Cancer Letters 530 (2022) 156–169

Contents lists available at ScienceDirect

Cancer Letters

journal homepage: www.elsevier.com/locate/canlet

Original Articles

Tumor microenvironment mechanisms and bone metastatic disease progression of prostate cancer

Juening Kang [a], Federico La Manna [a], Francesco Bonollo [a], Natalie Sampson [b], Ian L. Alberts [c], Clemens Mingels [c], Ali Afshar-Oromieh [c], George N. Thalmann [a,d], Sofia Karkampouna [a,*]

[a] Department for BioMedical Research, Urology Research Laboratory, University of Bern, Bern, Switzerland
[b] Department of Urology, Medical University of Innsbruck, Innsbruck, Austria
[c] Department of Nuclear Medicine, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland
[d] Department of Urology, Inselspital, Bern University Hospital, Bern, Switzerland

ARTICLE INFO

Keywords:
Extracellular matrix
Bone metastasis
Genetically engineered mouse models
Premetastatic niche
Stroma
PET/CT-imaging
Nuclear medicine therapy

ABSTRACT

During disease progression from primary towards metastatic prostate cancer (PCa), and in particular bone metastases, the tumor microenvironment (TME) evolves in parallel with the cancer clones, altering extracellular matrix composition (ECM), vasculature architecture, and recruiting specialized tumor-supporting cells that favor tumor spread and colonization at distant sites. We introduce the clinical profile of advanced metastatic PCa in terms of common genetic alterations. Findings from recently developed models of PCa metastatic spread are discussed, focusing mainly on the role of the TME (mainly matrix and fibroblast cell types), at distinct stages: premetastatic niche orchestrated by the primary tumor towards the metastatic site and bone metastasis. We report evidence of premetastatic niche formation, such as the mechanisms of distant site conditioning by extracellular vesicles, chemokines and other tumor-derived mechanisms, including altered cancer cell-ECM interactions. Furthermore, evidence supporting the similarities of stroma alterations among the primary PCa and bone metastasis, and contribution of TME to androgen deprivation therapy resistance are also discussed. We summarize the available bone metastasis transgenic mouse models of PCa from a perspective of pro-metastatic TME alterations during disease progression and give an update on the current diagnostic and therapeutic radiological strategies for bone metastasis clinical management.

1. Introduction

Prostate cancer (PCa) is the second most common type of cancer among men worldwide and one of the leading causes of cancer-related death [1]. While most PCa patients will receive a curative therapy, approximately one third of cases progress to advanced metastatic PCa, which represents a life-limiting stage of disease [2–4]. Although the overall incidence of PCa has declined, the percentage of patients with metastatic disease at diagnosis has increased over the last decade [5]. A number of complex factors may explain this finding, including decreased rates of screening as a result of the U.S. Preventive Services Task Force (USPSTF) recommendation against prostate specific antigen (PSA) screening for PCa, as well as improvements in imaging modalities and the detection of metastatic disease [6]. Metastatic spread is a complex biological phenomenon, that is associated with advanced stage disease, especially when PCa has become hormone independent.

Anti-androgen therapies remain standard-of-care in the clinical management of advanced PCa patients, since most PCa cells, like normal prostate tissue, depend on androgen receptor (AR) signaling for development and survival. Despite the initial effectiveness of this approach, a large number of patients with advanced PCa receiving anti-androgen therapies will develop castration-resistant PCa (CRPC) or treatment-induced neuroendocrine PCa (tNEPC), leading to poorer prognosis [7].

In addition, a large proportion of advanced PCa patients is diagnosed with multiple metastases, most frequently occurring to the lymph nodes adjacent to the prostate, but also to distant organs such as the axial bones (detected in 84% of metastatic patients), distant lymph nodes (11%), liver (10%), lungs (7%) and brain (3%) [8,9]. Visceral metastases were found predominantly in patients with CRPC and are associated with the transition to neuroendocrine phenotypes as well as an overall poorer outcome. The most prevalent locations of visceral metastases are the liver and lungs. However, no clear pattern of visceral metastatic spread emerges when histopathological or molecular features of the

* Corresponding author.
E-mail address: sofia.karkampouna@dbmr.unibe.ch (S. Karkampouna).

https://doi.org/10.1016/j.canlet.2022.01.015
Received 3 May 2021; Received in revised form 2 January 2022; Accepted 13 January 2022
Available online 17 January 2022

List of abbreviations: full name

α-SMA	α- smooth muscle actin
ADT	Androgen-deprivation therapy
AR	Androgen Receptor
BSP	Bone sialoprotein
CAFs	Cancer-associated fibroblasts
CNAs	Copy number alterations
CRPC	Castration-resistant prostate cancer
CTGF	Connective tissue growth factor
CXCL	Chemokine (C-X-C motif) ligand
CXCR	Chemokine (C-X-C motif) receptor
ECM	Extracellular matrix
ECs	Endothelial cells
ETS	E26 transformation specific
EVs	Extracellular vesicles
FGFs	Fibroblast growth factors
FN	Fibronectin
FSP-1 (also known as S100A4)	Fibroblast-specific protein-1
GEMMs	Genetically engineered mouse models
HGF	Hepatocyte growth factor
IGF	Insulin-like growth factor
ILs	Interleukins
MCP-1	Monocyte chemoattractant protein-1
M-CSF	Macrophage- colony-stimulating factor
MFBs	Myofibroblasts
MMPs	Matrix metalloproteinases
NEPC	Neuroendocrine PCa
OB-BMST	Osteoblastic bone metastasis-associated stroma transcriptome
OPN	Osteopontin
PCa	Prostate cancer
PDGF	Platelet-derived growth factor
PET/CT	Positron emission and computed tomography
PGE_2	Prostaglandin E_2
PIN	Prostatic intraepithelial neoplasia
PSA	Prostate-specific antigen
PSMA	Prostate specific membrane antigen
RANK (L)	Receptor activator of nuclear factor kappa-B (ligand)
scRNA-seq	Single-cell RNA sequencing
SPECT	Single photon emission computed tomography
TAMs	Tumor-associated macrophages
TGF-β	Transforming growth factor -β
TGFβRII	TGF-β receptor type II
TME	Tumor microenvironment
TNC	Tenascin C
TNF-α	Tumor necrosis factor- α
TRAMP	Transgenic adenocarcinoma mouse model
tNEPC	treatment-induced neuroendocrine PCa
VEGF	Vascular endothelial growth factor

primary cancer are considered [10,11]. Whilst PCa rarely metastasizes to the brain, the incidence of brain metastases has increased recently, particularly in NEPC patients [12,13].

