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Review Articles

Clinical challenges in prostate cancer management: Metastatic bone-tropism and the role of circulating tumor cells

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A B S T R A C T

Prostate cancer (PCa) metastasis is one of the leading causes of cancer-related mortality in men worldwide, primarily due to its tendency to metastasize, with bones of axial skeleton being the favored target-site. PCa bone-metastasis (PCa-BM) presents significant clinical challenges, especially by the weakening of bone architecture, majorly due to the formation of osteoblastic lesions, leading to severe bone fractures. Another complication is that the disease predominantly affects elderly men. Further exploration is required to understand how the circulating tumor cells (CTCs) adapt to varying microenvironments and other biomechanical stresses encountered during the sequential steps in metastasis, finally resulting in colonization specifically in the bone niche, in PCa-BM.

Deciphering how CTCs encounter and adapt to different biochemical, biomechanical and microenvironmental factors may improve the prospects of PCa diagnosis, development of novel therapeutics and prognosis. Moreover, the knowledge developed is expected to have broader implications for cancer research, paving the way for better therapeutic strategies and targeted therapies in the realm of metastatic cancer progression across different types of cancers.

Our review begins with analyzing the challenges in PCa diagnosis, treatment and management, and delves into the formation and dynamics of CTCs, highlighting their role in PCa metastasis and bone-tropism. We further explore the pivotal role of individual factors in dictating the predisposition of tumors to metastasize to specific secondary sites, such as the noteworthy tendency of PCa bone-metastasis. Finally, we highlight the unresolved questions and potential avenues for further exploration.

1. Introduction

Prostate cancer (PCa) is the second most commonly diagnosed cancer in men, with an estimated 1.4 million new diagnoses worldwide in 2020 [1]. The incidence of PCa varies across regions and populations, with higher incidence rates in developed countries [2,3] while the overall age-standardized mortality rate stands at 10 out of 100,000 men [4]. A systematic review of autopsy studies reported a prevalence of PCa in 5 % of the study population aged <30 years, increasing by an odds ratio of 1.7 per decade, to a prevalence of 59 % (48–71 %) by age >79 years [5]. PCa is therefore considered to be a predominant tumor type in older men, with a median age of 66 years at diagnosis [6]. PCa comes with not just the burden of the pathology, but also with the physiological, emotional and mental distress. Although localized PCa is curable at the initial stage, the 5-year survival rate of patients with initial diagnosis of metastatic PCa is less than 30 % and remains low despite the efforts to improve prognosis in recent years [7–9].

While 90 % of the cancer associated deaths are attributed to metastasis [10,11], the oncology research funding landscape unfortunately depicts a disproportionate picture. Research fundings, excluding those from Cancer Research UK, unveil a staggering 7768 awards (=11.7 % of total cancer research funding) aimed to unravel the complexities of metastatic disease. Astoundingly, these endeavors itself reached a whopping sum of $2.3 billion. Despite, it is worth noting that this amount devoted to the study of metastatic disease was less than 10 % of the total cancer research funding - a fraction seemingly inappropriate for the growing number of patients presenting with metastatic disease [12]. In particular, metastasis in the axial skeleton is observed in about 10 % of PCa cases diagnosed at an early stage and in up to 80 % of PCa patients diagnosed at a later stage [13]. This, in combination with

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the scenario in both low – and middle – income nations, where delayed clinical recognition often leads to later diagnosis at metastatic stage, emphasizes a major problem with diagnosis management and warrants further attention not only by researchers but also by policy makers. Several reports point towards an increasing number of patients confronting metastatic disease, further magnifying the incongruity in research investment [12].

Apart from the death burden associated with metastatic PCa disease, the physical and psychological toll for the patients due to the bone metastasis (BM) driven lesion formations and the following bone fractures are very challenging aspects of PCa. BM-PCa generally give rise to osteoblastic lesions [14] as opposed to osteolytic lesions, which are more common in breast cancer (BCa)-BM. However, PCa patients clinically presenting with osteolytic lesions have also been reported [15,16]. Tumor cell-driven (osteoblastic) *de novo* formed bones are under-mineralized and lack the physiological bone architecture, which makes them very weak and brittle, causing severe pathological bone fractures in patients. This issue is further exacerbated by the fact that the disease predominantly affects elderly men. In fact, the recent studies on cohort aged >65 years suggest that fragility fracture occurring at any skeletal site was associated with reduced survival for up to 6 years post-fracture [17]. Fig. 1 shows representative clinical images of bone metastases with osteoblastic and osteolytic lesions and a displaced bone fracture in BM-PCa patient.

Metastasis involves the spread of cancer cells from the primary tumor to other locations in a complex, multi-stage, sequential process. Although commonly simplified as a linear sequence of events such as: migrating from the initial tumor site and local infiltration, intravasation, surviving in the bloodstream, extravasation, and establishing new metastatic sites, it encompasses several intricate steps [18,19]. CTCs in the vasculature are "seeds" that circulate within the patient body, seeking suitable "soil" for further growth and proliferation [20]. Metastatic colonization of CTCs is a highly inefficient process – with the estimated success rate as low as 0.01 % [21]. However, metastasis can clinically manifest even after many years of initial treatment success [22]. The mechanism of elimination of the majority of CTCs, often termed "metastatic inefficiency," has been explored in the past but further research is required to strategically use this information for therapeutic targeting of the surviving CTCs [23–25]. Reports suggest a prolonged survival of the CTCs is possible after they exit circulation and infiltrate organs, thereby becoming disseminated tumor cells (DTCs). The possibility of DTCs remaining dormant in their secondary homing sites, waiting for the conducive conditions to arise for them to form micro- and macro-metastases has been backed by evidence in the recent years [26]. However, the crucial information on signaling circuitries that enable this are limited [27] and the prospects of exploiting DTC dormancy in therapeutic targeting needs further investigations.

Stage IV is clinically considered to be the point in PCa progression when the tumor metastasizes to distant sites or organs in the patient body, with secondary colonization in the bones being observed in most cases. The first and foremost ambiguity here is that the PCa cells can migrate, invade, and form CTCs much earlier than stage IV. This is clinically evidenced by the recurrence of tumor on the secondary sites even after radical prostatectomy (RP) and androgen deprivation therapy (ADT) [28,29]. In fact, CTCs have been shown to be detectable in PCa patients irrespective of the pathological stage [30], and from as early as stage I [31]. Similarly, in other cancer types with prominent bone-tropic metastasis pattern such as the BCa, micro metastases were observed in the early stage patients [32].

Although considerable efforts are being made to improve diagnosis, treatment strategies and prognosis of PCa, conclusive and definitive results on any of these domains are still lacking. In this review, we discuss the major challenges associated with PCa including under- and over-diagnosis, the consequent under- and over-treatment, novel therapeutic interventions and prognosis. We then focus on the PCa-BM progression, exploring the biochemical and biomechanical aspects of the metastasis sequence, while dissecting the adaptive mechanisms and the pivotal role of CTCs in enabling PCa-BM. Notably, while CTCs are the key drivers of PCa-BM initiation, they also hold significant potential as diagnostic markers, indicators of disease progression, and promising therapeutic targets to prevent or treat BM. This review further highlights how CTCs offer insights and potential solutions to the challenges posed

