

Review

# Nonbone Metastasis in Prostate Cancer: Characteristics, Tumor Microenvironment, Diagnosis and Treatment

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## Abstract

The incidence and mortality of prostate cancer (PCa) are increasing worldwide, affecting the health of millions of men. Metastatic PCa (mPCa) represents a critical challenge in terms of clinical treatment because of its aggressive invasiveness and metastatic potential, making it a main cause of death in this population. Although bone metastasis is more common in PCa patients, nonbone metastases, such as liver, lung, and brain metastases, are typically associated with a poorer prognosis. However, the mechanisms underlying nonbone metastasis in PCa are still not fully understood. This review summarizes the characteristics of tumor cells, the tumor microenvironment, research models, and diagnostic and therapeutic approaches for nonbone metastasis in PCa, with a particular focus on liver metastasis, and proposes feasible directions for future research.

**Keywords:** Prostate cancer; cancer metastasis; nonbone metastasis; tumor microenvironment; neuroendocrine

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## 1. Introduction

Prostate cancer (PCa) is a malignant tumor to which men are highly susceptible. The incidence and mortality of PCa are increasing worldwide [1–3]. It ranks first in new cancer cases among men and second in cancer-related deaths, highlighting its heavy disease burden [1,2]. The progression of PCa is characterized by multiple stages [4]. The growth of PCa relies on androgen, making androgen deprivation therapy (ADT) a critical treatment for PCa [5]. For patients with localized, nonmetastatic disease, primary treatments include radical prostatectomy or radiotherapy, with the selective use of transient ADT. However, most patients show increased disease burden after primary treatment, characterized by rising PSA levels and/or radiographic progression. Therefore, continued ADT treatment is warranted. When ADT fails, the resulting

castration-resistant PCa (CRPC) is treated with next-generation androgen receptor pathway inhibitors (ARPIs). Nevertheless, the majority of patients experience disease recurrence after ARPIs treatment, ultimately leading to death in these CRPC patients [4,6]. CRPC not only develops resistance to ADT but also exhibits further invasive proliferation, leading to metastatic CRPC (mCRPC), which is the primary cause of death in this population [4]. In China, approximately 28% of newly diagnosed patients have already developed distant metastasis, and this high metastatic rate leads to a poor prognosis and a significantly reduced survival rate [7]. The 5-year survival rate for patients with localized PCa without metastasis is 90–99%, whereas that for mCRPC patients is only 30–40%, underscoring the malignancy of mCRPC [2].

Regarding the organotropism of cancer metastasis, the classic "seed and soil" theory was proposed as early as 1889 [8,9]. PCa also exhibits significant organotropism, with bones and lymph nodes being the most common metastatic sites, followed by nonbone organs such as the liver, lungs, and brain [4,10]. Among various metastatic sites, nonbone metastases are associated with shorter survival periods and poorer prognoses than are bone metastasis [11]. The molecular mechanisms of PCa bone metastasis have been extensively studied [12,13]. However, the mechanisms of nonbone metastasis remain unclear, and owing to its insidious nature, early diagnosis is often challenging, leading to a poor prognosis. Moreover, there is still a lack of specific therapeutic strategies for PCa nonbone metastasis.

In recent years, molecular subtype studies based on androgen receptor (AR) and neuroendocrine (NE) gene expression features have provided new insights into the heterogeneity of mCRPC. According to AR and NE marker expression patterns, mCRPC can be classified into five clusters: AR<sup>+</sup>NE<sup>-</sup> tumors (ARPC), AR<sup>low</sup>NE<sup>-</sup> tumors (ARLPC), AR<sup>+</sup>NE<sup>+</sup> tumors (AMPC), AR<sup>-</sup>NE<sup>+</sup> tumors (NEPC), and AR<sup>-</sup>NE<sup>-</sup> tumors (DNPC) [14]. Among these subtypes, NEPC and DNPC exhibit increased migration, invasion, and metastatic capabilities, with significant differences in molecular characteristics, metastatic tendencies, and treatment responses. The proportions of NEPC and DNPC increase after ADT, and these tumors develop resistance to ARPIs (e.g., enzalutamide and abiraterone acetate [15–20]). Therefore, further research into the molecular mechanisms and biological behaviors of these PCa subtypes will not only help elucidate the heterogeneity of mCRPC but also provide a critical foundation for developing precision treatment strategies for nonbone metastatic PCa (mPCa).

This review summarizes the mechanisms of nonbone metastasis in PCa, focusing on the tumor characteristics and microenvironmental features of nonbone mPCa, particularly in the case of liver metastasis. Current research models and clinical diagnostic and therapeutic strategies are also reviewed with the aim of providing new insights and theoretical foundations for basic research and clinical treatment.

## 2. Hallmarks of Nonbone mPCa

Most PCa patients progress to mCRPC after ADT treatment [6]. At this stage, PCa cells not only exhibit aggressive proliferation capabilities but are also highly prone to distant metastasis. Compared with localized PCa, mCRPC shows significant differences in genomic characteristics [21–24]. Germline mutations in DNA damage repair (DDR) genes and mismatch repair-related genes

increase the likelihood of developing PCa [25,26]. Localized PCa typically has a low mutational burden [23,24]. However, mCRPC patients exhibit significantly increased mutational burdens and copy number alteration frequencies, reflecting therapy-induced genomic remodeling that results in the accumulation of numerous mutations [22,27]. For example, *BRCA2* mutations are found in 12.5% of mCRPC patients, whereas these mutations are rare in patients with localized PCa [22,27,28]. Certain nonbone metastatic sites present distinct characteristics. Compared with PCa with metastasis to other sites, brain metastatic PCa shows relative enrichment of homologous recombination deficiency (HRD) mutations [29]. In one study, patients with brain metastases from PCa were found to have at least one mutation or somatic copy number alterations in homologous recombination repair genes. Compared with high-grade primary prostate tumors in a TCGA cohort, primary tumors from patients with brain metastases presented higher levels of HRD-related mutations [29]. Therefore, mutations in *DDR* and mismatch repair-related genes are closely associated with brain metastatic PCa and could serve as risk stratification biomarkers for PCa progression to brain metastasis. Brain metastatic PCa exhibits a CpG island hypermethylation phenotype, but hypomethylation is observed at promoters of neuroactive ligand–receptor interactions and cell adhesion molecules (e.g., *GABRB3*, *CLDN8*, and *CLDN4*) [30]. This methylation pattern suggests that tumor cells undergo epigenetic reprogramming to adapt to the brain microenvironment. Additionally, brain metastatic PCa shows greater structural alterations in the genome, with chromothripsis and chromoplexy events predominating [31].