Among PCa distant metastases, bone is the most common site of colonization with approximately 70% of patients with advanced PCa diagnosed with bone metastases [14]. In contrast to the prevalence of osteolytic lesions in breast or lung cancers, the majority of PCa-related bone metastases comprise osteoblastic lesions that are characterized by excessive bone formation. In NEPC, where bone metastases are less common than visceral metastases, mixed lytic and blastic phenotypes are observed [15].

The diagnosis and treatment of bone metastases in PCa has been revolutionized in recent years with the advent of positron emission tomography/computed tomography (PET/CT), first with non-specific tracers such as Na[18F]F and choline, and recently with prostate specific membrane antigen (PSMA)-radioligands [16]. The early and precise identification of metastatic disease with PSMA-radioligands in both primary PCa and in biochemical recurrence allows for more accurate staging of disease and may be of assistance in the management of oligometastatic disease. The latter approach affords a theragnostic treatment strategy, where therapeutic PSMA-radioligands can also be used, providing a therapeutic option to patients who have exhausted all other treatment strategies. The high propensity of PCa to metastasize to the bone has been attributed to several factors, however the molecular mechanisms of bone metastasis formation have not been fully elucidated. Exosomes and microRNAs secreted by the primary tumor have been shown to exert stimulatory effects on the establishment of premetastatic niches and on bone remodeling, a finding further confirmed in PCa by recent studies [17].

In this review, we outline the role of the bone microenvironment and extracellular matrix (ECM) in bone metastasis, as well as the properties that facilitate tumor spread, colonization at distant sites, and preparation of the premetastatic bone niches (Fig. 1). We critically discuss the available diagnostic and therapeutic radiological strategies and the microenvironment-directed treatment options for PCa bone metastasis. Furthermore, the landscape of genetic alterations of advanced human PCa are discussed and an overview of the available transgenic mouse

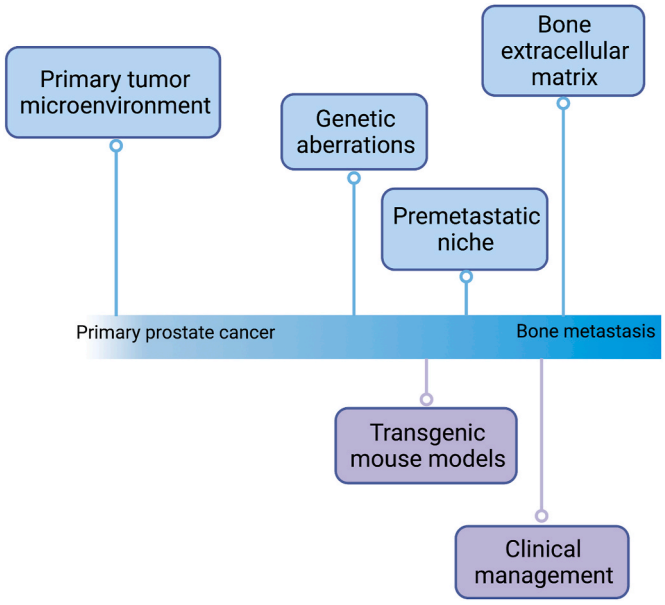

Fig. 1. Outline of tumor microenvironment implications in PCa bone metastasis progression, available models and clinical management.
Following the evolution of primary prostate cancer (PCa) to advanced metastatic progression (*blue*), the commonalities in tumor-promoting mechanisms provided by the microenvironment among primary, premetastatic niche and the bone extracellular matrix are compared. The most frequent genetic aberrations in advanced disease and in particular bone metastatic stage, along with the current-state-of-the-art imaging based clinical management of PCa bone metastasis are presented. The available bone metastasis transgenic mouse models are summarized from the perspective of progressive stroma alterations that occur within the orthotopic prostate tumor prior to metastasis.

models of bone metastatic PCa is provided, with particular focus on tumor microenvironment (TME) alterations.

2. Genetic alterations in advanced PCa and bone metastasis

Genetic alterations in PCa progression and metastasis have been widely recognized. Germline mutations in DNA damage repair genes (such as *BRCA2*, *CHEK2* and *ATM*) and in DNA mismatch repair genes (such as *MLH1*, *MSH2* and *PMS2*) have been noted to drive the development of PCa, but also somatic mutations are generally related to high incidence of metastatic disease and differential treatment response [18,30]. However, in contrast to most tumors that accumulate genomic changes through point mutations and short insertions/deletions, the primary oncogenic drivers of PCa are chromosomal rearrangements and extensive copy number alterations (CNAs) [19–21].

Compared to cancer cells in the primary tumor, metastatic cancer cells frequently show a higher degree of genomic plasticity, as reflected by an overall higher rate of mutation accumulation [22,23]. Overall aneuploidy and CNAs were shown to correlate with progression and with a more aggressive disease and recurrent genomic lesions have been found at the metastatic sites, supporting the notion of metastasis-enabling genetic hits. In particular, subclonal events are frequently associated with the acquisition of additional malignant features and can be traced to metastatic lesions [24,25]. The evolution of PCa to metastatic CRPC (mCRPC) can be associated with genomic changes that are traceable in most cases, to a few defined molecular clusters that include mutations in *SPOP*, *FOXA1*, and *TP53* as well as CNAs in genomic loci that include genes such as *BRCA2*, *PTEN*, and *CHD1*, interestingly, mutations in *AR*, *CDK12*, *ZFHX3*, *RB1*, *GNAS* and *OR5L1* were found exclusively in metastatic sites [21,26,27] (Table 1). Key mutations at this stage of the disease involve mechanisms to resist androgen deprivation and drug treatments [21,28]. Other common clonal, metastasis-enabling genomic lesions include mutations in *MYC* and *FOXA1* loci [28–30]. In fact, the genomic alterations most commonly observed in adenomatous CRPC (Adeno-CRPC) are associated with treatment resistance to AR-directed therapies [21,23,31]. However, no correlation has emerged so far between specific subsets of clonal or subclonal genomic alterations and metastasis tropism or resistance to chemotherapy [32–34].