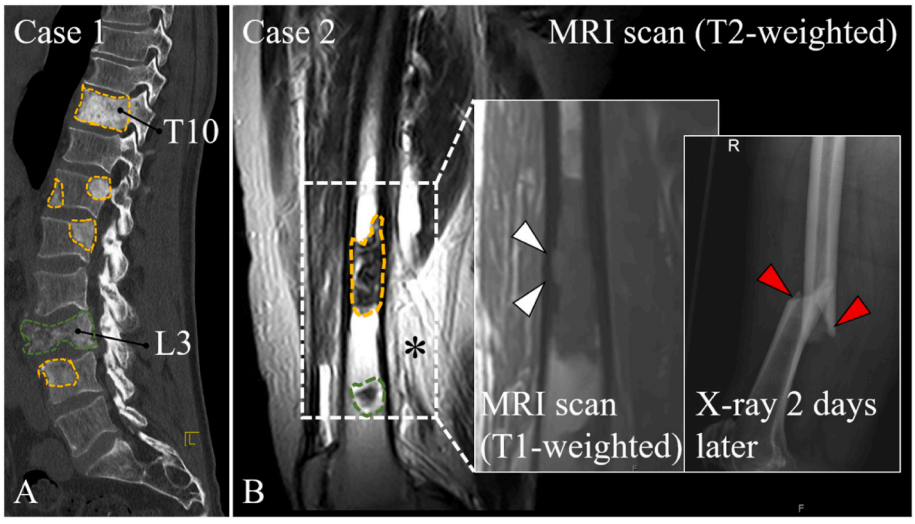

Fig. 1. Two illustrative cases with osseous metastases originating from the dissemination of a prostate carcinoma. A) Case 1: CT-scan of a 68-year-old patient with multiple osteoblastic metastases of the spine of varying degrees of severity (affected vertebral bodies are encircled with stippled lines) with pathological fracture of L3 (L3 encircled with green stippled line), exclusively osteoblastic lesions (orange stippled lines) with maximum involvement of T10. B) Case 2: 69-year-old patient with a known metastasis in the area of the right femur presented with persistent pain after undergoing radiotherapy twice (total dose 36 Gy and 20 Gy, respectively). The MRI scan (T2-weighted) showed an extensive bone metastasis in the femoral shaft with a perifocal bony edema zone with a total craniocaudal extent of circa 11 cm (orange stippled line). In addition, a second metastasis measuring circa 1.5 × 2 × 3 cm with perifocal bone edema zones in the distal femur (green stippled line). Periosteal localized soft tissue reaction (asterisk) most likely in the condition after radiotherapy. Close-up view (MRI scan T1-weighted) shows an osteolytic component of the tumor with cortical thinning (indicated by the white triangles). Only 2 days after the MRI scan, fracture of the osteoblastic metastasis with osteolytic components occurred most likely in the condition after weakening of the bone tissue by radiotherapy (see X-ray with red triangles).
CT, computed tomography; L3, lumbar vertebral body 3; MRI, magnetic resonance imaging; T10, thoracic vertebral body 10.

by PCa-BM.

2. Detection and diagnosis of PCa

The underdiagnosis of PCa can increase the risk of metastasis by delaying prompt treatment. Early detection through careful screening and monitoring of known lesions is crucial as it provides a higher chance of cure and allows less aggressive treatments with fewer side effects. Ironically, the overdiagnosis of PCa, which is mostly the consequence of prostate specific antigen (PSA)-based PCa screening, can also be potentially deleterious for the patient health and quality of life. A pivotal shift from the generally accepted 4-core biopsies occurred during the late 1980s when Hodge and collaborators proposed an alternative approach of a "sextant" biopsy scheme, advocating the acquisition of six cores [33]. In recent decades, a concept termed "saturation biopsies" has gained prominence within the medical field. This approach proposes the acquisition of biopsy cores from each cubic centimeter of the prostate tissue, totaling around 20–40 biopsy samples per patient [34,35]. One might argue that these well-intended yet exceedingly aggressive approach have, in all likelihood, led to the detection and diagnosis of indolent PCa that are probably harmless.

In the early 1990s, it was demonstrated that the blood testing for PSA antigen could be used as a primary screening method for PCa [36], which then led to the FDA approval of this test for early detection of PCa [37]. While the detection rate of PCa is typically over 50 % among patients with considerably elevated PSA levels (e.g., >10 ng/mL), it is generally low (typically below 30 %), especially among those with moderately elevated PSA levels (4–10 ng/mL) [38]. Thus, under-detection of PCa due to over-reliance on the PSA levels could result in exacerbation of the pathology and a possible diagnosis at an advanced stage of the disease. Conversely, the risk of relying solely on PSA levels for PCa screening and intervention decision has been evidenced by large scale studies and it confirmed that population-wide PSA-based PCa testing does not proportionately help save lives, in comparison to the repercussions due to increased false positive diagnoses [39,40].

Although the persistent global research for PCa specific biomarkers have resulted in the identification of genes such as the prostate cancer antigen 3 (*PCA3*), a predictive marker for pathology-confirmed, small-volume PCa with sensitivity range between 46.9 % and 82.3 %, and specificity range from 56.3 % to 89 %, TMPRSS2: ERG (transmembrane protease serine 2:v-ets erythroblastosis virus E26 oncogene homolog fusion gene) [41], and [−2]-proPSA (a premature form of PSA) [42], novel biomarkers are poorly adopted in clinics. However, a population-based PSA screening in men is not recommended according to the latest ESMO clinical guidelines, as it reduces PCa mortality at the expense of overdiagnosis and overtreatment [43].

3. Under- and over-treatment of PCa

Patients who get screened and are presenting with an elevated PSA level and/or after digital rectal examination (DRE) are further subjected to Magnetic Resonance Imaging (MRI) and multi-core biopsies to finalize the diagnosis. Repeated saturation biopsies are obtained in those cases where initial biopsies did not confirm PCa but PSA levels are still rising [44]. Upon PCa detection, the patients are assigned to specific categories by assessing several factors (clinical and histopathological) like the nature of tumor (aggressive or indolent), tumor/node/metastasis (TNM) classification, and Gleason score. Owing to the fact that practically any kind of prostate stimulation (e.g., DRE, sexual stimulation and ejaculation, etc.) can cause an elevated PSA level, the prevalent use of PSA testing followed by prostate biopsy has increasingly resulted in the detection of low-risk tumors; nonetheless, leading to over-treatment [45,46]. In addition, another finding suggests that while there is a prevalence of recognizable cancer-associated histological changes in more than 30 % of men above the age of 50 years, only ~1 out of 10 individuals develop the clinical disease [47]. This in turn can mean that the others – 9 out of 10 – may be receiving intensive treatments such as RP (according to the clinical guidelines) that may not be entirely necessary [43,48,48]. This is unfortunate, especially considering the patient's older age. The latest results of the European Randomized Study of Screening for Prostate Cancer (ERSPC: ERSPC - European Randomized Study of Screening for Prostate Cancer.) is summarized in Fig. 2 providing an overview of the rate of over-diagnosis and resultant over-treatment [49].

Among individuals clinically diagnosed with localized PCa, the choice of watchful waiting (WW) strategy rather than RP has shown a paradoxical outcome. While WW correlates with a reduction in voiding and erectile dysfunction, mortality rates and metastasis are increased compared to those undergoing RP. RP reduces mortality compared to WW for clinically localized PCa but causes significant harm [50]. Focal laser ablation is emerging as a secure and viable therapeutic option for the treatment of low-risk PCa, as an alternative to the conventional treatment. Currently, the efficacy of focal laser ablation is being rigorously assessed in several clinical trials (up to phase II trials) across multiple institutional settings (e.g.: ClinicalTrials.gov ID NCT00805883, NCT02357121, NCT04379362, etc.)

While over-diagnosis and/or over-treatment is certainly a cause of concern, its counterpart –under-diagnosis and/or under-treatment – is equally deleterious in nature. Under-diagnosis/treatment can occur for a number of reasons, such as socio-demographic factors, the impact of physician versus patient preferences on treatment selection, patient's age, and unsurprisingly even a rural or urban residence status, amongst others [51–53].

4. Therapeutic intervention and prognosis of PCa

The first line treatment regimen for PCa is determined by the stage and risk category of the patient. While WW may be recommended for low-risk group patients with localized tumor (which may or may not be indolent), active surveillance, surgery (radical prostatectomy), or radiation therapy (external beam or brachytherapy) are opted for the intermediate-risk group, in favorable conditions. For patients with stage IV PCa, chemotherapy, radiation therapy, RP and ADT are recommended even for those with predicted poor prognosis, where the best supportive care option is considered [54]. In general, these treatment regimens initially reduce the tumor burden and/or detectable blood PSA to minimal or undetectable levels, but eventually, the disease is observed to recur in most cases.