*PTEN*, the most frequently mutated tumor suppressor gene, plays a critical role in PCa development [4]. The loss of *PTEN* is significantly greater in mCRPC (>40%) than in localized and metastatic castration-sensitive PCa (mCSPC) tumors (12–17%) [21,22]. Genomic analysis of PCa tissue-specific metastasis revealed that mutations related to liver metastasis were more enriched in *PTEN* deletion, *MYC* amplification, and *PIK3CB* amplification than those related to metastasis to other sites [32]. However, no point mutations were found to be significantly associated with liver metastasis compared with metastasis to other sites [32]. Another study revealed that *PTEN* loss, as well as mutations in *APC* and *SPOP*, was more frequently enriched in the NEPC subtype, with a propensity for liver metastasis [33]. NEPC exhibits high migratory and invasive capabilities and plays a significant role in PCa liver metastasis [15,20]. Compared with other PCa subtypes, NEPC frequently harbors mutations in *RB1* and *TP53* [16,34,35]. Mutations in *Rb1* or *Trp53* alone are insufficient to form PCa, but their comutation leads to PCa with a neuroendocrine phenotype, which is prone to metastasis to the liver, lungs and other sites [36,37]. Studies have shown that in *Pten*-mutant mouse models of PCa, *Rb1* loss promotes lineage plasticity and metastasis, whereas additional *Trp53* loss induces resistance to ADT, explaining the ADT resistance and high visceral metastatic potential of NEPC [35]. A study of a patient with dural and brain metastases revealed that the dural metastasis coexpressed AR and NE markers, presenting as AMPC, whereas the brain metastasis exhibited NEPC characteristics. The AMPC-like metastasis showed elevated *FOXA1* activity, whereas the brain NEPC-like metastasis exhibited increased expression of *HOXC10*, *NFYB*, and *OTX2*, indicating that neuroendocrine features may also contribute to the propensity for brain metastasis [38]. According to Stand Up To Cancer (SU2C) data, the proportion of AR-negative and NEPC patients with lung

metastasis (14.3%) is lower than that of patients with liver metastasis (28.1%) but higher than that of patients with metastasis to other sites, such as the lymph nodes (6%) and bones (0.6%) [34,39].

DNPC is a unique mCRPC subtype accounting for up to 10%–25% of metastatic CRPC cases, especially after treatment with second-generation ARPIs [18]. The transcription factor KLF5 is upregulated in DNPC through demethylation, significantly enhancing tumor invasiveness [19]. While DNPC still demonstrates a notable incidence of liver metastasis and bone metastasis in most datasets, a subset of patient exhibits lung metastasis [14,16,40]. In DNPC, abnormal activation of the HGF/MET pathway significantly enhances Wnt/ $\beta$ -catenin signaling, further promoting DNPC formation and lung metastasis [41]. Additionally, the elevated activity of XPO1 and ribosomal proteins in DNPC suggests that inhibiting the XPO1 and ribosomal pathways may represent new therapeutic strategies for DNPC [41]. Loss of *Kmt2c* promotes the formation of PCa lung metastases. On the one hand, *Kmt2c* deficiency reduces the expression of the cell cycle inhibitor p16<sup>INK4A</sup>; on the other hand, it enhances Myc signaling and upregulates genes in the 5qE1 region (e.g., *Odam* and *Cabs1*), promoting lung metastasis [42,43]. Recent studies have highlighted the role of KMT2C in DNPC regulation. ADT induces KMT2C binding to enhancers of AR-regulated genes, preserving the adenocarcinoma lineage. KMT2C inactivation reduces ASPP2 expression, triggering Np63-dependent transdifferentiation. This DNPC transformation maintains fatty acid synthesis through Np63-mediated SREBP1c transactivation and promotes DNPC growth via HRAS palmitoylation and MAPK signaling activation [44]. These findings underscore KMT2C as an epigenetic checkpoint in DNPC development and provide new insights into the epigenetic mechanisms underlying PCa, particularly lung metastatic DNPC. In a subset of DNPC patients, tumor cells exhibit a squamous cell carcinoma phenotype [45]. The development and metastatic mechanisms of this phenotype, as well as its similarities to pulmonary squamous cell carcinoma, warrant further investigation.

Metabolic reprogramming, a hallmark of cancer, plays a pivotal role in tumor metastasis by enabling cancer cells to adapt to diverse microenvironments and overcome metabolic stress [46–50]. During metastasis, cancer cells undergo dynamic metabolic shifts, such as increased glycolysis, altered lipid metabolism, and increased glutamine utilization, to meet the energetic and biosynthetic demands of invasion, survival, and colonization in distant organs [51,52]. Camkk2 plays crucial roles not only in PCa cell metastasis to and colonization of the lungs but also in the disruption of normal metabolic processes, such as glucose and lipid metabolism, leading to complications such as metabolic syndrome [51]. Additionally, the regulation of glutamine metabolism can upregulate ARPC1A in PCa cells, inducing cytoskeletal changes that promote the migration and invasion of tumor cells into the lungs [52]. Our research revealed that NEPC appears to exhibit unique metabolic characteristics. NEPC accumulates many depolarized mitochondria and relies on glycolysis for energy metabolism, resulting in increased lactate levels [53]. NEPC also specifically overexpresses the ADORA2A adenosine receptor. Mechanistically, ADORA2A enhances proline synthesis and increases the production of the intermediate metabolite NAD<sup>+</sup> through the ERK/MYC/PYCR signaling axis, promoting SIRT6/7-mediated histone H3 deacetylation. Specific knockout of ADORA2A can reduce the occurrence of NEPC liver metastasis [54]. Enrichment

analysis showed that genes related to metabolic pathways such as folate metabolism, selenium micronutrient network, fat digestion and absorption and cholesterol metabolism are enriched in liver metastases compared with metastases at other sites, potentially contributing to the initiation and progression of PCa liver metastasis [55]. Therefore, tumor cells likely need to adapt to new environments by altering their metabolic pathways, thereby facilitating the process of metastasis.

### 3. Liver Metastasis of PCa

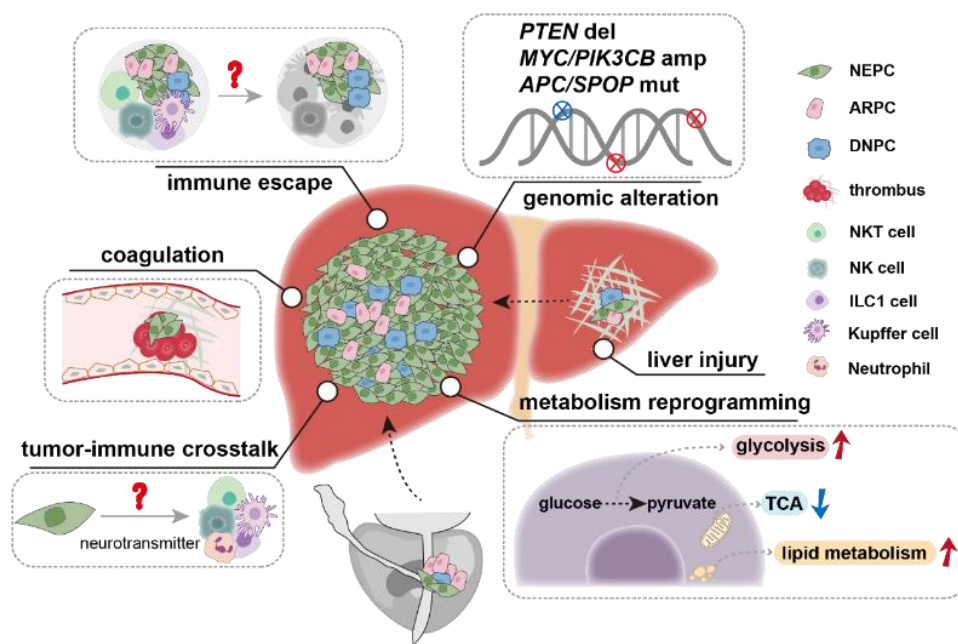
In clinical diagnosis, early metastases to organs such as the liver, lungs, and brain often present with minimal or no symptoms. By the time of diagnosis, the disease has typically progressed to an advanced stage. In multiple phase III clinical trials, the initial proportion of lung metastases in mCSPC patients was greater than that of liver metastases. However, after chemotherapy, the proportion of lung metastases did not increase significantly, whereas the proportion of liver metastases increased, indicating that liver metastasis is closely associated with disease progression [39]. Aggressive PCa tends to metastasize to the liver, particularly among those who experience relapse after ARPI treatment [39]. Moreover, the survival time of mCRPC patients is related to the site of metastasis, with liver metastasis being associated with the worst prognosis and a median survival of only 13.5 months, followed by lung (19.4 months) and bone (21.3 months) metastases [56]. Therefore, further research into the molecular and cellular mechanisms of PCa liver metastasis holds promise for improving the survival of patients with advanced PCa and liver metastasis (**Figure 1**).