The spectrum of genomic alterations is similar between adeno-CRPC and NEPC, with over 30% of the genome displaying aberrations and a higher mutation rate compared to localized PCa. However, the AR locus and AR signaling are less affected in NEPC compared to adeno-CRPC. Evidence suggests that decreased AR signaling is associated with new genomic and epigenomic drivers that support the evolution of CRPC to NEPC [31]. Genomic alterations directly associated to NEPC are *RB1* loss and *NMYC* amplification. *RB1* loss is highly enriched in NEPC and is frequently associated with *TP53* loss or loss-of-function mutations (*RB1* and *TP53* loss are detected in about 53% of NEPC [31,35]). Loss of *TP53* and, mostly, of *RB1* can shift the tumor from AR-dependent to AR-indifferent state, which is reflected by decreased expression of prostate epithelial markers such as PSA and NKX3.1 [36,37].

Notably, genetic alterations also act in concert with the TME response, leading to the development of PCa to a highly aggressive stage. For instance, depletion of *PTEN* is associated with stromogenic carcinoma [38] and with enhanced expression of CXCL molecules, followed by migration of monocytes/macrophages and myeloid cells to TME via CXCR1/2-mediated chemotaxis, which subsequently promotes tumor progression [39]. *SPOP* mutations are associated with limited $CD3^+$ and $CD8^+$ T cell infiltration, thus promoting immunosuppressive TME [40]. Loss of tumor suppressor genes *BRCA2, CHD1* and *RB1* leads to an immunogenic microenvironment indicative by elevated PD-L1 expression and highly T cell-infiltrated regions [41].

In the process of PCa bone metastasis, mutations in the E26 transformation specific (*ETS*) family (*ERG, ETV1, ETV4* or *ETV5*) are common, and one of the most frequent and well- characterized alterations in PCa; *TMPRSS2-ERG* gene fusions have been shown to increase bone tropism and metastatic development in PCa by regulating the transcription of cell migration/adhesion related genes, which is also related to bone physiology [42]. Evidence also suggests that *KRas* mutations in PCa increase the susceptibility to bone metastasis through CD24a expression, and that loss of *FBXL4* is a genetic driver event in PCa progression to bone metastasis, making these genes potential biomarkers for predicting PCa progression and outcome [43,44]. Although there is no clear evidence that aberrations of *AR*, *TP53*, *PTEN* and *FOXA1* could drive PCa bone metastasis, since they have been detected in a large number of bone metastatic biopsies, we can still speculate that they play a driving role in the process of bone metastasis, and deserve further study [45].

Table 1
Genetic alterations related to advanced metastatic PCa.

Gene	Alteration	Stages	Reference
AR	Amplification, point mutations	mCRPC	[21]
SPOP	Point mutations	mCRPC	[21]
FOXA1	Point mutations	mCRPC	[21]
TP53	Deletion, point mutations	mCRPC, NEPC	[21,31]
PTEN	Deletion, point mutations	mCRPC	[21,23]
CHD1	Deletion, point mutations	mCRPC	[21]
RB1	Deletion	mCRPC, NEPC	[23,31,35]
BRCA2	Deletion, point mutations	mCRPC	[27]
ZFHX3	Deletion	mCRPC	[26]
GNAS	Point mutations	mCRPC	[21]
OR5L1	CNAs	mCRPC	[26]
CDK12	CNAs	mCRPC	[26]
MYC	Amplification	mCRPC	[27]
TMPRSS2-ERG	Gene fusions	mCRPC, Bone metastasis	[42]
KRas	Point mutations	Bone metastasis	[43]
FBXL4	Deletion	Bone metastasis	[44]

3. Role of the tumor microenvironment during PCa progression to bone metastasis

Several studies have shown that the TME (also termed reactive stroma) surrounding the tumor plays a key role in the pathogenesis and progression of PCa [48]. The TME consists of different non-epithelial cell types including fibroblasts, immune cells, and endothelial cells (ECs), as well as ECM proteins such as collagen, laminin, fibronectin and hyaluronate. All these elements interact with tumor cells through a complex network of cell membrane receptors, cytokines, chemokines, growth factors and matrix remodeling enzymes [49] (Fig. 2A). Cancer-associated fibroblasts (CAFs) are the most abundant component of primary PCa TME [50], differently from the normal prostate stroma, where smooth muscle cells are predominant [51]. Multiple studies have demonstrated the PCa-promoting properties of CAFs, e.g. increasing tumorigenic potential, promoting androgen insensitivity and favoring the metastatic process [52,53]. During prostate tumorigenesis, CAFs undergo molecular and phenotypic changes such as transition from fibroblast to myofibroblast (MFBs) [51], which are characterized by acquisition of a contractile phenotype and co-expression of vimentin and α-smooth muscle actin (α-SMA), and this differs from normal prostate fibroblasts which only express vimentin [54]. These 'MFB-like' CAFs induce ECM remodeling that promotes PCa cell invasiveness and induces the release of ECM-bound growth factors (e.g. TGF-β, FGFs and HGF), thereby sustaining tumor cell proliferation [55].

Normal prostate fibroblasts are generally thought to confer anti-tumorigenic effects [56], or even subtypes of smooth muscle cells and fibroblasts within tumors may decrease tumor progression, (e.g. those with active Hedgehog signaling) [57]. Thus, a high degree of fibroblast heterogeneity and plasticity exists that is now starting to be elucidated by recent studies. For instance, single cell RNA-sequencing (scRNA-seq)

