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Research Progress on Brain Metastasis of Prostate Cancer

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Abstract: Prostate cancer (PCa) is one of the most common malignant tumors in men. While the prognosis is generally favorable in the early stages, the incidence of brain metastasis increases in the advanced stages of castration-resistant prostate cancer (CRPC). Brain metastasis of prostate cancer is relatively rare, accounting for only 1% to 3% of metastatic cases; however, once it occurs, the prognosis is poor. Clinical symptoms of brain metastasis often include headaches, cognitive impairment, and seizures. Studies suggest that the disruption of the blood-brain barrier and changes in the tumor microenvironment play critical roles in the metastatic process to the brain. Imaging techniques such as MRI and CT are commonly used for diagnosis, and liquid biopsy methods, such as cerebrospinal fluid analysis and ctDNA testing, offer new non-invasive diagnostic options. In terms of treatment, local therapies (such as surgery and radiotherapy), systemic therapies (such as chemotherapy and immunotherapy), and multidisciplinary approaches are commonly employed. Although targeted therapies and immune checkpoint inhibitors show potential in clinical settings, further research is needed to optimize treatment strategies and improve efficacy.

1. Introduction

Prostate cancer (PCa) is one of the most common malignancies among men worldwide, especially in Western countries, where the incidence continues to rise [1], [2], [3], [4]. While prostate cancer typically has a good prognosis in its early stages, the incidence of distant metastasis significantly increases in the advanced stages, particularly in patients with castration-resistant prostate cancer (CRPC). According to current clinical data, the most common sites of metastasis for prostate cancer are the bones and lymph nodes [5], [6], [7]. However, brain metastasis in prostate cancer is relatively rare, accounting for only 1% to 3% of all metastatic cases. Once it occurs, the prognosis is extremely poor, and the treatment is challenging. As the incidence of CRPC rises, the occurrence of brain metastasis is also increasing, especially in patients who have undergone multiple lines of therapy. Brain metastasis profoundly impacts the quality of life, with the median survival time for patients with prostate cancer brain metastasis ranging from 1 to 7.7 months [8], [9], [10], [11], [12]. Therefore, early diagnosis and effective treatment are critical.

Research on brain metastasis in prostate cancer is still evolving. While some clinical studies have provided valuable insights into this field, many issues remain unresolved, particularly regarding the molecular mechanisms of brain metastasis, immune escape mechanisms, and treatment strategies. This review aims to comprehensively summarize the latest research on prostate cancer brain metastasis, focusing on its clinical characteristics, molecular mechanisms, diagnostic methods, treatment strategies, and future research directions.

2. Clinical Features and Pathogenesis of Brain Metastasis in Prostate Cancer

2.1 Clinical Features

The clinical manifestations of brain metastasis in prostate cancer are often non-specific [13]. The most common symptoms include speech disorders, dysarthria, diplopia, facial numbness, headaches, weakness, delirium, and altered consciousness [14], [15], [16]. Headaches are one of the most prevalent symptoms, occurring in approximately 70% of patients, and are often caused by increased intracranial pressure. Seizures are another common symptom of brain metastasis in prostate cancer, affecting about 30% of patients, particularly when the metastatic lesions are located in the cerebral cortex [17]. Cognitive impairment, such as memory loss and difficulty concentrating, is also a significant feature, typically correlating with the number and location of the metastatic lesions. Neurological deficits, such as hemiparesis and speech impairment, usually indicate that the metastatic lesions have affected the brain's motor or language centers. Although the clinical presentation of brain metastasis often resembles that of other neurological conditions (such as intracranial tumors or stroke) and the symptoms tend to develop slowly, leading to misdiagnosis, clinicians should remain highly vigilant for the possibility of brain metastasis when prostate cancer patients exhibit these symptoms.

2.2 Pathogenesis

The occurrence of brain metastasis in prostate cancer involves complex molecular mechanisms. Current research indicates that brain metastasis is not solely dependent on hematogenous spread of tumor cells to the brain, but is also closely linked to factors such as the tumor microenvironment and the disruption of the blood-brain barrier (BBB). Prostate cancer cells spread to the brain through the bloodstream, a process that is particularly prominent in patients with castration-resistant prostate cancer (CRPC) [18]. Although prostate cancer typically metastasizes first to the bones and lymph nodes, studies have shown that CRPC cells can bypass the blood-brain barrier and metastasize to the brain. The BBB represents a major obstacle for tumor cells attempting to reach the brain. To overcome this barrier, prostate cancer cells secrete enzymes such as matrix metalloproteinases (MMPs) to degrade the structural components of the BBB. Additionally, tumor cells may increase the permeability of the BBB through direct interactions with endothelial cells in the brain vasculature, providing a passage for brain metastasis.