#### 3.1 Neuroendocrine phenotype with a propensity for liver metastasis

Research indicates that patients with advanced PCa liver metastasis often exhibit AR-negative or neuroendocrine differentiation. In various cancers, the neuroendocrine phenotype is a significant source of liver metastatic tumors [57]. Compared with neuroendocrine tumor metastases at other sites, neuroendocrine tumor liver metastases are associated with a poorer prognosis. Therefore, exploration of how the neuroendocrine phenotype promotes tumor liver metastasis not only holds great significance for PCa treatment but also provides new research directions for liver metastasis in other neuroendocrine tumors.

Neuroendocrine tumors have the ability to produce neuron peptides such as serotonin (5-HT) [58]. Our recent research revealed that NEPC-secreted 5-HT is taken up by neutrophils via the serotonin transporter (SERT), which induces TGM2-mediated histone H3Q5 seronylation. This process synergizes with PAD4-mediated histone H3 citrullination to promote NET release by neutrophils, thereby enhancing tumor cell liver metastasis. Inhibiting 5-HT uptake using the SERT inhibitor fluoxetine effectively reduces the occurrence of liver metastasis [59]. Neuroendocrine colon cancer (CRNE) is a common neuroendocrine phenotype that is often accompanied by liver metastasis in patients. Deng *et al.* systematically revealed significant differences in the cellular composition and microenvironment between primary lesions and liver metastases in CRNE liver metastasis (CRNELM) patients by integrating single-cell RNA sequencing and spatial transcriptomic sequencing. Pseudotime analysis revealed that pathways related to coagulation, hemostasis, and wound healing were

significantly activated after tumor cells underwent epithelial–mesenchymal transition (EMT), suggesting that these pathways play critical roles in late-stage CRNELM [60]. Additionally, NEPC can be classified into two subtypes based on gene expression profiles: NE-classic and NE-liver. The NE-liver subtype exhibits a greater propensity for liver metastasis, with significant enrichment of immune response and complement pathways, indicating a unique immune microenvironment in the liver and the potential role of the complement pathway in NE tumor liver metastasis [33]. Our study revealed that thrombosis significantly promotes liver metastasis in NE-type tumors [61]. Specifically, NEPC expresses high levels of O-GalNAc catalyzed by the glycosyltransferase GALNT9. These glycosylation modifications are enriched primarily in ANXA2 and induce platelet activation and thrombosis by binding to and activating the MBL coagulation pathway, thereby promoting NEPC liver metastasis. Targeting GALNT9 or O-GalNAc glycosylation effectively inhibits liver metastasis in NE tumors [61]. In summary, thrombosis induced by the coagulation cascade is a crucial mechanism for NE tumor liver metastasis, providing potential directions for developing targeted therapies. In summary, NE tumors appear to promote liver metastasis through multiple mechanisms. At the molecular level, activation of the coagulation cascade to promote thrombosis and colonization in the liver is a shared characteristic of NE tumor liver metastasis. Additionally, patients with NE tumors often experience neuroendocrine system dysregulation. Whether NEPC secretes neuroendocrine substances other than 5-HT requires further investigation.



**Figure 1 Characteristics and mechanisms of liver metastasis in prostate cancer.** NEPC has a high incidence of liver metastasis. Therapy-induced liver injury may facilitate the formation of a pre-metastatic niche. Genomic alterations, including PTEN loss, MYC/PIK3CB amplification, and APC/SPOP mutations, are more prevalent in PCa that has metastasized to the liver. PCa cells adapt to the liver microenvironment through metabolic reprogramming, such as enhanced lipid metabolism. NEPC exhibits increased glycolysis and impaired mitochondrial function, leading to a weakened TCA cycle. NEPC secretes neurotransmitters, such as 5-HT, that act on neutrophils and promote metastatic colonization in the liver. Elevated O-GalNAc glycosylation on the NEPC cell membrane activates thrombosis and facilitates tumor cell seeding in the liver. The liver contains abundant resident immune cells, including NKT cells, NK cells, ILC1 cells, and Kupffer cells. Understanding the mechanisms by which PCa cells evade killing by these liver-resident immune cells may help explain liver-specific metastatic tropism.

### 3.2 The role of the liver immune microenvironment in metastasis

The liver is enriched with various immune cells, including NKT cells, NK cells, Kupffer cells, neutrophils, T cells, and DCs, which collectively maintain the balance between clearing foreign antigens and preventing excessive immune responses that could cause tissue damage, thereby shaping a unique immune microenvironment in the liver [62]. Therefore, understanding the specialized microenvironment formed by these cells in the liver can better explain the propensity of tumor cells for liver metastasis.

Unlike those in other organs, many immune cells in the liver exhibit tissue-resident phenotypes. The most common tissue-resident immune cells include Kupffer cells, NKT cells, NK cells and ILC1 cells. Kupffer cells, the most frequently studied type, are a unique type of innate immune cell in the liver that play crucial roles in various liver diseases, homeostasis maintenance, injury repair, and tumorigenesis [63]. Kupffer cells can phagocytose tumor cells that metastasize to the liver, exerting antitumor effects. The ERMAP/Gal-9/dectin-2 axis, constituting an antibody-independent nonclassical "eat me" signal, specifically promotes Kupffer cell-mediated phagocytosis of tumor cells, thereby inhibiting liver metastasis. Activating the ERMAP/Gal-9/dectin-2 signaling axis could serve as a strategy to enhance Kupffer cell phagocytosis and antitumor innate immunity, offering potential clinical strategies for treating and preventing liver metastasis [64].  $\beta$ -Glucan activates Kupffer cells, inhibits cancer cell proliferation, and elicits productive T-cell-mediated antimetastatic responses in pancreatic cancer mouse models [65]. Thus, Kupffer cells are the first line of defense against tumor liver metastasis. However, TAMs are known to promote tumor growth in many cancers, and whether Kupffer cells have similar protumor mechanisms remains to be further studied. NKT cells, NK cells, and ILC1 cells are generally considered to have strong tumor-killing capabilities and can reside in the liver, maintaining the capacity for self-renewal and differing from peripheral circulating cells, thereby forming a unique phenotype in the liver [66–68]. Compared with other organs, NKT cells are more enriched in the liver, where they perform unique functions [66,69]. The gut microbiota can influence the balance of primary and secondary bile acids, affecting CXCL16 secretion by liver sinusoidal endothelial cells and regulating NKT cell aggregation, which is crucial for NKT cell antitumor functions [70]. However, certain NKT cell subtypes, such as iNKT17 cells, have been shown to release IL-22, which acts on endothelial cells to induce endothelial aminopeptidase N, increasing endothelial permeability and promoting tumor cell extravasation [71]. Under steady-state conditions, the liver contains conventional NK cells (cNK cells), defined as CD49a<sup>+</sup>CD49b<sup>+</sup> cells, and tissue-resident CD49a<sup>+</sup>CD49b<sup>-</sup> type 1 innate lymphoid cells (ILC1 cells) [72,73]. NK cells are cytotoxic lymphocytes that play a significant protective role in tumor development and metastasis [74,75]. The size of the NK cell pool in the liver itself can determine metastatic growth. In preclinical models, maintaining NK cell abundance through IL-15-based adjuvant immunotherapy successfully prevented liver metastasis and prolonged survival [76]. NK cells can also eliminate hepatic stellate cells and inhibit hepatocyte proliferation to inhibit liver fibrosis, thereby reducing the occurrence of tumor liver metastasis [77–79]. Compared with those in primary lesions, T cells, NK cells, and NKT cells in CRNELM exhibit a stressed-like phenotype, with reduced cytotoxicity scores and an immunosuppressive state, indicating severe functional impairment [60]. In fact, a recent study by Ducimetière *et al.* revealed that NK cells have durable