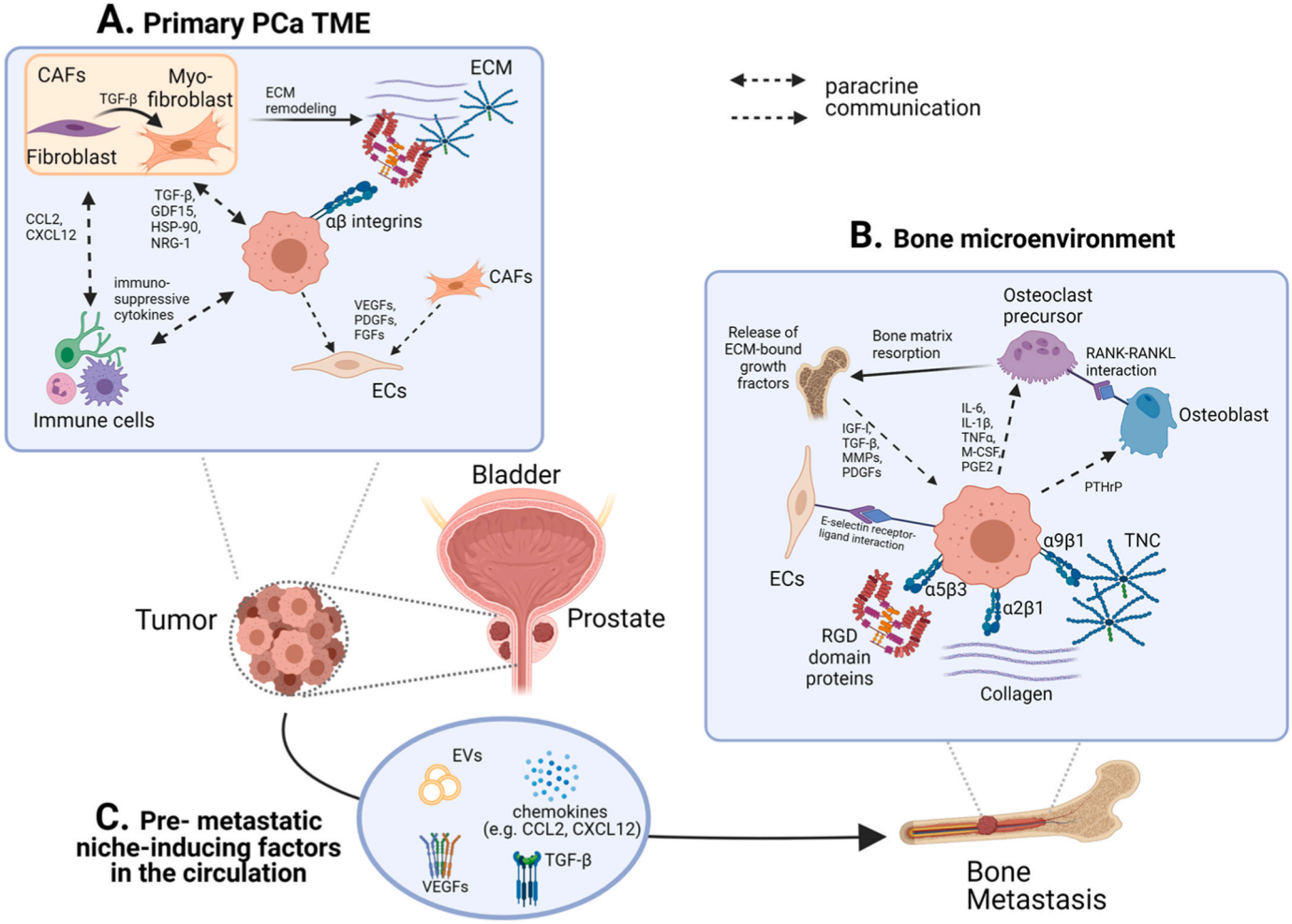

Fig. 2. Cellular and molecular interactions of prostate tumor in primary, pre-metastatic and bone metastasis microenvironment.
A. During primary PCa tumorigenesis and progression, the crosstalk among the TME components promotes tumor cell spread and colonization to distant sites. Cancer cells establish paracrine signaling interactions with cancer associated fibroblasts (CAFs), endothelial cells (ECs), and immune cells, by means of immune-modulatory cytokines (e.g. CCL2, CXCL12), growth factors (e.g. TGF-β, VEGF, GDF15), and other signaling molecules (e.g. NRG1).
In addition, TGF-β signaling promotes myo-fibroblastic features in CAFs, inducing ECM remodeling, and contributing to the recruitment of additional tumor-infiltrating cells. ECM components bind αβ-integrins on PCa cells, influencing cell adhesion and motility, and modulating intracellular signaling mechanisms.
B. PCa tumor cells and possibly also TME-derived components affect the activity of the bone microenvironment and other distant sites for metastatic colonization. PCa cells in the blood circulation interact with surface proteins on ECs (for instance through E-selectin ligand-receptor interaction), extravasating in the bone microenvironment. Afterwards, they adhere to bone ECM proteins (e.g. collagen, fibronectin, TNC), through the expression of αβ-integrins on their cell surface. In the bone microenvironment, PCa cells influence the crosstalk between osteoblasts and osteoclasts mediated by RANK-RANKL interaction through the secretion of PTHrP, and alter osteoclast activity through the secretion of cytokines such as IL-6, IL-1β and TNF-α. This results in bone matrix resorption, which leads to the release of ECM-bound growth factors that support tumor cell growth in the metastatic site. **C.** The formation of a 'pre-metastatic niche' in secondary organs is a long-term process that is initiated prior to the arrival of tumor cells and aims to induce tumor permissive changes such as vascular leakiness, ECM remodeling, and immune suppression. The formation of the 'pre-metastatic-niche' might be caused by signaling factors (such as interleukins, VEGFs and TGF-β) and extracellular vesicles (such as exosomes) secreted from the primary tumor. Scheme created with BioRender.com.

studies on normal and cancerous human prostate revealed heterogeneity among immune components, CAFs and endothelial cells in terms of genes involved in cell adhesion, ECM production and immune system regulation [58]. Three main CAF clusters have been identified that are characterized by a universal vimentin expression and unique expression patterns of MFB markers as α-SMA, FSP-1 and FAP [58].

The pro-tumorigenic properties of the TME result from a co-evolution process with cancer: the growth-limiting conditions associated with the TME (e.g. hypoxia, inflammation or exposure to carcinogens or chemotherapeutic drugs [59]) induce selective pressure that favors survival of tumor cells with more aggressive traits and stromal components that support their growth and distant spread [60–62]. Relying on the observation that the skeleton has an affinity for PCa cells, studies have shown that the microenvironment provided by bone is at least as important as the proliferating tumor cells [63] in promoting metastatic colonization and progression.

3.1. *Extracellular matrix in the bone metastasis microenvironment*

Bone microenvironment consists of a complex system of hematopoietic and mesenchymal cell types, vascular network, and bone ECM. As an important component of TME in the primary tumor (Fig. 2A), as well as in the in bone (Fig. 2B), ECM provides solid support for the growth and colonization of tumor cells. The bone ECM consists of multiple, highly organized proteins whose function is to generate and coordinate the maintenance of the structural function of the bone. The most abundant of these proteins are collagens and in particular collagen-I, which accounts for up to 90% of the organic content of the bone tissue and confers it fundamental mechanical properties [64].

