopsy (TBx) in MRI-positive patients has become increasingly prominent. At present, mpMRI-guided TBx combined with SBx is regarded as an important strategy for improving overall diagnostic efficacy, particularly for initial biopsy, repeat biopsy, and re-evaluation in patients under active surveillance. Meanwhile, the transperineal approach has attracted increasing attention in recent years because of its lower risk of infection and more adequate sampling of the anterior prostate. Overall, PCa biopsy strategies are shifting from traditional random sampling toward an "image-guided + precise sampling" model, with the core objective of improving the detection rate of csPCa while reducing overdiagnosis.

3. Molecular basis and genetic susceptibility of PCa

In recent years, research on the molecular basis and genetic susceptibility of PCa has continued to deepen. Relevant understanding has gradually expanded from common single-nucleotide polymorphisms to moderate- and high-penetrance germline variants, and has increasingly demonstrated clinical value in risk assessment, screening stratification, genetic counseling, and precision treatment. PCa is one of the solid tumors with a relatively high genetic contribution, and its genetic basis involves the combined effects of common low-penetrance variants and rare moderate- to high-penetrance germline variants [15]. With the development of sequencing technologies, the germline susceptibility genes currently considered to have relatively high clinical relevance mainly include BRCA2, HOXB13, ATM, CHEK2, BRCA1, and DNA mismatch repair-related genes [16,17]. Meanwhile, in addition to germline susceptibility factors, somatic molecular alterations such as FOXA1 also play important roles in the occurrence, development, and treatment resistance of PCa [18].

3.1. BRCA2 and HRR-related germline susceptibility genes

Among the known germline susceptibility factors for PCa, BRCA2 is one of the genes with the most sufficient evidence and the clearest clinical significance. In addition to BRCA2, homologous recombination repair (HRR)-related genes such as ATM, CHEK2, BRCA1, and PALB2 are also associated with increased risk of PCa and enhanced disease aggressiveness [19]. Among them,

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BRCA2 variants are not only associated with a higher risk of disease onset, but also often indicate higher grade, more advanced stage, and poorer prognosis, and thus are of important value in genetic counseling, risk stratification, and precision treatment of advanced disease [20]. Overall, abnormalities in HRR-related genes have become an important molecular basis linking research on genetic susceptibility of PCa with clinical precision treatment.

3.2. HOXB13 and other germline susceptibility genes

In addition to HRR-related genes, HOXB13 is also one of the representative germline susceptibility genes in PCa. Studies have shown that HOXB13 variants are closely associated with an increased risk of PCa and are of particular research value in familial and early-onset PCa. In addition, DNA mismatch repair-related genes, such as MSH2, MSH6, MLH1, and PMS2, are also associated with genetic susceptibility to some PCa cases and suggest that they may be related to tumorigenesis in the context of Lynch syndrome [21]. It should be noted that the strength of evidence for different germline susceptibility genes is not entirely consistent, and their distribution frequencies and clinical significance also differ among populations; therefore, comprehensive interpretation still requires consideration of ancestry background and family history.

3.3. FOXA1 and other key somatic molecular alterations

In addition to germline susceptibility genes, the occurrence and development of PCa are also accompanied by a series of important somatic molecular alterations. FOXA1 is one of the representative molecules among them. It encodes forkhead box transcription factor A1 and is an important pioneer factor regulating chromatin accessibility and androgen receptor (AR) transcriptional programs. Recent studies have shown that FOXA1 abnormalities can affect chromatin accessibility and AR-related transcriptional programs, and are associated with disease progression, lineage plasticity, and treatment resistance [22]. Therefore, key somatic molecular alterations such as FOXA1 not only help deepen the understanding of the molecular heterogeneity of PCa, but may also provide a theoretical basis for future optimization of molecular subtyping and targeted intervention.

4. Precision treatment of PCa

4.1. Local treatment of localized PCa

Localized PCa usually refers to a disease state in which the tumor is confined to the prostate and has not yet developed distant metastasis; however, its biological behavior and clinical risk stratification differ substantially and it is not equivalent to a homogeneous disease with low malignant potential [23]. Some patients may maintain a relatively indolent course for a long time, whereas others may have a higher risk of progression. Therefore, treatment decisions for localized PCa should comprehensively consider factors such as tumor stage, pathological grade, PSA level, life expectancy, and patient preference [24].

For patients with localized PCa who are suitable for radical treatment, radical prostatectomy and radiotherapy remain the currently recognized main local curative treatment modalities [25]. In addition to the above standard treatments, some novel local treatment techniques, such as cryoablation, high-intensity focused ultrasound, and photodynamic therapy, are also under continuous exploration; however, according to current guidelines, such whole-gland or focal ablative

DOI: 10.54254/2753-8818/2026.AU32645

treatments are still mainly limited to clinical trials or prospective registry studies [26]. Some focal therapies have shown certain potential in short-term functional preservation, but their long-term oncological outcomes and the boundaries of indications still require further clarification through more high-quality studies.