The prevailing challenge in the field of PCa is not simply timely detection but rather the accurate differentiation between aggressive PCa warranting immediate attention and the indolent ones requiring surveillance-based approach. While the choice of treatment depends on factors such as the stage of the cancer, the patient's age and general health, and the potential side effects of each treatment option, the prognosis for patients with localized disease is markedly better in comparison to the patients with BM-PCa and castration resistant PCa. This is substantiated by the 2001–2016 PCa statistics which suggests that the 10-year survival rates dramatically contrast, plummeting from nearly 100 % for localized disease to a dismal 5-year survival rate of one-out-of-three for individuals afflicted with BM-PCa [55].

Although it is still in the stage of infancy, the prospects of using CTCs for early detection of clinically relevant cancer is emerging in recent years [56]. As a result of constant efforts to improve the prognostic predictions in the last couple of decades, enumeration of circulating tumor cells (CTCs) has been identified to have great potential as a disease progression indicator and as a means to assessing response to the treatment [57,58]. Notably, the recent results published from a prognostic study conducted in 1313 men initiating systemic hormonal therapy for metastatic hormone-sensitive PCa, who participated in the prospective phase 3 randomized clinical trial, concluded that the elevated CTC count at baseline was indeed associated with statistically

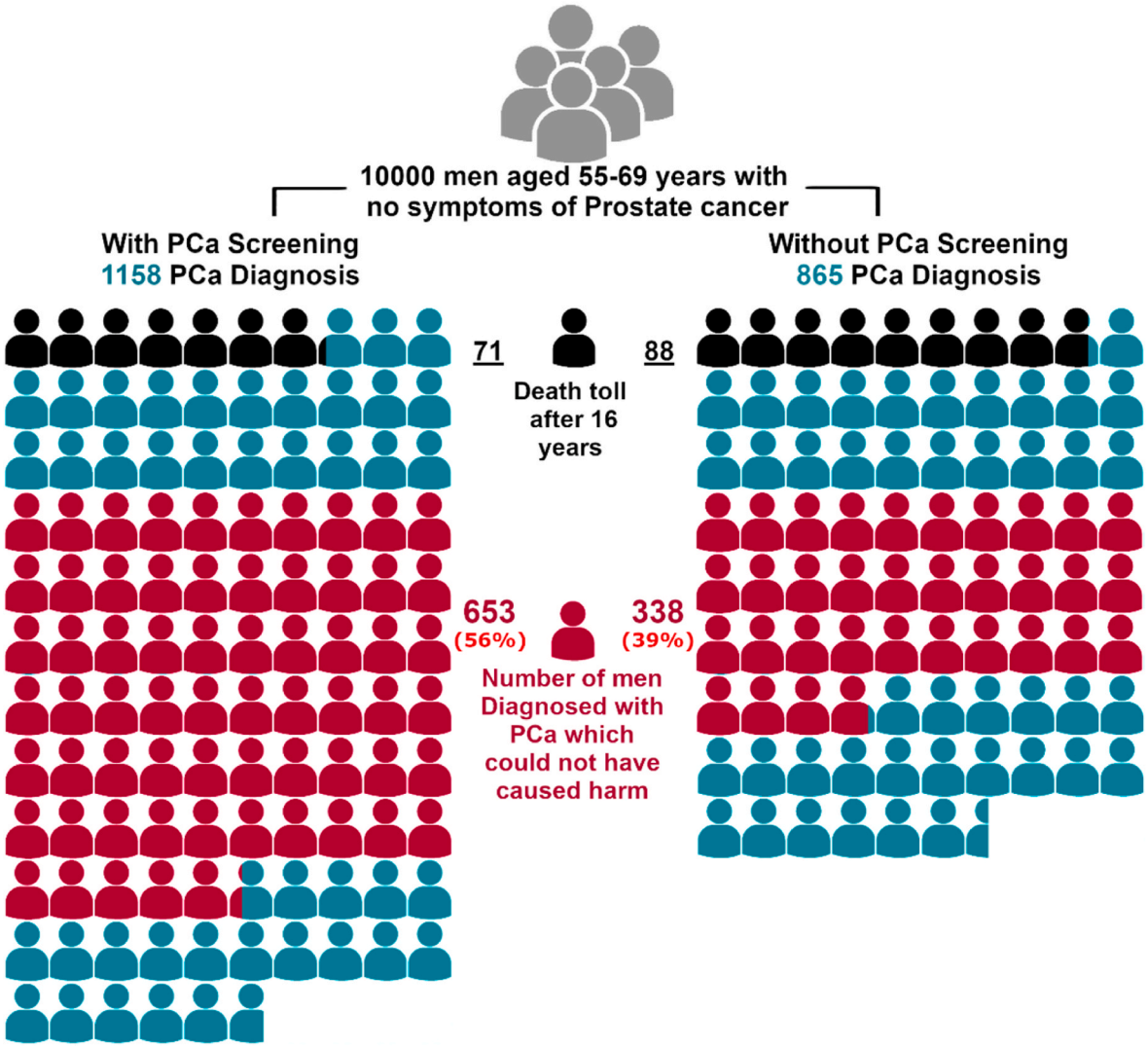

Fig. 2. The empirical data of ERSPC (ERSPC - European Randomized Study of Screening for Prostate Cancer.) study. The data suggests that PSA-based PCa screening can reduce the late detection (advanced stages) of PCa, indicated by the reduced number of death toll with PCa screening. However, the PSA-based screening also results in (over) detection of low-risk/indolent PCa, which would not have caused any harm if left untreated. This in turn affects a significant number of patients' quality of life both physiologically and psychologically. Adapted from Ref. [49] with permission from Elsevier, copyright 2019.

significantly worse overall survival, progression-free survival, and treatment response [59]. These results validate the use of CTC count as a robust prognostic biomarker, enhancing the predictive power of existing prognostic factors and revealing significantly divergent survival outcomes, irrespective of subsequent treatment regimens.

CTC enumeration, beyond being useful as a simple predictive modelling tool for tumor prognosis, can reveal much more information about tumor aggressiveness. The analysis of CTC specific microRNA, biomechanical stress adaptations, molecular adaptive transformations, differential responses to the microenvironments, and secretory factors that might support metastasis can provide further predictive insights [60–64]. The in-depth understanding of these aspects could potentially help in targeting the disseminated tumor "seeds" to prevent metastasis. In addition, the establishment of a CTC-based predictive modelling would drastically reduce the number of invasive biopsies that the patients have to undergo (especially in the early stages), which would further improve the quality of life for the elderly patients.

Further understanding of the PCa-BM sequential events and the associated pathways enable us to identify the specific and therapeutically targetable molecular cascades. Table-1 summarizes the key pathways in the context of PCa-BM, their target molecules and modes of regulation, potential therapeutic compounds, and relevant references. Interestingly, it can be observed that each step in the metastasis cascade have promising molecular targets that can be pharmacologically and therapeutically exploited.

5. Steps in PCa bone metastasis progression

The metastatic sequence of events in PCa-BM follows the general pattern comparable to any other tumor type, with invasion into the surrounding tissues at the primary tumor site being the first step. The tumor cells evolve and adapt to the TME changes during the subsequent metastasis steps such as intravasation, survival in the circulation, extravasation, survival as disseminated tumor cells (DTCs) in the bone niche, and eventually forming micro- and macro-metastases.

5.1. *Invasion, migration and intravasation*

The characteristic close-knit architecture of epithelial cells whereby they form tightly bound tissue structures, is achieved through the unique arrangement of cell-cell and cell-extracellular matrix (ECM) adhesion molecules into the tight junctions, adherens junctions, desmosomes, and

Table 1
The key molecular pathways in PCa-BM and possible target molecules that can be therapeutically exploited for the treatment of PCa-BM. The therapeutic compounds or molecules marked with an asterisk are in the clinical stage of testing.