In addition to diverse structural functions, the non-collagenous

proteins of bone ECM participate in the coordination of ECM deposition and diverse cellular functions [65] (Fig. 2B). They provide a reservoir of growth factors, including TGF-β, FGF, ILs, and PDGFs, that can in turn affect tumor growth. Of particular interest for the metastatic colonization of the bone microenvironment are ECM proteins containing RGD (Arg-Gly-Asp) domains, including fibronectin (FN), bone sialoprotein (BSP) and osteopontin (OPN) [66]. Integrin α5β3 on PCa cells can bind the RGD domain of ECM proteins, recruiting FAK and activating downstream signaling cascades that promote cancer cell survival and migration [67]. Similarly, interaction between collagen and integrin α2β1 promotes cytoskeletal rearrangements and PCa cell adhesion in bone metastasis [68]. The ECM glycoprotein Tenascin C (TNC), whose expression is absent in bone physiological conditions [69], also supports the establishment of PCa cells in the bone microenvironment. Secreted TNC acts as a local reservoir of growth factors and interacts with membrane-bound proteins such as integrins [70], to modulate cell adhesion and migration [69,71]. Its deposition in the bone metastatic niche promotes PCa cell homing to the bone, via interaction with α9β1 integrin on the tumor cell membrane [69]. Another adhesion mechanism of metastatic PCa cells to bone ECM may occur via CD44, which can bind both protein elements such as connective tissue growth factor (CTGF) as well as non-proteic elements like hyaluronate. This in turn triggers specific cellular programs and matrix remodeling, ultimately altering the physiological and biochemical network of the bone tissue [72].

Among the triggered biochemical programs, one of the most prominent is osteomimicry - the expression of bone-specific markers by PCa cells. This allows tumor cells to avoid immune detection within the bone microenvironment thereby increasing their survival [73]. PCa cells have been shown to degrade different types of ECM, a feature required for tissue colonization [74]. In the metastatic cascade model, bone-metastatic PCa cells acquire migratory capability and invasiveness, enter the blood or lymphatic circulation by reducing the adhesion to the cells and ECM of the TME and home to the bone marrow via multiple factors such as the CXCR4-CXCL12 axis and integrin interactions [75]. Once in the bone marrow, a pathological remodeling of the bone tissue may occur, involving metastatic cancer cells as well as bone-resident cells like osteoblasts, osteoclasts, and stromal cells [76].

Bone-engrafted cancer cells can stimulate osteoblasts to induce new bone formation by multiple mechanisms. Cancer cells secrete inflammatory cytokines such as IL-6, IL-1β, TNF-α, M-CSF or PGE_2 that recruit and activate both osteoprogenitor cells and osteoclast precursors. In a second phase, the bone matrix resorbed by osteoclasts will release additional trophic growth factors and matrix remodeling factors like IGF-I, TGF-β, MMPs and PDGF that can fuel bone formation and directly contribute to metastatic tumor growth. Cancer cells may also alter the RANKL/OPG balance by secreting these factors in the metastatic niche [77,195]. The net result will be a constant remodeling phase, in which functional bone tissue will be progressively replaced by disorganized bone deposition (Fig. 2B), further recruiting osteoclasts and releasing growth factors in a pathologic feedback loop that many authors have identified as the “vicious cycle” of bone metastasis [14,78–81]. Molecular events occurring during bone metastases have been extensively summarized by other recent reviews [82,83].

Most of our knowledge of PCa metastatic microenvironment comes from xenograft and transgenic animal models, which do not always recapitulate the mechanisms and the pathophysiology of human bone metastasis. Experimental models of bone metastasis are mainly intracardiac or intraosseous injection of human PCa cells that bypass the first stages of active metastatic spread (invasion and intravasation). Moreover, the bone microenvironment of mouse models is vastly different compared to humans and other large animals, in terms of structural aspects (e.g. collagen organisation), bone-derived stromal cells, and the blood vascular network [84]. The immunodeficient mouse models used in oncological studies have altered bone marrow composition as they lack multiple fully functional immune cell compartments and could have an impaired cytokine signaling network [85]. Overall, bone niche remodeling is a long-term process, fostered by the tumor cells long before their appearance at the bone site. Elucidation of these signals from primary towards secondary tumor sites is crucial for understanding the underlying mechanisms that occur early in the metastatic cascade.

3.2. Premetastatic niche formation and osteotropism

The existence of a premetastatic niche, which is defined as the formation of a permissive secondary microenvironment induced by tumor cells in preparation of their metastatic process, has been demonstrated in many cancer types [86]. This induction of a premetastatic niche, is mainly orchestrated by secreted factors and extracellular vesicles (EVs) from the primary tumor towards the distant microenvironment (Fig. 2C). Ultimately organ-specific metastatic patterns towards the most favorable niche for tumor growth, seem to take place for the selection of the premetastatic niche. Organ-specificity of metastasis is particularly valid for PCa and the occurrence of osteoblastic metastases [87]. This process is possibly due to a preference towards the hematopoietic and vascular niche [88], as exhibited in the stroma of osteoblastic PCa mouse xenografts [89]. In contrast, the stromal signature of osteolytic PCa metastases (PC-3 cell xenografts) is uniquely enriched in genes involved in vascular/axon guidance [90].

The metastatic pattern of the DU145 cell line (which was originally isolated from a brain metastasis) constitutes another paradigm of preferential premetastatic niche tropism that is dependent on signaling pathway activation [91]. For example DU145 cells exhibit differential organ tropism to brain or skeletal system, with Ras^{V12}, Ras^{V12S35}, and Ras^{V12C40} mutations leading to Raf/ERK-activation and brain metastasis, whereas activation of the RalGEF pathway (Ras^{V12} and Ras^{V12G37} mutations) change the ability of DU145 cells to grow in the murine bone microenvironment and lead to long bone metastasis formation [92].