antimetastatic functions in MC38-injected mice, whereas tissue-resident ILC1 cells are essential for inhibiting CRC liver metastasis in the early stages [80]. The microenvironment of colorectal cancer liver metastases results in the formation of a CD49a<sup>+</sup> NK cell subset with ILC1 cell-like characteristics, and these cells exhibit the strongest cytotoxicity among infiltrating NK cells. CXCR3 drives NK cell accumulation in CXCL9- and CXCL10-enriched regions, promoting their colocalization with macrophages. Macrophages regulate NK cell plasticity through dual mechanisms of CXCL9 chemotaxis and TGF- $\beta$  induction, modulating their antitumor functions [81]. Tissue-resident ILC1 cells in the liver specifically express GPR34, and tumor-derived lipid metabolites such as lysophosphatidylserine can inhibit ILC1 cell antitumor activity via GPR34. Antagonizing GPR34 induces potent ILC1 cell-mediated antitumor immunity, suppressing the growth of liver cancer, colorectal cancer, and other solid tumors [82]. However, the mechanisms by which tumor cells, especially PCa cells, evade the killing effects of liver-resident immune cells remain to be elucidated. In conclusion, diverse immune cells in the liver, including Kupffer cells, NKT cells, NK cells, and ILC1 cells, play complex and critical roles in tumor liver metastasis. These cells participate in antitumor immune responses through mechanisms such as phagocytosis, cytotoxicity, and immune regulation, but they can also be exploited by tumor cells to promote colonization and metastasis.

### 3.3 The role of non-immune cells in liver metastasis

Liver injury and fibrosis create a favorable microenvironment for tumor metastasis through multiple mechanisms. Clinical evidence shows that colorectal cancer patients with liver fibrosis have a higher risk of developing liver metastasis compared to those without fibrosis [83]. Mechanistically, liver damage promotes excessive extracellular matrix (ECM) deposition, and activated hepatic stellate cells produce abundant fibronectin. These changes not only alter liver architecture but also recruit bone marrow-derived immune cells, collectively establishing a niche that supports tumor cell colonization and growth [84,85]. In PCa, systemic therapies such as hormonal therapies and chemotherapy may unintentionally promote liver metastasis by inducing hepatotoxicity [86,87]. ARPIs like bicalutamide and abiraterone are associated with varying degrees of liver damage [88,89]; abiraterone, for instance, causes elevated liver enzymes in ~6% of patients [89]. Therapy-induced hepatic injury may foster metastasis via paracrine signaling, stellate cell activation, fibrotic and inflammatory feedback loops, ECM remodeling, and immune modulation [90]. Notably, under conditions of liver injury, activated stellate cells can suppress NK cell proliferation, thereby impairing NK-mediated maintenance of tumor dormancy and ultimately facilitating tumor awaken [76]. These findings suggest that ARPI-induced liver injury may establish a pre-metastatic niche while simultaneously activating stellate cells to reactivate dormant tumor cells. At the molecular level, the hepatocytes express AR in both the cytoplasm and nucleus [91]. Androgens regulate hepatic expression of key cytokines such as TGF- $\beta$  and VEGF [92]. Notably, TGF- $\beta$ , a central mediator of liver fibrosis, is also highly upregulated in PCa liver metastases, where it facilitates invasion, immunosuppression, and supportive stroma formation [93–95]. E-cadherin regulation is another critical factor during PCa liver metastasis. Downregulation of E-cadherin at the primary site enables EMT and cell migration. However, within the hepatic microenvironment, hepatocytes may suppress EGFR signaling to induce mesenchymal-epithelial transition,

restoring E-cadherin expression to promote metastatic colonization [96,97]. Subclones lacking E-cadherin undergo apoptosis, while those re-expressing it survive through downstream kinase activation [98]. These findings highlight the need for management of treatment-related hepatotoxicity and support the development of combination strategies targeting liver fibrosis and pre-metastatic niche.

#### 4. PCa Nonbone Metastasis Models

Compared with other cancers, such as colon cancer, lung cancer, pancreatic cancer, and melanoma, which are prone to nonbone metastasis, research on the cellular and molecular mechanisms of nonbone metastasis in PCa remains limited. This is largely due to the lack of well-established models for studying nonbone metastasis in PCa. Initially, researchers induced oncogene expression in the mouse prostate to promote PCa formation and metastasis. The TRAMP model, which utilizes high SV40 T antigen expression in the prostate, successfully induces PCa development [99,100]. TRAMP mice effectively mimic the natural progression of PCa and can be used to study different disease stages, which correlate with the age of the mice. TRAMP mice develop prostatic intraepithelial neoplasia (PIN) at approximately 12 weeks, which progresses to adenocarcinoma. By 28–32 weeks, TRAMP mice typically develop advanced disease, leading to lymph node and distant metastases [99,100]. With advances in gene-editing technology, transgenic mice expressing Cre recombinase under the probasin (Pb) promoter have provided a foundation for generating other genetically engineered mouse models (GEMMs) with prostate epithelial-specific gene deletions. The *Pten* conditional knockout model recapitulates human disease progression, starting with PIN and advancing to invasive adenocarcinoma and subsequent metastasis [101]. Homozygous *Pten* knockout successfully induces PCa and lung metastasis, although the number of metastases is limited [101]. This was the first PCa mouse model in which metastasis was induced by the knockout of an endogenous gene. To increase tumorigenicity and malignancy, researchers began developing double-gene knockout models, such as  $\text{PbCre}^+\text{Pten}^{\Delta/\Delta}\text{P53}^{\Delta/\Delta}$ ,  $\text{PbCre}^+\text{Rb1}^{\Delta/\Delta}\text{P53}^{\Delta/\Delta}$ , and  $\text{PbCre}^+\text{Pten}^{\Delta/\Delta}\text{Rb1}^{\Delta/\Delta}$  [35,36,102,103]. Similar to  $\text{PbCre}^+\text{Pten}^{\Delta/\Delta}$ ,  $\text{PbCre}^+\text{Pten}^{\Delta/\Delta}\text{P53}^{\Delta/\Delta}$  primarily shows occasional lung metastasis and more frequent lymph node metastasis [102].  $\text{PbCre}^+\text{Rb1}^{\Delta/\Delta}\text{P53}^{\Delta/\Delta}$  and  $\text{PbCre}^+\text{Pten}^{\Delta/\Delta}\text{Rb1}^{\Delta/\Delta}$  exhibit more distant metastases to organs such as the liver, lungs, and lymph nodes [35,36]. The triple-knockout  $\text{PbCre}^+\text{Pten}^{\Delta/\Delta}\text{Rb1}^{\Delta/\Delta}\text{P53}^{\Delta/\Delta}$  model displays a more aggressive phenotype, with a median survival of only 16 weeks and rapid metastasis to the liver, lungs, and bones, making it a suitable model for studying spontaneous PCa with liver and lung metastasis [35]. In addition to GEMM-derived tumor models, the RapidCaP method involves surgical injection of lentiviral Cre-luciferase (LV-Cre/Luci) into the prostate of  $\text{Pten}^{\text{loxP/loxP}}$  mice, leading to *Pten* and *Trp53* deletion and triggering mPCa. High rates of metastasis to the lymph nodes, spleen, and liver are observed within months [104].