4.2. Androgen deprivation therapy

At present, systemic treatment decisions for PCa usually need to be stratified according to factors such as disease stage, metastatic status, castration-sensitive or castration-resistant status, and prior treatment exposure. Because the occurrence and development of PCa are markedly androgen-dependent, androgen deprivation therapy (ADT), by reducing androgen levels or blocking their action, has become an important foundation for the treatment of locally advanced, recurrent, and metastatic PCa. In localized or locally advanced disease, ADT is often used in combination with radiotherapy; in metastatic disease, ADT is also an important foundational component of systemic treatment [27].

Metastatic PCa usually shows a certain response to initial ADT, but most patients eventually progress to metastatic castration-resistant prostate cancer (mCRPC), that is, disease progression despite testosterone having reached the castration level. It should be noted that in current clinical practice, although ADT remains the foundational treatment, monotherapy with ADT is no longer the only treatment strategy for metastatic patients eligible for treatment intensification, and combination treatment models have become more common. With the development of molecular subtyping and novel drugs, the treatment of advanced PCa is gradually shifting from ADT alone toward combination and sequential treatment based on clinical features and biomarkers [28].

4.3. Biomarker-based precision treatment and emerging treatments

With the continuous deepening of research on molecular subtyping and targeted treatment, the precision treatment of PCa is gradually shifting from traditional empirical treatment to biomarker-guided individualized treatment. At present, the more representative strategies mainly include targeted treatment based on specific molecular abnormalities, radioligand treatment based on tumor surface molecular expression, and immunotherapy for a small number of specific molecular subgroups. For patients with HRR-related gene abnormalities in mCRPC, PARP inhibitors have become an important precision treatment option, with the most sufficient evidence of benefit in patients with BRCA1/2 variants [29]. Meanwhile, for advanced patients with positive prostate-specific membrane antigen (PSMA), PSMA-targeted radioligand treatment has entered clinical practice and its scope of application in mCRPC continues to expand. For patients with a small number of specific molecular subgroups such as MSI-H/dMMR, immune checkpoint inhibitors may serve as a potential treatment option guided by biomarkers [30]. These advances indicate that molecular subtyping and biomarker testing are driving the treatment of advanced PCa toward greater precision and individualization.

In contrast, although gene therapy has a certain research basis in PCa, it is still mainly in the stage of clinical research and exploration and has not yet become a routine standard treatment. Its clinical translation still faces challenges such as delivery efficiency, safety, and stability of efficacy; therefore, it is more appropriate to discuss it as one of the emerging research directions in PCa rather than as the main component of current precision treatment.

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5. Conclusion

The early diagnosis of PCa has long faced two core challenges: first, the insufficient specificity of traditional PSA screening, which easily leads to unnecessary needle biopsy and overdiagnosis of indolent tumors; second, how to more accurately identify aggressive tumors requiring clinical intervention. Meanwhile, with the continuous development of mpMRI, biomarker testing, and risk prediction models, early identification of PCa is gradually shifting from a single-indicator-driven approach to precise evaluation based on multidimensional information integration. In the treatment field, recent advances in PCa diagnosis and treatment have mainly been reflected in advanced disease, especially in the biomarker-guided precision treatment of castration-resistant prostate cancer and the continuous optimization of combination treatment strategies. The development of biomarker-based targeted treatment, radioligand treatment, and sequential treatment models is driving the treatment of PCa from an empirical model toward an individualized and precision model. Looking to the future, the development of PCa diagnosis and treatment will mainly show the following trends. First, the integration of diagnosis and treatment will be further strengthened, and the linkage among early screening, risk stratification, molecular testing, and treatment decision-making will become closer. Second, artificial intelligence-driven clinical decision support systems are expected to play a greater role. From radiomics to pathomics, and then to genomics and clinical information integration, artificial intelligence will provide more precise support for the early diagnosis, prognostic assessment, and treatment selection of PCa. Third, treatment strategies will continue to be optimized and upgraded, shifting from monotherapy to multi-mechanism synergistic combination treatment, with the aim of further delaying the development of resistance and improving survival benefits. Finally, while diagnostic and therapeutic technologies continue to advance, how to improve standardized diagnosis and treatment, narrow medical disparities among different regions and populations, and promote the accessibility and equity of precision medicine will remain important challenges for future clinical practice in PCa. In summary, the field of PCa diagnosis and treatment is developing at an unprecedented pace. The noninvasive and precise nature of early diagnosis, together with the synergistic and individualized nature of treatment for advanced disease, is jointly driving PCa toward a chronic disease management model that is preventable, controllable, and amenable to precise intervention.

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