Bone homing chemokines and other secreted factors, EVs, as well as osteomimicry of PCa are some of the mechanisms of premetastatic niche induction. PCa-derived exosomes are associated with and can promote tumor progression [93,94] by affecting proliferation and survival of cancer cells as well as altering the physiology of target tissues, as assessed in cell line xenografts and PCa patient plasma, seminal fluid or urine specimens. Secreted cytokines from primary PCa such as interleukins, bone morphogenetic proteins, VEGF, TGF-β and chemokines including monocyte chemoattractant protein-1 (MCP-1 or CCL2) and CXCL12 can cause endothelial cell and vessel remodeling and influence osteoblast activity [95–98]. Activation of osteoclast and osteoblast activity is a key step in facilitating tumor growth, as discussed in the previous section. Chemotactic signals from cells within the tumor and CAF-derived chemokines, such as CCL2, are responsible for recruitment of immune cells in the primary PCa, whereas CCL2 expression by bone marrow endothelial cells facilitates bone homing and metastatic growth [99–101]. Recent studies have shown that tumor-derived exosomes mediate cell-cell communication in osteoblastic bone metastasis. In particular, osteoblasts could be reprogrammed by PCa-shed exosomes, to support PCa cells homing and local growth [102]. Human bone marrow stromal cells can take up PCa cell-derived exosomes, which leads to alterations in their transcriptome and intracellular signaling cascades in a manner that favors cancer cell metastasis [103]. Within the bone metastasis, tumor-derived exosomes can induce osteogenic differentiation of the local mesenchymal cell pool, while osteoblast-derived exosomes may regulate cancer cell proliferation in the metastatic microenvironment [104,105].

A recent study analyzed the impact of tumor-derived exosomes from enzalutamide-resistant models on recipient cells in premetastatic bone marrow samples. Bone marrow myeloid cells took up EVs by a cholesterol-mediated route, increased NF-kB signaling and osteoclast activity in an intracardiac bone metastasis experimental model of enzalutamide-resistant PCa cells [106]. Tumor exosomes expressing specific organotropic integrins were shown to directly migrate to target

sites as shown in PCa and other cancers [107]. The presence of specific integrins at the PCa-bone marrow interface has been reviewed by Peinado et al. [86]. Exosomes secreted under hypoxia modulate matrix metalloproteases in the premetastatic site [108] and exosomal pyruvate kinase promotes formation of the bone premetastatic niche [109]. In lymph nodes of a patient with localized PCa, T cells were found to express PSA following the uptake of tumor-derived exosomes and prior to any detectable metastatic lesion, possibly identifying a mechanism of immune tolerance induction [58].

3.3. Similarities of PCa-induced stromal changes in the bone and the premetastatic prostate

Normal and malignant prostate cells show osteoinductive properties affecting both osteoblasts and osteoclasts [110]. Increasing evidence indicate that bone-specific feature acquisition by either cancer cells or their associated TME components may be initiated even prior to metastasis. scRNA-seq identified a cluster of tumor associated macrophages (TAMs) with enriched osteoclast-related signatures (e.g. mineral absorption), both in CRPC and in primary tumors, indicating TME remodeling also in early onset disease [58]. Bone remodeling, osteoblast and immune-related pathways were enriched in the stroma of high Gleason score primary PCa cases [111]. The osteoblastic bone metastatic, CRPC-derived PDX LAPC9 tumor induces bone-specific transcriptional changes of the infiltrating mouse stromal component in subcutaneous PDX tumors [71]. When compared to BM18, an androgen-sensitive bone metastatic PDX model, the stromal cells from LAPC9 subcutaneous tumors showed an enrichment for genes involved in osteoclast differentiation and chemokine pathway compared to those from BM18 [71]. This suggests the existence of an osteomimetic microenvironment induced by prostate tumor cells.

Additional evidence of the generation of an osteomimetic microenvironment was derived from VCaP and C4–2B intraosseous xenograft studies that identified a specific PCa osteoblastic bone metastasis-associated stroma transcriptome (OB-BMST) signature [89]. The OB-BMST signature (periostin *(Postn),* asporin *(Aspn),* SPARC-like 1 *(Sparcl1),* melanoma cell adhesion molecule *(Mcam),* platelet-derived growth factor receptor beta *(Pdgfrb),* fascin homolog 1 *(Fscn1)* and prostate transmembrane protein androgen induced 1 *(Pmepa1)*) was also conserved in the stroma of (1) intraprostatic and ectopic VCaP and C4–2B xenografts, (2) bone metastases from the subcutaneous patient-derived xenografts BM18 and LAPC9 [71], and (3) primary PCa stroma [112].

Moreover, the interplay between PCa cells and their surrounding TME/stroma is important for AR signaling regulation and response to androgen-deprivation therapy (ADT). The importance of androgen-responsive stroma is highlighted by observations that decreased stromal AR expression in PCa is associated with poor prognosis and earlier disease progression, suggesting an antitumorigenic role of stromal AR during the early, hormone-naïve stages of PCa [113–115]. Perturbed AR signaling alters the ECM composition, leading to looser adhesion of tumor and supportive stroma, possibly facilitating cell invasion [116]. Stromal AR expression is also found in human bone marrow [117]. The pro/anti-tumorigenic role of prostate stroma is still debated; however, stromal marker inclusion may complement the current prognostic tools in patient stratification. Several studies have shown the prognostic potential of stroma protein biomarkers or gene signatures that are able to distinguish patients at high risk of biochemical relapse and disease progression [71,111,118,119].

ADT influences the prostatic stroma [120,121] and may contribute to castration-resistance acquisition via mechanisms involving CAFs such as neuregulin secretion and HER3 signaling activation [122] as well as increased secretion of the protumorigenic inflammatory cytokines CCL2 and CXCL8 [123]. Stromal cells lacking the TGFβRII receptor, upregulate Wnt ligands in response to bicalutamide, promoting the survival of prostatic epithelial ducts [124]. Moreover, castration induces rapid bone turnover, which in turn influences growth of dormant PCa tumor cells in the bone marrow [125,126]. Transcriptomic characterization (scRNA-seq) of bone, liver and lymph node metastasis of CRPC patients, has identified differential composition of metastasis-infiltrating immune cells in matched samples from before and after enzalutamide treatment [127]. Similar studies, assessing the composition and molecular characterisation of fibroblast populations or bone marrow stromal cells prior and after treatment, will be invaluable, as the past decade has seen increasing evidence on stroma-mediated therapy (ADT or chemotherapy [128]) resistance.