In the tumor microenvironment, the conditions within the prostate cancer brain metastasis microenvironment play a crucial role in the growth and drug resistance of tumor cells. Studies have shown that tumor-associated macrophages (TAMs) and other immune cells provide supportive roles during brain metastasis by secreting various cytokines, which promote the proliferation and invasion of tumor cells.

3. Advances in Diagnosis of Brain Metastasis in Prostate Cancer

With the development of imaging technologies, early diagnosis of brain metastasis in prostate cancer has become increasingly precise. Magnetic resonance imaging (MRI) and computed

tomography (CT) are the most commonly used diagnostic tools for brain metastasis. MRI, particularly when combined with dynamic contrast-enhanced MRI (DCE-MRI) and magnetic resonance spectroscopy (MRS) [19], provides detailed information on the localization, size, shape, and relationship of the metastasis with surrounding brain tissue.

In recent years, liquid biopsy technologies have also made significant progress in the early diagnosis of brain metastasis. Cerebrospinal fluid (CSF) analysis, along with ctDNA and exosome analysis in blood, have provided new non-invasive diagnostic methods. These technologies can detect even small metastatic lesions in the brain and may also serve as important biomarkers for prognostic evaluation.

4. Treatment Strategies for Brain Metastasis in Prostate Cancer

The treatment of brain metastasis in prostate cancer is a multidimensional and individualized process, often requiring comprehensive assessment of the patient's overall condition, the number and location of brain metastases, and the patient’s response to prior treatments. If diagnosed early with localized prostate cancer, treatment options such as active surveillance or prostatectomy may be pursued. However, in the advanced or metastatic stages, current treatment options include radiotherapy or androgen deprivation therapy (ADT) to reduce cancer progression [20], [21], [22]. Treatment choices not only need to focus on local control of the tumor but also on the management of systemic disease, particularly in patients with castration-resistant prostate cancer (CRPC). Current treatment strategies encompass local therapy, systemic therapy, and multidisciplinary combination therapy, with each approach having its indications and limitations.

4.1 Local Treatment

The goal of local treatment is to directly eliminate brain metastases and alleviate symptoms caused by the tumor. For patients with single or a few brain metastases, local treatment may significantly improve clinical outcomes and prolong survival. Common local treatment modalities include surgical resection and stereotactic radiotherapy (SRT).

Surgical resection is primarily indicated for single, easily accessible brain metastases, especially when the tumor is located in a non-functional area of the brain. Surgical removal of brain metastases can rapidly alleviate symptoms such as headache, seizures, and neurological deficits, and improve local control rates. However, as brain metastases in prostate cancer are often associated with the progression of systemic disease and are frequently found in patients with castration-resistant prostate cancer (CRPC), surgery is often combined with other treatment modalities to improve overall efficacy. For patients with multiple metastases or tumors located in critical brain regions, the effectiveness of surgery may be limited.

SRT is another commonly used approach for local control of brain metastases. SRT delivers high doses of radiation precisely to the brain metastases while minimizing damage to surrounding healthy brain tissue. For patients with single or a few brain metastases, SRT has been shown to effectively delay the progression of brain metastases, alleviate clinical symptoms, and improve local control rates. Compared to traditional radiotherapy, SRT offers greater treatment precision and lower side effects, making it particularly suitable for patients who cannot tolerate extensive radiation therapy.

4.2 Systemic Treatment

The primary goal of systemic treatment is to control the spread of cancer throughout the body, particularly in patients with castration-resistant prostate cancer (CRPC) who have developed brain metastases. Current options for systemic therapy include chemotherapy, hormonal therapy, targeted

therapy, and immunotherapy. As brain metastases in prostate cancer often occur in CRPC patients, systemic therapy is frequently combined with local treatments to enhance efficacy.