Metastasis sequence	Molecular pathway/Mechanism	Target molecule and mode of regulation	Potential therapeutic compounds/ molecules	References
EMT Transition at the primary tumor site	EMT paracrine signaling	EGFR inhibitor	Cetuximab*, Afatinib	[65,66]
		FGFR inhibitor	Dovitinib*, Nintedanib*	[67]
		c-MET inhibitor	Crizotinib*	[68]
		TGF-β inhibitor	Metformin, Galunisertib*, IN-1130, Fresolumimab	[69–71]
	Intracellular EMT signaling	SPOCK1-snail/slug axis inhibitor	Apigenin	[72]
		STAT3 inhibitor	Galiellalactone, GPB730, Metformin	[73–75]
		ERK inhibitors	PD325901, Trametinib*	[76,77]
		PI3K-AKT-mTOR axis inhibitor	Ipatasertib*	[78]
	Mesenchymal markers and maintaining the mesenchymal state	Vimentin degradation	Withaferin A	[79]
		Axl inhibitor	BGB324	[80]
	Notch pathway	Notch inhibitors	RO4929097, (Gamma Secretase Inhibitors)	[81,82]
	Wnt/β-catenin pathway	β-catenin inhibitors	CWP232291	[83]
		WNT/FZD antagonists	Ipafricept*, BERA-Wnt5a siRNA	[84,85]
		PORCN inhibitors	LGK974	[86]
	Hedgehog pathway	SHH inhibitors	Cyclopamine, Genistein, Curcumin	[87,88]
		SMO inhibitors	Cyclopamine, Vismodegib, Itraconazole*	[89–91]
Migration and invasion	Matrix metalloproteinase inhibition	MMPs inhibitor	Batimastat	[92]
	CAFs assistance for migration and invasion	Blocking CAF activation (FGFR inhibitors, Hedgehog inhibitors)	Cyclopamine, Vismodegib, Itraconazole*	[87,88, 91]
		ECM remodeling	Losartan	[93]
		CAF elimination	Sibrotuzumab, dmrFABP5	[94,95]
	Rho pathway/ROCK	RhoA, ROCK I and II inhibitor	Simvastatin, Y-27632, Fasudil	[96,97]
	YAP/TAZ pathway	YAP/TAZ intracellular inhibitors	Verteporfin, XAV-939	[98]
		Nuclear translocation inhibitor	Pazopanib	[99,100]
	Tumor-ECM interaction	Integrins antagonist	Vitaxin, ATN-161	[101,102]
		LOXL family inhibitor	Beta-aminopropionitrile	[103]
Anoikis resistance	Anoikis restoration	AKT inhibitor	MK-2206	[104]
	Apoptosis induction	PI3K inhibitors	LY294002, Magnolol	[105,106]
Survival in vasculature	Disruption of tumor cell - platelet interactions	Antithrombosis	RA-233*	[107]
Tumor cell entrapment and adhesion to endothelial wall	Selectin-mediated interactions	Selectin antagonists	GMI-1271 (Uproleselan)	[108]
	Hyaluronic acid – CD44 interaction	CD44 promoter activity inhibitor	Silibinin,	[109]
		Hyaluronan synthase inhibitor	4-methylumbelliferone	[110,111]
Extravasation	Chemokine – mediated chemoattraction at distant sites	CXCR4 antagonists	Plerixaflor	[112,113]
		CXCR3 antagonist	AMG487	[114,115]
Micro/macro metastatic colonization	MET signalling	Similar targets as enumerated in the EMT pathway	Similar therapeutic molecules as listed in the EMT pathway	
	MMP signalling inhibition	MMPs inhibitor	Batimastat	[92]
	Angiogenesis inhibition	Tyrosine Kinase Inhibitors	Sorafenib*	[116]
		VEGF/c-MET antagonists	Thalidomide, Bevacizumab,	[117,118]

many others [119]. In neoplastic pathologies, this architecture of tumor epithelium is severely disrupted by downregulation of the adhesion molecules, leading to the disintegration of adherens and tight junctions, and causing loss of cell polarity. The loss of cell polarity is accompanied by acquisition of mesenchymal/stem-like cell properties, termed as epithelial-mesenchymal-transition (EMT) [18]. EMT is the driving force behind the migratory and invasive characteristics gained by the tumor cells [120]. Metastasis begins with the collective migration of primary tumor cells that invade other surrounding tissues.

Cancer invasion at the primary site frequently displays characteristic features of collective cell migration, in which cohorts of cells migrate in unison. This particular phenomenon encompasses the distribution profiles of stress and force, cytoskeletal reorganization, and responses to mechanical stimuli arising from the surrounding environment and adjacent cells (reviewed in detail elsewhere) [121]. Further, the cells must permeate the basement membrane in order to initiate metastasis. The basement membrane is predominantly composed of laminins and collagen IV and acts as an efficient structural barrier against infiltration of malignant cells. The process of basement membrane invasion by the tumor cells has been shown to utilize both proteolytic and physical mechanisms [122–124]. The role of cytoskeletal components is also crucial in facilitating tumor cell migration and invasion. The actin cytoskeleton plays a critical role in forming lamellipodia, enabling tumor cell invasion and metastasis [125]. Additionally, mechanical cues also impact the cell migration and invasion through ECM networks. Tugging forces generated during migration can influence the cell behavior, leading to changes in cellular mechanical properties that affect metastatic potential. The same study also explained the requirement of cofilin and actin for mechanically stimulated invasion [126]. The ability of cells to extravasate into the surrounding tissue by degrading basement membrane and ECM is considered a major rate-limiting step in metastasis. In the hematogenous metastasis route, the tumor cells then cross the vascular endothelial layer, enter into the circulation and start their journey to distant sites to form metastatic colonies. The complex sequalae of cellular transformations allow intravasation, enabling the tumor cells to enter the circulation and, become the CTCs observed in the migrating and invasive tumor types.

5.2. Survival of CTCs in the circulation

In addition to the attack of the immune system, CTCs face various biomechanical and functional challenges in the bloodstream, including fluid shear stress (FSS), deformation in the microcirculation (through the microvasculature/microcapillaries), and forces generated through adhesive interactions with blood-cells and the vascular wall. These forces can also impact the survival and metastatic potential of CTCs [127]. While high fluid shear stress in the bloodstream has the potential to diminish the viability of suspended CTCs and elicit significant apoptosis, it is imperative to note that the fluid shear stress can also induce EMT by activating c-Jun N-terminal kinase (JNK) signaling in CTCs, thereby enabling their survival throughout the hematogenous dissemination [128]. Using a custom-designed microfluidic circulatory system that produces exercise-mimetic shear stresses, Regmi et al. reported that prolonged exposure to high shear stress, such as that experienced during intensive body exercise, can reduce the viability of highly metastatic BCa cells [129]. The significance of this inference is very striking, if one considers that physical exercise has been shown to have a positive impact on the prognosis of BCa patients in clinical studies [130,131]. This is further clinically backed by another study published by Sheinboim et al., suggesting that high-intensity exercise may reduce the risk of metastatic BCa by up to 72 % [132]. It is possible that these results may stay true in the PCa patients also, owing to the fact that both PCa and BCa exhibit significant similarities in terms of their metastatic pattern and progression.

The vascular capillaries in our body have a narrower lumen diameter (5–10 μm) as compared to the size of an average CTC (larger than 10 μm). The microcirculation/microvasculature, which consists of a complex arrangement of small vessels and capillaries, exhibits a distinctive blood microenvironment characterized by intricate branching patterns and narrow constrictions that possess the ability to decelerate and trap the CTCs [133]. This presents the possibility of both positive and negative effects on the CTCs. The CTCs forcing itself through the microcirculation in the microvasculature could compel the cell to modulate the cell stiffness, morphology, etc. which can in turn influence cell survival and metastasis potential. This modulation could either push the cellular adaptative limits of the CTCs further, enabling their survival or it could destroy the CTCs by extreme constraints and cellular deformation. The entrapment of CTCs in the microvasculature may also allow extravasation and transmigration (thereby forming the DTC), resulting in the formation of additional micro- and macro metastasis, due to the ability of DTCs to adapt in the metastatic niche.