Although GEMMs better mimic disease progression, metastasis remains inconsistent, highly variable among individuals, and time-consuming to develop, requiring extensive breeding of multiple genetically modified mouse lines. Therefore, there is an urgent need for rapid and stable models to support

research on nonbone metastasis in PCa. Current animal models of tumor metastasis can be established through various methods, including intracardiac injection [105], tail vein injection [71], metastatic site inoculation [106], and spleen implantation [98]. In PCa, intracardiac [107], intrasplenic [98], or hemisplenic injections [108] can induce metastasis to the liver, lungs, and spleen. While these methods effectively establish metastatic models, they do not fully replicate the process of tumor cell dissemination from the primary prostate site in the context of nonbone metastasis. To address this, our team developed a novel metastasis model by orthotopically injecting PCa -derived organoids from  $PbCre^{+}Rb1^{\Delta/\Delta}P53^{\Delta/\Delta}$  mice into immunocompetent mice, generating a stable, rapid, and highly efficient liver metastatic PCa model [109]. This method is not only efficient but also suitable for studying interactions between PCa cells and immune cells.

*In vitro* studies rely primarily on PCa cell lines, patient-derived organoids (PDOs), and patient-derived xenografts (PDXs) to investigate metastatic features in clinical PCa patients [110]. Currently, most PCa cell lines are derived from metastatic tumor tissues. However, among these, only DU145 cells originate from brain metastases, whereas others are derived primarily from lymph node metastases (e.g., LNCaP, NCI-H660, ALVA-55, and LAPC-4) and bone metastases (e.g., PC-3, ALVA-41, ALVA-101, MDA PCa 2a, and MDA PCa 2b) [110]. Cell lines derived from liver, lung, or other solid-organ metastases are lacking. PDOs also serve as valuable *in vitro* models, retaining the molecular features observed in patient tumors [111,112]. Studies have shown that approximately 70% of soft tissue tumor samples and 30% of bone tumor samples can generate organoids stably cultured for 1–2 months, but stable organoids passaged for more than six months are derived mostly from bone and lymph node metastases [111]. The lack of PDOs from solid-organ metastases is partly due to current culture methods favoring normal epithelial cell growth, making isolation of tumor cells from liver and lung metastases challenging. PDX models involve direct transplantation of freshly isolated tumor tissues, such as primary or metastatic lesions, from patients into immunodeficient mice. PDX models preserve the unique mutational characteristics and heterogeneity of the original tumor and hold promise for personalized treatment. PDX models can also be used to study PCa metastasis in mice. A method involving subrenal capsule transplantation in SCID mice combined with androgen level modulation achieves >95% tumor formation rates and induces metastasis to the liver, lungs, kidneys, and spleen [113]. While this method can generate nonbone metastases and retain patient tumor characteristics, the lack of immune and stromal cell interactions in SCID mice limits the ability of this model to fully replicate the *in vivo* microenvironment. Therefore, the use of humanized mice may better simulate the mechanisms of nonbone metastasis in PCa.

## 5. Diagnosis and Treatment of mPCa

### 5.1 Diagnosis of mPCa

In the study of nonbone metastasis in PCa, ultrasound, CT, MRI, and PET are the most commonly used imaging modalities.  $^{68}\text{Ga}$ - or  $^{18}\text{F}$ -labeled PSMA PET has shown promising results in detecting distant metastasis of PCa [114–118]. In the detection of liver metastasis,  $^{68}\text{Ga}$ -labeled PSMA PET may have an advantage over  $^{18}\text{F}$ -labeled PSMA PET, as  $^{18}\text{F}$ -PSMA tends to be excreted

through the liver, leading to increased physiological uptake that can compromise detection accuracy [119]. However, a significant proportion of metastatic lesions (22.3%) lack PSMA expression, as PSMA expression is indirectly regulated by AR, and PCa with nonbone metastasis are often AR-negative [120–122]. Therefore, PSMA PET still has the potential for missed diagnoses.  $^{18}\text{F}$ -FDG PET-CT is widely used in various cancers, but its application in PCa is limited due to the low glucose metabolism of PCa cells [123]. However, PCa with nonbone metastasis, especially visceral metastatic NEPC, often exhibit high uptake on FDG-PET, suggesting unique glycolytic characteristics, which may be related to microenvironmental reprogramming in metabolically active organs such as the liver [124]. In tumors with low AR and PSMA expression, changes in genes related to  $^{18}\text{F}$ -FDG uptake are positively correlated with increased glucose uptake [125]. This evidence suggests that  $^{18}\text{F}$ -FDG PET-CT may perform better than PSMA PET-CT in detecting tumor lesions with low PSMA expression. Recently, Ahumada *et al.* conducted a paired clinical study using three imaging agents— $^{18}\text{F}$ -FDG for glucose metabolism, PSMA, and somatostatin receptor (SSTR) for neuroendocrine tumors—and found that among 273 lesions in 8 NEPC patients, PSMA was positive in only 174 lesions, SSTR was positive in only 59 lesions, and  $^{18}\text{F}$ -FDG was detected the most, in 182 lesions [126]. The false-negative rate of PSMA PET-CT for liver lesions was as high as 20%, with most of these lesions being positive for  $^{18}\text{F}$ -FDG. Therefore, PET imaging with the above radiotracers provides some supportive value in the diagnosis of NEPC. PSMA PET has limited diagnostic performance for nonbone metastases in PCa, especially in NEPC. DLL3 is expressed on the surface of small cell lung cancer and NEPC cells. A PET tracer has been developed using a DLL3-targeted antibody SC16 labeled with  $^{89}\text{Zr}$  ( $^{89}\text{Zr}$ -DFO-SC16), enabling noninvasive identification of DLL3-positive NEPC lesions [127]. In a phase 1/2 clinical trial (NCT04199741),  $^{89}\text{Zr}$ -DFO-SC16 PET-CT has been demonstrated to be safe and feasible [128]. Thus  $^{89}\text{Zr}$ -DFO-SC16 PET-CT holds promise as a NEPC-specific imaging. A multimodal imaging approach holds promise for improving the accuracy of nonbone metastasis detection. Taranda *et al.* used serial two-photon tomography (STPT) combined with traditional histology in a genetically engineered RapidCaP mouse model to characterize PCa and its metastasis. STPT can detect single tumor-initiating cells throughout the prostate, and subsequent IF analysis revealed the transition from normal to transformed epithelial tissue and the escape of cells from tumor foci. STPT imaging of the liver and brain revealed the distribution of multiple metastatic foci in the liver and the invasion of early metastatic cells in the brain. This imaging and data analysis pipeline provides a highly versatile whole-organ platform for studying the mechanisms of cancer initiation and progression [129]. Together, there is an urgent clinical need to study the molecular mechanisms of PCa progression and metastasis, explore noninvasive and effective diagnostic and therapeutic strategies, and develop new methods and technologies for the effective treatment and evaluation of mPCa, which is of great clinical importance for timely intervention and prolonged survival. PCa metastases often involve multiple organs throughout the body, and their treatment focuses on systemic therapy, making highly sensitive and specific diagnostic imaging modalities for systemic mPCa of great clinical value (**Table 1**).