4. Progressive TME alterations in transgenic mouse models of bone metastases

Due to the tendency of PCa cells to metastasize to the bone, it is crucial to establish functional bone metastasis models based on genetic changes to guide further study and development of clinical treatment. Transgenic mouse models mimicking the early stages of PCa progression from hyperplasia to prostatic intraepithelial neoplasia (PIN) to adenocarcinoma have been successfully generated. However, genetically engineered mouse models (GEMMs) that accurately recapitulate the "natural" transition of the primary tumor towards bone metastases are limited. The majority of GEMMs lead to lymph node, lung or liver metastases with only a few modeling skeletal or long bone metastases, despite being the predominant metastatic site of human PCa adenocarcinoma [15].

The well-characterized transgenic adenocarcinoma mouse model (TRAMP), expressing the oncogenic T antigen under the control of probasin promoter (secretory epithelial cells), shows infrequent bone metastasis occurrence [129]. Moreover, many of the GEMMs that do give rise to bone metastasis in fact show NEPC phenotype rather than luminal adenocarcinoma, the most common form occurring in humans. This may occur as a response to androgen deprivation/castration [130] or due to use of promoter expressed by neuroendocrine cells to drive transgenic oncogene expression, such as the *Cryptin-2* gene (CR2-T-Ag model) [131]. Mixed epithelial and NEPC phenotypes were also observed in the 12T-10 LPB-*Tag* line (LADY) [132] and in the fetal gamma globin SV40 GEMM both of which lead to bone micrometastasis [133]. In contrast, PCa with NEPC phenotype in humans typically gives rise to soft tissue metastases (liver, lung) [15]. Tissue morphology and reactive stroma composition in primary PCa is potentially altered among cases that show disease progression (biochemical recurrence) and those that do not progress [134]. Genetic and molecular events driving prostate tumorigenesis have been demonstrated to play precise but distinct roles in remodeling TME [135].

Utilizing GEMMs to capture snapshots of stroma alterations in orthotopic prostate tumors [57], both before and during macrometastasis occurrence may provide important information regarding the temporal dynamics of TME corruption, particularly since micrometastatic events seem to occur early in the disease; in parallel with primary tumor growth, 70% of localized cases have detectable DTCs [136]. However, few models exist that can show linear disease progression, while these models have been analyzed from the tumor-specific or bone marrow microenvironment component, but not from a time-lapse perspective of the prostate microenvironment. To identify models relevant to human PCa natural history, we specifically looked at GEMMs that give rise to bone metastasis after occurrence of orthotopic prostate tumor formation (Table 2). Therefore, intracardiac or intraosseous cell line xenografts models will not be discussed here. In the TRAMP model, stroma hypertrophy occurs in parallel to malignant epithelial proliferation. This is evident from normal acini with single or two-layered stroma (at 9 weeks) to stroma hypercellularity (at 19 weeks, adenocarcinoma stage) [129]. Progressive stroma alterations were observed in a time dependent manner in the CR2-T-Ag model, in which remodeling of the reactive prostate stroma occurred concordant with the progression to invasive adenocarcinoma [131]. Specifically, initial

Table 2
Transgenic mouse models simulating bone metastasis from primary PCa.

Gene	Modification	Phenotype	Reference
PB-Cre^{+}*/Pten* $^{L/+}$*/KRas* $^{L/+}$	Conditional loss of *Pten* & activation of *KRas*	Liver & lung metastasis Micrometastasis in bone marrow	[154]
Nkx3.1$^{CreERT2/+}$*/Pten*$^{L/L}$*/KRas*$^{LSL-G12D/+}$	Conditional loss of *Pten* & activation of *KRas*	Liver & lung metastasis DTCs bone marrow micrometastasis	[138]
Nkx3.1$^{CreERT2/+}$*; Pten*$^{flox/flox}$*; Kras*$^{LSL-G12D/+}$*; R26R-CAG-*$^{LSL-EYFP/+}$ *Nkx3.1*$^{CreERT2/+}$*; Pten*$^{flox/flox}$*; Kras*$^{LSL-G12D/+}$*; R26R-CAG-*$^{LSL-EYFP/+}$*; ARR2PB-Myc*	Conditional loss of *Pten* & activation of *KRas* Combined with *MYC* overexpression	Liver, lung and bone metastasis	[137]
PB-Cre4/Pten$^{L/L}$*/Rb1*$^{L/L}$*/Trp53* $^{L/L}$	Conditional triple knockout of *Pten*, *Rb1* and *Trp53*	Bone metastasis Small cohort of animals	[36]
LPB-*Tag* (12T-10 subline, LADY)	Conditional activation of large T antigen	Liver, lymph node and lung metastasis Bone micrometastasis	[132]
CR2-T-Ag	Conditional activation of T antigen	Bone metastasis	[131]
G3/4 *LSL-mTert PB-Cre4-Pten*$^{L/L}$*/p53* $^{L/L}$	Telomerase reactivation in *p53*, Pten$^{-/-}$ following telomere dysfunction	Skeletal metastasis	[140]
Hoxb13-MYC/ *Hoxb13-Cre/Pten*$^{L/L}$	Conditional MYC overexpression and Pten knockout	Liver, lung and rare thoracic bone metastasis	[147]
Nkx3.1$^{CreERT2/+}$*/Pten*$^{L/L}$*/Braf*$^{CA/+}$	Conditional gain of Braf mutant and Pten loss	Liver, lung metastasis Bone micrometastasis (DTCs)	[155]