In an alternative perspective, these obstacles can also be regarded as means of filtration through a rigorous selection criterion that exclusively allows the survival and progress of only the most triumphant "seed cells" to establish colonies at the favorable metastatic location. This perspective has to be emphasized and further investigated, owing to the fact that less than 0.01 % of the cancer cells introduced into *in vivo* model organisms are able to induce the formation of metastatic tumors [25].

5.3. Extravasation and micro-macro-metastasis

The arrival of CTCs at the metastatic site is followed by a reverse process of mesenchymal-epithelial-transition (MET) for successful extravasation, micro- and macro-metastasis and colonization [119]. The initiation of extravasation by the tumor cells can be influenced by multiple factors. Previous studies have suggested that adhesion of tumor cells to the endothelial wall, facilitated by proteins of the selectin family, is the first step in extravasation, followed by rolling through the vascular endothelium in an integrins-mediated process known as diapedesis or transmigration [134]. Successfully transmigrated cells are again under immense adaptive pressures due to factors present in the microenvironment of the metastatic niche, such as presence of immune cells, together with their intrinsic drive to recruit growth factors and cancer associated fibroblasts (CAFs) for proliferation and stabilization. If the transmigrated cells, also termed as “seeds” are able to adapt at the new location where they have been *“implanted”* (thus forming a DTC), they will form a micrometastasis [20,135]. The micrometastasis (<0.2 mm) can further progress in one of the two major ways; either it can stay dormant or the cells can proliferate and develop into macrometastasis (>2 mm) [136]. In particular, one study reported that the micrometastasis outgrowth into macrometastasis is enabled by the formation of filopodia-like protrusions mediated by cytoskeletal changes [137]. These findings suggest an unequivocal role of biomechanical properties and the enabling proteins and molecules in the development and progression of micro-macro metastasis. Fig. 3 depicts the sequence of PCa metastasis, and the CTC-DTC dynamics involved in promoting PCa metastasis to bone, providing an overview of PCa metastatic spread and bone-tropism driven by CTCs.

6. Dissecting the role of CTCs in PCa-BM

Dissemination of tumor cells from the primary PCa tissue can occur at the earliest stages of neoplastic malignancy and, unfortunately, in most cases, this goes undetected [138]. PCa “seeds” or CTCs in the bloodstream need to settle in an appropriate “soil” – and it is well known from clinical and experimental reports that they preferentially migrate to the bone as the suitable “host-land” [55–57]. Interestingly, it has been observed that the pattern of metastases in patients with BCa shows striking similarity to that of PCa metastases, with the most preferred site for metastasis for BCa also being bones [58]. It is also noteworthy that both BCa and PCa cohort estimates show a 10-year relative survival rate of ~76 %, indicating that a majority of the patients survive after the disease diagnosis [139]. These statistics are ostensibly reassuring yet concerning, considering the possibility that resident CTCs or the dormant extravasated/DTCs may survive in the patient body and eventually cause disease relapse months, years or decades [140,141]. The mechanisms by which CTCs ‘decide’ their secondary homing site and how the tumor cells stay as DTCs for years in the secondary sites are still unclear. However, the changes in biochemical as well as biophysical adaptive signaling, cell-cell interactions, and cell-ECM interactions might provide further insights into this.

6.1. Platelets and immune cell interactions

In the past, it was believed that most of the CTCs are immediately destroyed as they enter the bloodstream [25,142], either by the natural killer (NK) cells and $CD8^+$ T cells [143,144] or by the biomechanical or hemodynamic stresses that the CTCs encounter while in circulation [145]. However, CTCs are evidenced to have direct interactions with platelets, forming associations with them and promoting their activation, which in turn may provide them with adaptive advantages [146]. Furthermore, activated platelets can form a fibrin-clot surrounding CTCs, which promotes the CTCs survival by protecting them from NK cell mediated destruction [147]. In addition, regulatory T cells (Tregs) have the capability to deliver essential signals for the survival of CTCs by generating receptor activation of nuclear factor-kappa B ligand (RANKL) on the tumor cells [148]. However, the role of immune cells in the successful transformation of CTCs into metastatic colonies is controversial, due to the contradictory research literature associated with this topic. One noteworthy example is neutrophils, which are one of the first line responders of cell-mediated immune defense. Neutrophils were initially known to play only a passive role in the tumor inflammatory response cascade. However, recent studies suggest their active involvement in both pro-tumor and anti-tumor manner, depending on the type and nature of interactions with the tumor cells and the tumor secretory factors [149,150]. Recently, neutrophils have also been implicated as mediators of metastatic PCa progression, specifically in bone, through the regulation of PCa growth independent of transforming growth factor beta (TGF)-β [151].