**Table 1 Diagnostic Strategies for mPCa**

Category	Modality	Principle	Key Findings/Limitations	Implication for Mets
Imaging	<sup>68</sup> Ga-/ <sup>18</sup> F-PSMA PET-CT	PSMA targeting via AR regulation	Good for bone and soft tissue; <sup>18</sup> F excreted via liver → false positives; ~22% lesions PSMA-negative [114–122]	Limited sensitivity in liver metastasis and AR-negative NEPC; may miss lesions
Imaging	<sup>18</sup> F-FDG PET-CT	Glucose metabolism	Limited in classic PCa due to low glycolysis; high uptake in NEPC and liver metastases [123–126]	May outperform PSMA PET in AR-low, PSMA-negative lesions, esp. NEPC
Imaging (Preclinical)	<sup>89</sup> Zr-DFO-SC16	DLL3 target	DLL3 is specifically expressed in NEPC, serves as a target for NEPC imaging [127,128]	May useful for detecting NEPC with nonbone metastasis
Imaging (Preclinical)	STPT (Serial Two-Photon Tomography)	Whole-organ 3D imaging in GEMMs	Visualizes early escape, liver/brain micromets in mouse models [129]	Preclinical only; informs spatial metastasis evolution
Tissue Biopsy	Biopsy of metastases	Histopathologic confirmation	Gold standard for diagnosis; limited in advanced mCRPC due to patient condition	Useful for subtyping (e.g., AMACR <sup>+</sup> , CK7 <sup>-</sup> , CK20 <sup>-</sup> for liver mets) [4]
Liquid Biopsy	ctDNA/cfDNA, Serum markers (CHGA, CEA, NSE)	Tumor DNA from plasma/ Protein markers for NEPC	High concordance with metastasis tissue; captures AR/NE drivers and epigenetic patterns [16,22,130–148]	Non-invasive, useful in advanced mCRPC; applicable to NEPC subtyping

This table summarizes current imaging and molecular diagnostic tools used in identifying nonbone mPCa. Special emphasis is placed on the strengths and limitations of each modality in detecting visceral metastases (particularly liver and NEPC), highlighting the clinical value of multimodal imaging and liquid biopsy in mCRPC staging and subtype classification.

When the imaging diagnosis is uncertain, image-guided biopsy can be used to confirm the presence of metastasis. Biopsy of metastatic lesions can help determine the histological type of metastatic cancer cells, such as adenocarcinoma or NEPC. Therefore, biopsy remains the gold standard for diagnosing PCa metastases and provides information for selecting the best treatment strategy. For example, liver metastases originating from PCa can be identified by positive AMACR, negative cytokeratin 7, and negative cytokeratin 20 expression [149]. However, since mCRPC patients are in the advanced stages of the disease, they often refuse biopsy, so diagnosis requires the integration of multiple sets of clinical information and the development of more specific and sensitive, less invasive diagnostic methods.

In recent years, liquid biopsy, as a representative *in vitro* tumor diagnostic and monitoring method, has gradually shown advantages. For example, peripheral blood CHGA, CEA, and NSE levels can be used as alternative markers for diagnosing NEPC [16,130–132]. Circulating tumor DNA (ctDNA) is an emerging biomarker for a range of solid malignancies, including mCRPC [133]. ctDNA analysis is theoretically applicable to any patient who can provide a blood sample and can be performed repeatedly on the same patient with minimal invasiveness and moderate cost. Cell-free DNA (cfDNA) is shed into the blood by both nonmalignant and cancer cells [134,135]. In mCRPC patients, the proportion of tumor-derived cfDNA often exceeds 1%, making it possible to detect tumor genomic profiles from cfDNA [136–139]. Mutations

and copy number changes in plasma cfDNA from mCRPC patients are consistent with the somatic landscape established through metastatic tissue profiling [22,136,138–143]. W. Wyatt *et al.* collected 45 matched metastatic tissues and liquid biopsies from mCRPC patients and quantified the concordance of somatic changes in key driver genes [144]. ctDNA detection is sufficient to identify all driver DNA alterations present in matched metastatic tissues and supports the development of DNA biomarkers to guide the management of mCRPC patients based solely on ctDNA [144,145]. The concordance between cfDNA and biopsy tissue genomic changes is significantly greater in NEPC patients than in CRPC patients, indicating that cfDNA has promise as an effective biomarker for diagnosing NEPC [146]. Evaluation of the methylation-based NEMO panel in cfDNA provides a scoring system for the NEPC phenotype and can be used for the noninvasive detection of pathologically confirmed NEPC [147]. Genomic sequencing of cfDNA can also aid in identifying NEPC subtypes that are sensitive to platinum-based therapies [130,148]. Moreover, the methylation patterns of cfDNA can be used to characterize tumor-associated epigenetic changes [146]. Therefore, liquid biopsy is expected to serve as a less invasive detection method for disease progression in the future.

## 5.2 Treatment of mPCa

In recent years, treatment strategies for mPCa have undergone significant changes, transitioning from traditional ADT to multidrug combination therapies, especially in cases of nonbone metastasis, where the complexity and heterogeneity of treatment are greatly increased [150,151]. ADT typically involves reducing testosterone production through surgical or medical castration, achieved via orchiectomy or gonadotropin-releasing hormone agonists or antagonists. For patients with mCSPC, current treatments advocate early combination therapy to delay resistance progression and maximize overall survival (OS) [150,152–158]. Several phase III trials, such as CHARTED [159], STAMPEDE [160], and LATITUDE [89], have consistently shown that combining ADT with docetaxel and novel ARPIs such as abiraterone, enzalutamide, and apalutamide can prolong progression-free survival (PFS) and OS in mCSPC patients. Additionally, the PEACE-1 [161] and ARASENS [162] studies have advanced triple therapy (ADT + docetaxel + ARPI) into clinical practice, demonstrating significant survival benefits in mCSPC patients with high-volume disease. In the ARASENS study, the median OS of patients with visceral metastasis who received triple therapy improved by 7 months compared with that of patients who received only docetaxel treatment (49.0 months vs. 42.0 months) [162]. In addition to using ARPIs, therapies such as RIPTAC and PROTAC-mediated AR degradation are also under exploration [163,164]. Taken together, some mPCa tumors retain AR pathway dependence, and AR-directed therapy remains of clinical relevance. However, existing evidence has not sufficiently differentiated the efficacy of this approach in cases of nonbone metastasis *versus* bone metastasis, suggesting that individualized treatment based on burden and organ specificity is needed in clinical practice (**Table 2**).