Chemotherapy is not commonly used in prostate cancer treatment but remains an option for certain advanced-stage patients. Docetaxel and carboplatin are chemotherapy agents commonly used for treating CRPC [23], [24], [25], although their efficacy against brain metastases is limited. Due to the challenge of penetrating the blood-brain barrier, chemotherapy drugs typically show poor efficacy against brain metastases. However, research into nanomedicine drug delivery systems and novel chemotherapy agents is providing new directions to overcome the blood-brain barrier.

Hormonal therapy plays a crucial role in the treatment of prostate cancer, particularly in the early stages of androgen-sensitive prostate cancer. However, in CRPC, the continued activation of the androgen receptor (AR) pathway is a major driver of tumor progression [26]. Therefore, AR antagonists (such as enzalutamide, abiraterone) and castration therapy are commonly used to control disease progression. Although these drugs effectively delay progression, their efficacy in brain metastasis remains limited, as changes in the AR signaling pathway may lead to drug resistance. Consequently, hormonal therapy is often combined with other treatments, such as radiotherapy or immunotherapy, to enhance therapeutic outcomes.

Targeted therapy specifically targets molecules or signaling pathways within cancer cells to inhibit tumor growth and metastasis. For CRPC patients, targeted therapies targeting the PI3K/Akt/mTOR pathway, VEGF pathway, and others have shown some positive effects. The PI3K/Akt/mTOR pathway plays a key role in prostate cancer growth and metastasis, and drugs that inhibit this pathway, such as PI3K inhibitors, Akt inhibitors, and mTOR inhibitors, have emerged as potential therapeutic options. Additionally, VEGF inhibitors, which block tumor angiogenesis and suppress tumor blood supply, have been used in combination with radiotherapy or other systemic treatments, yielding good therapeutic results.

Immunotherapy, particularly immune checkpoint inhibitors (such as PD-1/PD-L1 inhibitors), has shown significant promise in recent cancer therapies [27]. PD-1/PD-L1 inhibitors have been approved by the U.S. Food and Drug Administration (FDA) for their unprecedented advantages in treating various cancer types, including melanoma, urothelial carcinoma, and renal cell carcinoma. Immune escape is a major challenge in prostate cancer brain metastasis, and inhibition of immune checkpoints can restore the immune system's ability to surveil and target tumors. PD-1/PD-L1 inhibitors are gradually showing potential in prostate cancer treatment, especially when combined with other therapies (such as radiotherapy, chemotherapy, or targeted therapies)[28],[29],[30]. Although the efficacy of immunotherapy in prostate cancer brain metastasis is still under exploration, early successes have been reported in some patients.

4.3 Multidisciplinary Combined Therapy

Multidisciplinary combined therapy is a crucial component in the management of brain metastasis in prostate cancer. The treatment of prostate cancer brain metastasis typically relies on a combination of various modalities, including radiotherapy, surgery, systemic therapy, and immunotherapy, working synergistically to achieve the best possible outcome. Collaboration between multiple disciplines, including oncology, neurosurgery, radiology, and immunology, enables the provision of more individualized and precise treatment plans for patients.

With the continuous advancement of precision medicine and personalized treatment approaches, the management of prostate cancer brain metastasis will increasingly focus on the patient's specific pathological characteristics and genetic background. Through multidisciplinary collaboration, treatment teams can better assess the risks and benefits of different therapies, thereby optimizing the treatment plan. For instance, combining targeted therapies with immunotherapy can overcome

immune escape and drug resistance, thus improving treatment efficacy and survival rates in patients.

5. Future Research Directions and Challenges

Despite the progress made in the treatment of prostate cancer brain metastasis, numerous challenges remain. First, overcoming the blood-brain barrier (BBB) continues to be one of the major obstacles in treating brain metastases from prostate cancer. Future research should focus on developing more effective drug delivery systems using emerging technologies such as nanotechnology and gene editing to bypass the limitations of the blood-brain barrier. Second, a multidisciplinary collaborative treatment approach is likely to become a future trend. Treating prostate cancer brain metastasis requires close collaboration between oncologists, neurologists, radiologists, and other specialists to create individualized treatment plans for patients.

6. Conclusion

Prostate cancer brain metastasis, as a challenging complication, continues to present significant clinical treatment and prognostic challenges. However, with ongoing advancements in molecular biology, immunology, and precision medicine, the treatment outlook for prostate cancer brain metastasis is gradually improving. Future research should focus on breakthroughs in crossing the blood-brain barrier, optimizing immunotherapy strategies, and exploring new targeted therapies, with the aim of improving patients' quality of life and extending survival.

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