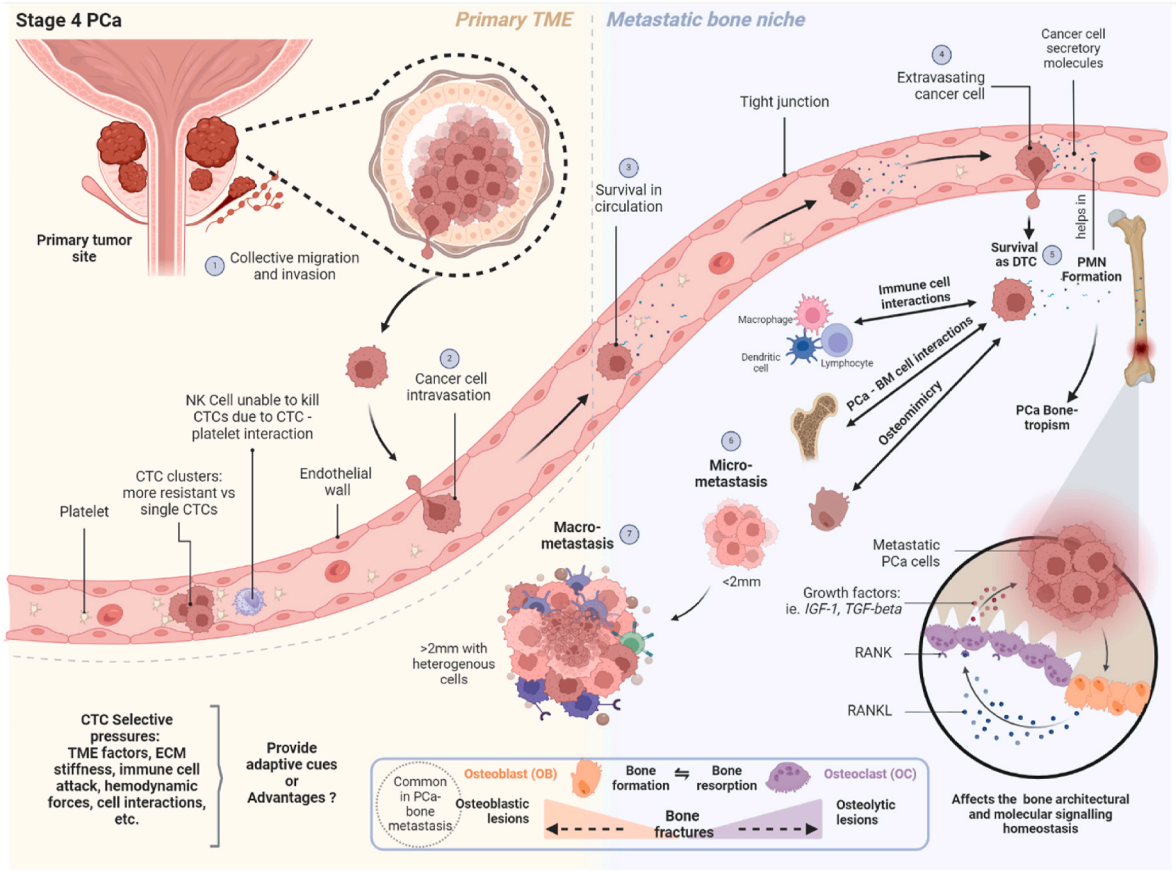

Fig. 3. Circulating Tumor Cell (CTC) formation and dynamics in PCa bone-tropic metastasis cascade. The figure illustrates the progression of PCa metastasis, highlighting the formation and journey of CTCs from the primary tumor site to the formation of bone metastases. Primary Tumor Site: Prostate cancer cells originate in the primary tumor and enter the circulation as CTCs (Intravasation); Circulatory transit: CTCs travel through the bloodstream, encountering various selective pressures including differential microenvironmental factors, immune cell attacks, hemodynamic forces, etc.; CTC survival and interactions: CTCs interactions (e.g. With platelets) promote their survival; Extravasation: CTCs extravasate from the bloodstream (also known as diapedesis), guided by chemokines and other signaling molecules, towards the bone niche (where PMN formation is mediated by the CTC/tumor secretory factors); Bone metastasis formation: CTCs interact with osteoblasts (OB) and osteoclasts (OC), affecting bone homeostasis and leading to osteoblastic (common in PCa) lesions. Micrometastasis: DTC becomes small clusters of cells called micrometastases; Macrometastasis: further growth results in macrometastases, characterized by the presence of heterogeneous cells and larger metastatic tumor volume. The steps of metastasis sequence are indicated with the encircled numbers. Disseminated PCa cells, micro- and macro-metastatic tumor tissues influence bone remodeling through the secretion of growth factors (IGF-1, TGF-beta) via RANK/RANKL pathways, contributing to bone resorption and formation imbalances, leading to pathological bone fractures. The representative clinical images showing pathological bone fracture due to BM-PCa is depicted in Figure-1.

6.2. The role of pre-metastatic niche

The role of a pre-metastatic niche (PMN), is increasingly emphasized, which is seen as "fertile ground" that supports the survival and settlement of metastatic "seeds". This has been further explained and dissected in depth by several groups, leading to the latest and most supported suggestion that PMN formation itself is an intricate process involving several steps, such as 1) the migration of tumor-secreted extracellular vesicles (EVs) and non-vesicular tumor-secreted factors to the prospective metastatic organ, 2) the reprogramming of stromal cells in the metastatic target organ and 3) the recruitment of vascular endothelial growth factor receptor positive (VEGFR+) hematopoietic stem/progenitor cells (HSPC) that differentiate into myeloid-derived suppressor cells (MDSC) to exert immunosuppressive effects [152–155]. Intriguingly, some elements of the PMN formation are evidenced in clinical samples of PCa such as the neutrophil accumulation in blood and bones [156].

Based on quantitative mass spectrometry analysis, another study found that integrins, an important component in PMN and representing cell adhesion receptor proteins in exosomes, play a pivotal role in metastatic organotropism. It has been reported that integrins α6β4 and α6β1 are expressed by lung-tropic exosomes migrated to the lung niche, whereas the pancreatic-tropic exosomes expressing αvβ5 integrin preferred the liver niche [157,158]. However, the presence of tumor cell-derived exosomes expressing specific integrins that can facilitate CTCs migration specifically to the bone niche remains to be explored.

6.3. Role of bone marrow vasculature

Malignant circulating cells of PCa preferably invade and proliferate in the bones of the axial skeleton, such as the spine (lumbar rather than the thoracic or cervical vertebrae), ribs and pelvis where red bone marrow is most abundant [159]. This supports the hypothesis that the prominent route of metastatic tumor spread to bone is hematogenous [160]. The vascular network of red bone marrow consists of arterioles (providing oxygen and nutrients) and an intricately intertwined reticulation of sinusoidal venules that facilitates the movement of hematopoietic cell derivatives in and out of the blood circulation [161–163]. The unique architecture of the sinusoidal venules is characterized by the presence of fenestrations with an incomplete basement membrane and a discontinuous vascular epithelium for the facilitation of blood cells trafficking [164,165]. From a biomechanical perspective, these physical attributes of the bone marrow sinusoidal vasculature provide a suitable microenvironment for a potential CTC arriving in this niche. Firstly, the

pervasive fenestrations on the sinusoidal walls could help in the anchorage of CTCs on the luminal side. Secondly, the presence of a discontinuous or an incomplete basement membrane could make the extravasation step easier for CTCs. Finally, the unique discontinuous organization of the vascular endothelium of sinusoids – synergistically with the high deformability of the tumor cells – could further facilitate the extravasation of CTCs into the bone niche.

There is a strong possibility that the dormant DTCs at the preferred metastatic sites can become quiescent with the help of local micro environment and other DTCs at non-preferred metastatic sites eventually die due to the non-permissive microenvironment. Another possibility is that the intrinsic tumor cell adaptability at the preferred metastatic sites is higher (due to PMN formation) than at the non-preferred metastatic sites. Or both these factors could play a role in the development of a successful metastatic colonization. Either way, the ambiguity surrounding these questions warrant further explorative investigations to find plausible answers.

6.4. CTC interactions with bone and marrow cells

The potentially fatal feature of human PCa is metastases to bone, which follow an osteoblastic phenotype rather than osteolytic [166]. This characteristic of PCa-BM implies distinct interactions between PCa cells and various cell types in the bone microenvironment, such as osteoblasts, osteoclasts, adipocytes, fibroblasts, and endothelial cells. An interesting report has shown that the RNA cargo within the PCa-derived extracellular vesicles is enriched in genes related to cell surface signaling, cell-cell interaction, and protein translation. This corresponds to increased expression of the same factors in the osteoblasts, which may contribute to the communication between PCa cells and bone cells [167]. In addition, a proposed vicious cycle between PCa cells and bone cells involves soluble factors such as matrix metalloproteinases (MMPs), stem and progenitor cell chemokines - including stromal derived factor-1 (SDF-1) and fibroblast growth factor (FGF), TGF-β1, connective tissue growth factor (CTGF), and others [168–170], serving as key mediators of communication among cancer cells, host bone cells, and the surrounding environment [171].

6.5. Osteomimicry

Although controversial from a cause-and-effect perspective, another important property of PCa cells in the bone metastatic niche is osteomimicry. Osteomimicry refers to the PCa cells' capability to express specific bone proteins like osteocalcin, osteopontin, and bone sialoprotein, potentially promoting cancer cells growth and survival at preferred skeletal locations [172,173]. Moreover, cyclic AMP was evidenced to be a robust stimulator of the protein kinase A signaling pathway, which regulates osteomimicry exhibited by PCa cells [173]. The soluble factor β2 microglobulin (β2M), secreted by PCa, bone, and inflammatory cells alike, plays a key regulatory role in promoting the growth of PCa within the bone microenvironment. Experiments with overexpression of β2M in human PCa cells have demonstrated increased angiogenesis and rapid tumor proliferation, specifically within the bone niche. These findings suggest that β2M functions as a potent regulatory factor influencing PCa cell growth and acts as a crucial signaling molecule orchestrating the intricate interplay between PCa and bone cells [174]. Another study found that certain proteins like the secreted frizzled related protein 2 (SFRP2) overexpression can also induce an osteoblast-like phenotype in PCa cells, enhancing the Osteomimicry [175]. This ability to mimic bone cells intensifies as cancer cells acquire increased malignancy potential in bone and visceral organs, emphasizing that further research is required to identify the adaptive genetic fine-tuning in PCa cells that enables osteomimicry.