**Table 2 Treatment Strategies for mPCa.**

Disease Stage	Main Treatments	Key Evidence	Outcomes/Challenges	Future Directions
mCSPC	Triple therapy: ADT + Docetaxel or ARPI (abiraterone, enzalutamide, apalutamide)	CHAARTED [159], STAMPEDE [160], LATITUDE [89], PEACE-1 [161], ARASENS [162]	Prolonged PFS/OS; triple therapy improves OS in visceral metastases (e.g., ARASENS: 49.0 vs. 42.0 months)	Stratified treatment by metastatic burden and organ type
mCRPC-Lung metastasis	Docetaxel +ARPIs (e.g., enzalutamide)	AFFIRM [165], PREVAIL [166,167]	Better prognosis vs. liver metastasis (e.g., PREVAIL: 32.4 vs. 18.9 months); relatively preserved AR signaling	Standard CRPC protocols apply
mCRPC-Liver metastasis	Docetaxel; ARPI (limited efficacy); <sup>177</sup> Lu-PSMA-617	AFFIRM [165], PREVAIL [166], VISION [168]	Poor prognosis; AR loss, NE phenotype, high genomic instability; low PSMA expression limits radioligand use	Novel ligands (e.g., FAP-PET) [169], PARPi [170,171], immunotherapy + TGF-β inhibition [172–174]
NEPC subtype	Platinum chemo for NEPC (cisplatin + etoposide or carboplatin + docetaxel); SLC16LD6.5 for DLL3-expressing NEPC (Preclinical); AURKA inhibitor (Preclinical)	NEPC trials [15,20,131,148,175,176]	Insufficient objective response rate	NEPC specific target selection; improve drug safety and efficacy
DNPC subtype (under research)	FGFR inhibitor; Gremlin1 antibody	DNPC research [18,177,178]	Lacks AR and NE markers; subset with FGFR activation	Molecularly targeted trials; FGFR pathway inhibition
Novel therapy (under research/preclinical)	AR targeted; non-AR targeted; DDR targeted; Immunotherapy	RIPTAC [163], PROTAC [164]; EZH2 [179,180]; PROPEL [181], MAGNITUDE [182], TALAPRO-2 [183]; T-cell engagers, vaccines, CAR-T [184]	Insufficient efficacy or toxicity concerns	More specific biomarkers targets and safety

This table summarizes current treatment strategies and challenges in mPCa patients with nonbone metastasis (lung, liver), focusing on both mCSPC and mCRPC stages. Treatment selection depends on site-specific biology, AR signaling status, subtype features (e.g., NEPC, DNPC), and novel therapy.

When the disease progresses to the mCRPC stage, treatment strategies increasingly rely on precise stratification based on tumor molecular characteristics and metastatic sites. Docetaxel remains the foundational first-line treatment, and for patients with lung or liver metastasis, ARPI treatment still provides clear survival benefits, although its efficacy varies among subgroups [165,166,185,186]. Data from studies such as AFFIRM and PREVAIL show that the median OS for patients with lung metastasis treated with enzalutamide is superior to that of patients with liver metastasis (e.g., in the

PREVAIL trial: 32.4 months for lung metastasis vs. 18.9 months for liver metastasis), indicating a significantly worse prognosis and limited response to current treatments in patients with liver metastasis [165–167]. Further research revealed that liver metastasis in PCa is often associated with decreased AR expression, neuroendocrine transdifferentiation, and high genomic instability, which are closely related to ARPI treatment resistance [39]. NEPC is typically treated with chemotherapy regimens derived from those used for small cell lung cancer, primarily consisting of a combination of cisplatin and etoposide [15,131,148]. AURKA is highly expressed in NEPC, and using the AURKA inhibitor alisertib can improve patient prognosis [176]. In addition, EZH2 inhibitors are also potential therapeutic targets [179,180]. Although conventional immune checkpoint inhibitor therapies have shown limited benefit in PCa, novel approaches such as T-cell engagers, vaccines, and CAR-T therapies still represent meaningful research directions for mPCa [184].

For patients with liver metastasis, current standard treatments include chemotherapy, ARPIs, and radioligand therapy, but overall efficacy remains poor [39]. Although radionuclide therapy (e.g., the VISION study) has improved OS in the overall mCRPC population, its efficacy is limited in patients with low PSMA expression and neuroendocrine phenotypes, necessitating further evaluation [168,187]. As a result, some studies are exploring immunotherapy combination strategies or novel radioligands targeting PSMA-negative markers (e.g., FAP-PET) to improve treatment outcomes, although these are still in the exploratory stage [169]. NEPC is more prone to liver metastasis, making NEPC-specific targets promising for targeted therapy. DLL3 is highly expressed in NEPC, and treatment of DLL3-expressing NEPC with the antibody-drug conjugate SC16LD6.5 has shown effective responses, suggesting DLL3 as a potential therapeutic target for NEPC [175]. In addition, the development of liver metastasis often accompanies tumor clonal evolution induced by treatment selection pressure, with some tumor cells potentially evading traditional treatments by acquiring neuroendocrine phenotypes or enhancing DNA damage response pathway activity [32,188]. As mentioned in Part 2, DDR gene mutations are enriched in mPCa, and PARPs play a key role in DNA repair. Phase III trials such as PROPEL [181], MAGNITUDE [182], and TALAPRO-2 [183] have shown that patients with mCRPC derive significant radiographic progression-free survival benefits from the combination of PARP inhibitors and ARPIs. These findings suggest that the use of PARP inhibitors or combination therapies targeting DDR-related pathways may hold promise in these patients [170,171]. The immune microenvironment of liver metastasis is highly immunosuppressive, with mechanisms such as TGF- $\beta$  signaling, MDSC recruitment, and T-cell exhaustion rendering immunotherapy ineffective [39]. Thus, liver-directed radiotherapy or TGF- $\beta$  inhibitors may help alleviate immune evasion and enhance the efficacy of systemic immunotherapy [172–174].

Notably, while lung metastasis in mCRPC is associated with a worse prognosis than bone metastasis, it is still better than that associated with liver metastasis. In studies such as PREVAIL, lung metastasis patients responded relatively well to ARPIs, indicating that the biological characteristics of their tumors are more similar to those of classic AR-driven CRPC [165,166]. For those with NEPC or AR-negative tumors, platinum-based chemotherapy (e.g., carboplatin + etoposide) or participation in clinical trials exploring novel immunotherapy combination strategies is recommended [155,189]. However, there is currently no established

standard treatment for DNPC patients. Our team has identified Gremlin1 as an important therapeutic target in advanced PCa, with particularly high expression in DNPC. Gremlin1 promotes PCa progression and androgen deprivation resistance by directly binding to FGFR1 and activating the FGFR1/MAPK signaling pathway, which is closely associated with FGF signaling activation. We have developed monoclonal antibodies against human or murine Gremlin1 and demonstrated their efficacy and safety in mouse models. Therefore, under a suitable dosing window, the use of Gremlin1 antibodies in patients may avoid unnecessary side effects and represent a novel approach for DNPC treatment [177]. As a key pathway in DNPC, the FGFR signaling pathway represents a promising therapeutic target [18]. Thus, future strategies targeting FGFR1 and GREM1 hold potential for the treatment of DNPC patients [178].

In summary, current treatments for nonbone mPCa, especially PCa with lung and liver metastasis, face significant challenges. Patients with lung metastasis have a relatively favorable prognosis with existing ARPI therapies and are recommended to follow standard CRPC treatment pathways, whereas patients with liver metastasis should be considered a high-risk subtype and treated with multimodal combination strategies and novel targeted interventions. Future efforts could focus on establishing liver metastasis-specific biomarker screening systems, developing more precise imaging and liquid biopsy methods, and conducting multicenter clinical trials to validate personalized treatment plans, ultimately improving the prognosis of these patients.

## 6. Conclusion and Perspective

Cancer metastasis is the leading cause of patient death, yet the mechanisms underlying metastasis and effective interventions remain poorly understood [68,190–192]. PCa is one of the most common malignancies in men, and its metastatic mechanisms and clinical treatment strategies have long been key areas of research. Although bone metastasis is relatively common in PCa patients, patients who experience recurrence after treatment often present with nonbone metastases, which pose a serious threat to their survival.

The mechanisms of nonbone metastasis in PCa involve multiple factors, including genomic mutations, PCa phenotypes, microenvironmental regulation, and metastatic organ-specific microenvironments. Common genomic alterations in PCa include *TMPRSS2-ERG* fusion, *AR* amplification, gain-of-function mutations in *FOXA1*, and loss-of-function mutations in *SPOP* [4]. Moreover, mutations in DNA damage repair genes are frequently observed in mPCa, particularly in brain metastatic PCa. Notably, the loss of *PTEN* in mPCa is considered a major driver of metastasis, followed by the loss of *RB1* and *TP53*, as well as the double loss of *RB1* and *TP53*, resulting in the NEPC phenotype.