6.6. Acquired mechanical compliance

During invasion, migration, intra/extravasation, and metastatic colonization, cancer cells persistently interact with the surrounding cells and micro-environment, undergoing mechanical deformations as well as developing adaptive cellular-phenotypic and molecular responses during the process. Thus, the enhanced mechanical compliance of cancer cells is suggested to play a critical role in metastatic progression [176]. Additionally, it has been previously reported that non-palpable tumors are biologically less aggressive than palpable ones, indirectly suggesting that tissue stiffness indeed has a role in tumor aggressiveness [177]. Since palpability of PCa is directly correlated to tissue stiffness, studies have been carried out to identify the differential elastic modulus (E) of tumor tissues and corresponding normal tissues. Focusing on the metastasis cascade of PCa from a mechanistic point of view, it is noteworthy that PCa cells initially developed in the prostate is growing/infiltrating on a rather soft substrate, i.e., the soft glandular tissues of the prostate, while the cancerous tissue may become stiffer exhibiting a higher elastic modulus (Young's modulus: denoted as E) value. In a study using atomic force microscopy (AFM) based indentation tests, the mean E for tumor and normal tissue regions of the prostate was found to be 24.1 ± 14.5 kPa and 17.0 ± 9.0 kPa, respectively. Moreover, tumors with Gleason score of 8 or more, and with tumor volume >5 cm^3 had higher E values than other tissues, implicating that advanced PCa leads to stiffening of the primary cancerous tissue [178]. These results are consistent with the higher Young's modulus observed in PCa tissues by compression loading [179] or shear wave elastography [180,181] compared to normal tissues or benign lesions. Contradictorily, a more recent AFM nanoindentation study demonstrated a reducing Young's modulus with progression of PCa, reporting a decrease in elasticity from benign prostatic hyperplasia (BPH) tissue to intermediate (Gleason score 6–7) and to high risk PCa (Gleason score 8–10) tissues [182]. While the consensus view is that most cancer cells become softer with aggressiveness, in vitro PCa cell-based experiments have shown a contradictory relationship between PCa cell resilience and metastatic potential. The study by Faria et al., investigated Young's modulus of cells derived from BPH tissue, bone metastatic (PC3) and lymph-node metastatic (LNCaP) PCa tissue using AFM and Hertz model. The Young's modulus was the highest for benign prostate hyperplasia (BPH) cells, lower in the highly invasive PC-3 cell line and the lowest in the less aggressive LNCaP cells (LNCaP: 287 ± 52 N m^{-2}, PC-3: 1401 ± 162 N m^{-2} and BPH: 2797 ± 491 N m^{-2}) [183]. Similarly, other studies have shown that the more aggressive PC3 cells are significantly stiffer than the less aggressive LNCaP cells [184] but significantly softer than normal prostate tissue cells [182]. Another investigation by Pogoda et al., focused on discerning the nanomechanical properties of cell lines derived from normal prostate gland (RWPE-1), primary malignant prostate cancer (22RW1), lymph node metastatic (LNCaP), brain metastatic (Du145) and bone metastatic (PC3) sites. This study also confirmed a reduced cellular stiffness of malignant cells compared to normal or benign cells, but higher Young's modulus was correlated with aggressiveness of the PCa cell type (RWPE1 > 22Rv1 > PC3 > Du145 > LNCaP) [185].

One of the major differences between these mechanical studies is that the in vitro studies are performed on 2D cell culture models, while PCa patient tissues represent the actual pathology in 3D - clinical form. The distinguishing hallmark of an effective cancer cell could lie in its remarkable biophysical capacity to rapidly adapt to the constraints of various microenvironments throughout its progression and to continuously reshape its characteristics in response to external signals - known as plasticity. Hence, the tumor cells must face and overcome biophysical hurdles that they may encounter throughout the stages of metastasis, such as ECM stiffness in different microenvironments: the stiffness of primary tumor tissue itself followed by that of the environment near the primary tumor site and the invasion sites through the basement membrane during intra and extravasation. Once the tumor cells become CTCs, there are further obstacles such as the physical constraints of

microvasculature and hemodynamic shear stress [186]. Despite the controversies, the common consensus is that cancer cells indeed possess an enhanced mechanical compliance as compared with the benign or normal cells in order to form successful metastasis.

The stiffness at the metastatic niche is completely different from the stiffness of the primary tumor niche. The tissue stiffness of bone is of the order of ~10 GPa, whereas that of the bone marrow, where successfully extravasated PCa cells are initially arrived is in the range 0.5–24.7 kPa, as shown in a porcine model system that most closely resembles human anatomy [187]. It is important to note that the mechanical properties of bone marrow are still relatively poorly characterized. The properties of metastatic cancer cells also depend, among many other factors, on the composition and anatomic location of the tumor, as well as the age, sex and bone density of the patient [188–190]. Furthermore, the stiffness of tumor ECM is generally much higher than that of healthy tissues (tens of kilopascals vs. hundreds of pascals) [191], which correlates with changes in the metastatic potential of cells within the tumor [192]. Owing to the fact that PCa is common among older men with a median age of 66 years at diagnosis [6], the role of aging associated molecular signaling and biophysical signatures of the bone in the PCa metastatic pattern with bone-tropism demands extensive further research.

7. Conclusions and future directions

Although significant progress has been made in identifying the factors associated with the bone metastatic niche in recent years, there remains a lack of clarity in understanding how the CTCs and their adaptive mechanisms contribute to the organotropism exhibited by PCa. The lack of causal analysis of the correlation between observed metastatic niche properties and the tumor cell behavior at the metastatic niche also contribute to the ambiguity. Addressing these knowledge gaps could provide valuable insights into metastatic disease progression and organotropism.

While the inherent challenges posed by CTCs such as their short lifespan in circulation and high level of heterogeneity are indeed formidable, they could simultaneously provide us the required information to target them therapeutically. This in turn suggest that there are challenges as well as prospects associated with CTCs in the context of PCa-BM, that warrants the attention of basic researchers and clinicians alike (Fig. 4).

CTCs could serve as key clinical indicators of bone-tropism in PCa, as studies suggest that the presence of specific surface markers such as CXCR4 can predispose the CTCs to migrate to the bone niche [193]. Characterizing the CTCs and monitoring the CTC phenotypes in blood samples, at regular intervals may help identify the high-risk patients who are more likely to develop bone metastases in the future. Identification and precise therapeutic targeting of the bone-tropic CTCs could prevent their secondary homing and colonization, offering a potential strategy to reduce BM [194]. In an alternative approach, targeting CTC-secreted EVs or disrupting their cargo may prevent the establishment of a supportive niche for PCa cells in the bone.

Identification of bone microenvironment specific cellular adaptations of the CTCs, DTCs dormancy cues in bone niche, and osteomimicry of DTCs calls for further explorative investigations to identify the targetable molecular pathways that can be used for development of therapeutic strategies for clinical management of PCa-BM. In addition, by analyzing the age-associated bone microenvironment markers, molecular signaling and biophysical signatures, and understanding their