During the progression of PCa, lineage plasticity leads to the emergence of various subtypes. NEPC, a highly aggressive subtype of PCa, exhibits strong metastatic capabilities, particularly a significantly increased incidence of liver metastasis [15,20]. The development and progression of NEPC are unclear and involve lineage plasticity acquisition and the expression of neuroendocrine markers. Studies suggest that NEPC may have unique metabolic pathways, with its specific metabolites and secreted neuroendocrine factors potentially serving as therapeutic targets. Furthermore, the tendency of NEPC to metastasize to the liver provides important insights for research on other

neuroendocrine tumors. DNPC represents another aggressive phenotypic variant of PCa. However, its diagnosis relies primarily on exclusion methods, as it is negative for both AR and NE markers. There is a lack of definitive therapeutic targets for DNPC. Future research could integrate multiomic data, including genomic, transcriptomic, proteomic, and metabolomic data, to construct molecular profiles of DNPC and identify specific biomarkers and potential therapeutic targets.

Different types of cancer exhibit distinct organotropism. Differences in organ-specific microenvironments are key determinants of this organotropism. This selective metastasis is regulated by multiple mechanisms, including chemokines, cell-cell interactions, and immune modulation, which collectively guide tumor cells to migrate, colonize, and grow in specific organs. The bone is the most common site of metastasis in PCa. The bone microenvironment contains unique components, such as osteoclasts, osteoblasts, osteocytes, mineralized bone matrix, and abundant cytokines that together create a “fertile soil” supporting tumor growth [193–195]. Furthermore, the bone marrow serves as a critical niche for dormant tumor cells, where factors such as Gas6, BMP4, and BMP7 regulate the homing and dormancy of PCa cells [196].

In contrast to the well-studied PCa bone metastases, the mechanisms of PCa nonbone metastases remain incompletely understood. The liver is rich in immune cells and maintains an “immune-tolerant” microenvironment to balance immune surveillance and tolerance to external antigens [62]. This suppressive environment facilitates tumor immune evasion. Although circulating tumor cells can enter the liver parenchyma via sinusoidal vessels, they often encounter initial growth suppression and may remain dormant for a long time [11,197,198]. This dormancy is at least partly mediated by immune regulation, such as the secretion of IFN- $\gamma$  by liver-resident NK cells, which is essential for maintaining dormancy of breast cancer disseminated tumor cells [76]. Studies have shown that chemotherapy may induce the awakening of dormant tumor cells [199]. In PCa patients receiving ARPIs, treatment-associated liver injury and fibrosis may stimulate the awakening of dormant cancer cells in the liver, potentially triggering recurrent liver metastases. The lung, with its extensive vasculature and large capillary surface area, provides a favorable site for circulating tumor cells arrest, extravasation, and colonization. Moreover, tissue-resident macrophages in the lung, such as alveolar and interstitial macrophages, play key roles in regulating metastasis [200,201]. In summary, organ-specific metastasis in PCa reflects distinct organotropism, which is shaped by multiple interactions within each organ’s microenvironment. A deeper understanding of how different organ microenvironments regulate tumor cell fate may offer new therapeutic directions to prevent and manage PCa metastases.

Among all nonbone metastatic sites, metastasis to the liver is associated with the worst prognosis, making understanding liver metastasis in PCa crucial for improving patient outcomes. Here, we elaborate on the liver metastasis of PCa and provide biologically significant insights. Patients with PCa liver metastasis typically present with advanced-stage disease. Notably, ARPI-induced liver injury may potentially facilitate liver metastasis progression. Under liver injury conditions, activated hepatic stellate cells can further reactivate dormant tumor cells. These mechanisms provide important insights for understanding liver metastasis in PCa, particularly in the context of treatment-induced NEPC.

Moreover, PCa as a typical immunosuppressive "cold tumor", evades elimination by various resident immune cells in the liver through mechanisms that remain unclear. In the future, research on resident immune cells in the liver may explain the specificity of liver metastasis in PCa and lead to the development of new targeted therapeutic strategies.

The role of the nervous system in PCa has gained increasing attention in recent years [202]. Nerves and neural factors have potential clinical applications as biomarkers for patient stratification. However, in other cancer types, the roles of different nerves, including sympathetic, parasympathetic, and sensory nerves, are not entirely consistent [203]. Whether these nerves exert protumor or antitumor effects in PCa remains to be elucidated. Moreover, the nervous and immune systems share extensive crosstalk in signal transduction, with neurotransmitters directly modulating immune cell function by binding to their cognate receptors on immune cells [204]. Therefore, investigating the differential immunomodulatory effects of distinct neural subtypes in PCa represents a significant research frontier. Beyond the regulation of tumor metastasis by nerves at the primary site, it remains unclear whether nerves at the nonbone metastatic site further promote tumor growth.

Although nonbone metastatic models of PCa have been partially established, significant areas for improvement remain. First, while bone metastasis is more prevalent in PCa patients, mouse models predominantly develop nonbone metastases, a discrepancy largely attributed to interspecies differences. Consequently, findings from murine studies may not always translate effectively to patients. Future research could prioritize clinically relevant phenomena observed in patients before experimental validation in models. Second, existing murine nonbone metastasis models lack heterogeneity. For example, liver metastasis studies often rely on NEPC models while ignoring non-NEPC subtypes. Only through stable establishment of representative nonbone metastatic models can the underlying mechanisms be thoroughly investigated.

The diagnosis and treatment of nonbone mPCa face significant challenges due to disease heterogeneity. Imaging techniques, including PSMA PET and <sup>18</sup>F-FDG PET-CT, are crucial for detecting metastases, although PSMA PET has limitations in detecting AR-negative tumors. Emerging liquid biopsy technologies now enable noninvasive profiling of tumor subtypes such as NEPC and mutational signatures through ctDNA analysis, facilitating real-time monitoring of disease progression and therapeutic response. In terms of treatment, there is still a lack of highly specific and effective therapeutic approaches. In the future, developing more precise diagnostic methods, defining optimal treatments for different PCa mutations and subtypes, and investigating novel targeted therapeutic strategies are expected to further improve patient prognosis.

## Abbreviations

The following abbreviations are used in this manuscript:

PCa	prostate cancer
mPCa	metastatic prostate cancer
ADT	androgen deprivation therapy
ARPI	androgen receptor pathway inhibitor

CSPC	castration-sensitive prostate cancer
CRPC	castration-resistant prostate cancer
mCRPC	metastatic castration-resistant prostate cancer
mCSPC	metastatic castration-sensitive prostate cancer
NEPC	neuroendocrine prostate cancer
DNPC	double-negative prostate cancer
DDR	DNA damage repair
HRD	homologous recombination deficiency
CRNE	neuroendocrine colon cancer
CRNELM	neuroendocrine colon cancer liver metastasis
EMT	epithelial-mesenchymal transition
GEMM	genetically engineered mouse model
PDO	patient-derived organoid
PDX	patient-derived xenograft
ctDNA	circulating tumor DNA
cfDNA	cell-free DNA

## Declarations

### Ethics Statement

Not applicable

### Consent for Publication

Not applicable

### Availability of Data and Material

Not applicable

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### Competing Interests

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### Author Contributions

H.H.Z, N.J, and G.Y.D drafted the manuscript. P.H.X assisted in creating cartoon elements in Graphical drawing. All authors reviewed and approved the final manuscript.

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