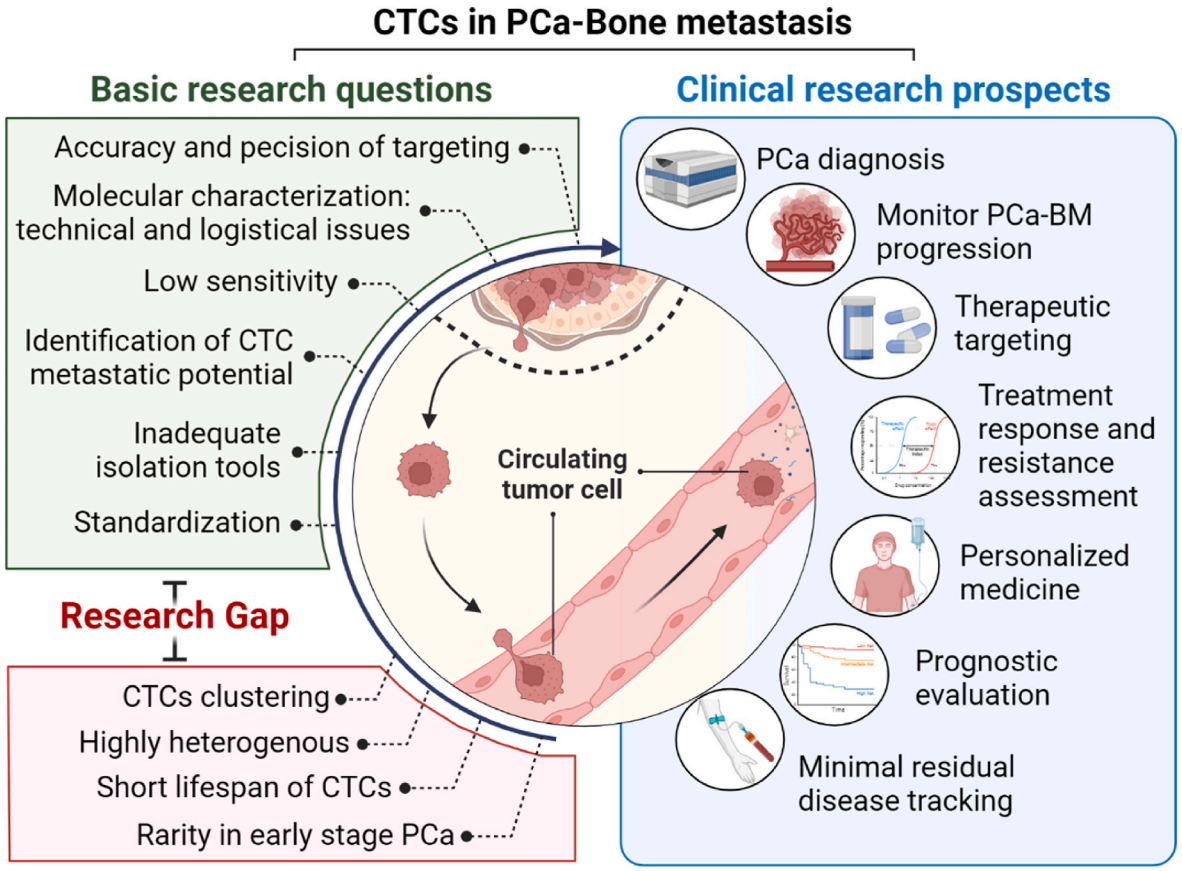

Fig. 4. The challenges and prospects of CTCs in PCa-BM. The inherent challenges such as heterogeneity, rarity and limited lifespan in the bloodstream, presented by CTCs can be addressed by a combinatorial approach of basic and clinical research. Basic research is required to refine the tools and techniques for isolation and characterization of CTCs, and simultaneously, robust clinical involvement and experimentation are necessary to assess the efficacy of CTCs-based methods in various aspects of PCa and bone PCa-BM management – ranging from the initial diagnosis to minimal residual disease tracking.

potential role in chemotaxis of CTCs towards the bone niche, we may be in a better position to predict the likelihood of PCa-BM progression more accurately.

Our current understanding of how tumor cells, especially CTCs, perceive biochemical and biomechanical stimuli is mainly based on studying the microenvironment of the primary tumor (e.g., extravasation) and the circulation of CTCs in the blood and lymphatic vascular systems. With the older age of patients and the associated bone-cellular and microenvironmental changes taken into consideration, future investigations encompassing not just the mechanical microenvironment but also the composition of the mineralized and marrow tissues, will help to elucidate the impact of both molecular signaling and biomechanical factors on the progression of metastatic PCa to the bone tissues. In addition, understanding the differential properties of CTCs in the patients, and molecular dissection of PCa organotropism could potentially pave the way for development of targeted therapies for personalized cancer medicine focused on the prevention of BM.

In retrospect, for PCa management (as for many other pathologies of the elderly), the question of who is being treated is equally important as what is being treated and how. Considering the older age of majority of the patients, it is essential that the treatment does not cause more harm than the pathology itself. Therefore, it is crucial to focus research efforts on metastatic tumor progression and organotropism to therapeutically target CTCs and DTCs, prevent them from either reaching a potential metastatic site or surviving in the metastatic niche, and prevent the formation of micrometastases formation at the onset of metastatic colonization.

CRediT authorship contribution statement

Gayathri K. Guruvayurappan: Writing – review & editing, Writing – original draft, Visualization, Software, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Tina Frankenbach-Désor:** Writing – review & editing, Visualization, Data curation. **Markus Laubach:** Writing – review & editing, Visualization, Formal analysis, Data curation. **Alexander Klein:** Visualization, Data curation. **Michael von Bergwelt-Baildon:** Writing – review & editing. **Monica Cusan:** Writing – review & editing. **Attila Aszodi:** Writing – review & editing. **Boris M. Holzapfel:** Writing – review & editing. **Wolfgang Böcker:** Writing – review & editing. **Susanne Mayer-Wagner:** Writing – review & editing, Supervision, Formal analysis.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviations

2D: Two Dimensional
3D: Three Dimensional
ADT: Androgen Deprivation Therapy
AFM: Atomic Force Microscopy
AKT: Serine/Threonine Kinase
Axl: AXL receptor tyrosine kinase
BCa: Breast Cancer
BM: Basement Membrane
BM-PCa: Bone Metastatic Prostate Cancer
BPH: Benign Prostate Hyperplasia
c-MET: Tyrosine-Protein Kinase MET
CAFs: Cancer Associated Fibroblasts
CD44: CD44 Molecule (IN Blood Group)
CLPC: Clinically Localized Prostate Cancer
CRPC: Castration Resistant Prostate Cancer
CT: Computed Tomography
CTCs: Circulating Tumor Cells
CTGF: Connective Tissue Growth Factor
CXCR3: C-X-C Motif Chemokine Receptor 3
CXCR4: C-X-C Motif Chemokine Receptor 4
DER: Digital Rectal Examination
DTCs: Disseminated Tumor Cells
E: Young's modulus
ECM: Extra Cellular Matrix
EGFR: Epidermal Growth Factor Receptor
EMT: Epithelial-Mesenchymal Transition
ERK: Extracellular Signal-Regulated Kinase
FDA: Food and Drug Administration
FGF: Fibroblast Growth Factor
FGFR: Fibroblast Growth Factor Receptor
FSS: Fluid Shear Stress
FT-IR: Fourier-Transform Infrared
FZD: Frizzled
GPa: Giga Pascal
HSPC: Hematopoietic Stem/progenitor Cells
JNK: c-Jun N-terminal Kinase
KPa: Kilo Pascal
L3: Lumbar vertebral body
LOXL: Lysyl Oxidase Like
MDSC: Myeloid-Derived Suppressor Cells
MET: Mesenchymal to Epithelial Transition
MMPs: Matrix Metalloproteinases
MRI: Magnetic Resonance Imaging
mTOR: Mechanistic Target of Rapamycin Kinase
NK Cells: Natural Killer Cells
PCa: Prostate Cancer
PCA3: Prostate Cancer Antigen 3
PI3K: Phosphatidylinositol-4,5-bisphosphate 3-kinase
PMN: Pre-Metastatic Niche
PORCN: Porcupine O-Acyltransferase
PSA: Prostate Specific Antigen
RANKL: Receptor Activation of Nuclear Factor-B Ligand
RhoA: Ras homolog family member A
RNA: Ribonucleic Acid
ROCK: Rho-associated, coiled-coil-containing protein kinase
RP: Radical Prostatectomy
RS: Raman Spectroscopy
SDF-1: Stromal Derived Factor-1
SHH: Sonic Hedgehog
SMO: Smoothened
SPOCK1: SPARC (osteonectin), cwcv and kazal like domains proteoglycan 1
STAT3: Signal Transducer and Activator of Transcription 3
T10: Thoracic vertebral body 10
TAZ: WW domain-containing transcription regulator protein 1
TGFβ: Transforming Growth Factor β
TMPRSS2: ERG: Transmembrane Protease Serine 2: v-ets Erythroblastosis Virus E26 Oncogene Homolog
TNM: Tumor, Node, Metastasis
Treg: Regulatory T Cells
UK: United Kingdom
VEGFR: Vascular Endothelial Growth Factor Receptor
WNT: Wingless-related integration site
WW: Watchful Waiting
YAP: Yes-associated protein
β2M: β2 Microglobulin