microinvasion through the basement membrane into the fibromuscular stroma can be observed (12 weeks), followed by substantial stromal invasion over time (16 and 24 weeks). Histology of these prostates revealed extensive stromal invasion and glandular structure loss at 24 weeks- a stage at which macrometastases in bone and liver have already occurred [131]. *KRas* mutations have been reported to increase the susceptibility of bone metastasis, as shown in the luminal *NKX3.1*-driven *PTEN* loss and *KRas* activating GEMM (*NPK: NKX3.1*$^{CreERT2/+}$*; PTEN-*$^{flox/flox}$*; KRas*$^{LSL-G12D/+}$), which gives rise to liver, lung metastases and bone micrometastasis, at a higher incidence compared to the *NKX3.1*-driven *PTEN* loss (NP) model alone [133]. By crossing *NPK* mice with the *Rosa-CAG-LSL-EYFP-WPRE* reporter allele, the resulting *NPK*^{EYFP} model (*Nkx3.1*$^{CreERT2/+}$*; Pten*$^{flox/flox}$*; Kras*$^{LSL-G12D/+}$*; R26R-CAG-*$^{LSL-EYFP/+}$) has even higher sensitivity and thus improved detection of bone metastases [137]. Apart from the oncogene-dependent effects distinguishing the two transgenic models, additional reactive stroma-related transcriptomic events, such as the CAF hallmark pathways PDGF and focal adhesion signaling, were also enriched in the NPK versus NP bulk tumor [138]. The *NPK* leads to ~45% de novo bone metastases and together with *NPK*^{EYFP} they represent models of bone metastasis with high epistasis, linking it to specific genetic alterations and human disease. Furthermore, this demonstrates that other models may overlook bone metastases due to the challenges associated with their detection and highlights the power of GEMMs that integrate sensitive lineage tracing [137,139]. Telomerase reactivation, following genomic instability due to initial telomerase dysfunction, in *PB-Cre4/p53* $^{L/L}$*/Pten*$^{L/L}$ animals, leads to 25% penetrance of bone metastasis [140]. The underlying mechanism is proposed to be deregulation of the TGF-β pathway and in particular loss of function of the *Smad4* tumor suppressor, which is frequently mutated in human primary PCa [21]. Loss of *Smad4* in the *PB-Cre4/p53* $^{L/L}$*/Pten*$^{L/L}$ animals leads to invasive carcinoma with a relatively low (12%) penetrance of bone metastasis [140] that may be due to direct invasion from the primary tumor rather than hematogenous metastases to the bone marrow [141]. It should be noted that *Smad4* mutations are uncommon in human CRPC/metastasis. However, deletion of Smad4 exclusively in luminal epithelial cells did not allow for characterization of TGF-β pathway and its orchestrating role in fibroblasts and ECM composition, and thus their effect on tumor growth. Instead, *Smad4* deletion drives progression of *Pten*$^{-/-}$ prostate tumors to invasive adenocarcinoma, with evident stromal reaction and lymph node/ lung metastasis but not bone metastasis [142]. Other genetic aberrations such as combined loss of *p53* and *Pten* are associated with loss of androgen dependency and occurrence of CRPC metastases [143]. Further combinatorial loss of *p53*, *Pten* along with *Myc* amplification, a frequent genomic amplification in CRPC and NE, also led to invasive adenocarcinoma and lymph node metastasis (*Myc*+/*Pten*-het/*p53*-ko GEMM) [144]. The levels of *Myc* overexpression is proportionately associated to more aggressive disease stages; Lo-Myc model exhibits PIN lesions while the Hi-Myc models lead to invasive adenocarcinoma [145] and even bone metastasis (B6CaP, via intravenous not orthotopic route) [146]. In the bone metastatic *NPK*^{EYFP} model, subsequent transcriptional activation of Myc pathway was specifically detected in the bone metastases and not in the matched primary tumors, showing that Myc is an important contributor to metastasis formation [137]. However, crossing the *NPK*^{EYFP} with the Hi-Myc transgenic mouse (*NPKM*^{EYFP}) did not result in higher frequency of bone metastases compared to the original NPK [137]; no particular stroma alterations reported in the matched prostate or bone tissues. Bone metastasis occurrence has been also modelled via overexpression of *Myc* combined with *Pten* loss in luminal HoxB13^{+} cells which leads to linear progression from PIN to invasive and metastatic adenocarcinoma (lymph node, liver, lung, and bone), yet of low frequency [147]. In this model, stroma hypercellularity was evident surrounding the progressed (late) PIN lesions, while the histomorphology of the stroma component in the invasive PCa stage seemed completely absent. However, it should be noted that specific stromal markers were not specifically analyzed in this study [147].

In summary, bone metastasis GEMM models established to date have improved our understanding of the role of tumor driver/suppressor genes deregulated in human PCa and have helped to delineate the differences from model organism to human disease, which ultimately provides valuable tools for guiding clinical research and improved therapeutic strategies. However, the lack of available spontaneous bone metastasis mouse model from primary PCa still remains a challenge. It has been hypothesized that the intrinsic differences in the prostate anatomy, extensively reviewed in Ref. [139], the hematopoietic and immune system and the overall physiology among mice and humans [148] impede modeling prostate bone metastasis in mice. Instead, lymph node, lung or liver are the predominant sites of metastasis in the mouse models, making these very different from the human bone metastasis scenario. The murine femur has different bone organization and growth rate, with higher content of less organized woven bone and less organized fibrolamellar structure that what is found in larger animals [149] along with the different lymphoid and myeloid cell content [85], resulting in major alterations of the bone microenvironment.

Newer research directions such as humanized models, which include *in vivo* tissue-engineered xenografts, *in vitro* microtissue-engineered models and *ex vivo* manipulation and serial retransplantation, hold potential in recapitulating human bone marrow [150–152], as well as human prostate, cellular and microenvironment composition such as CAFs, endothelial cells [153], and facilitate research of specific tumor-stroma interactions. Such novel approaches, along with study of the ECM and TME composition changes during disease progression in human PCa and in the mouse models (as discussed in this review) would

improve our understanding on how to tackle the limitations of developing the ideal bone metastasis preclinical model.

5. Bone metastasis detection and treatment

The early diagnosis of bone metastasis is often a limiting factor in the successful management of the disease. The identification of molecular mechanisms of PCa bone metastasis in the past decades, along with advances in radiology and nuclear medicine, have led to the development of imaging-based diagnostic and therapeutic tools for improved detection and treatment of this disease. An overview of the evolution of imaging techniques, and the advantages and limitations of the current state-of-the-art theragnostic and nuclear medicine therapy approaches (Fig. 3) are given.

5.1. Imaging of bone metastasis

Traditionally, the detection of bone metastasis relied on conventional imaging techniques such as computed tomography and the nuclear medicine imaging technique of single photon emission computed tomography (SPECT) with ^{99m}Tc-labelled phosphates (so called "bone scans"). However, these modalities are associated with poor diagnostic yield and were of limited value in assessing biochemical failure [156], although they still have a role in the assessment of bone turnover prior to therapy with ^{223}Radium (XOFIGO®). The introduction of multimodal imaging with the combination of PET/CT at the turn of the 21st century represented a significant step-forward in molecular imaging [157]. The traditional PET radiotracer, the radioactive 2[^{18}F]FDG (2-Fluor-2-desoxy-D-glucose) is of limited value in PCa, where only highly aggressive forms of PCa are FDG avid. As a result, choline-based

	Approach	Advantages	Challenges
Diagnostic Imaging	1. SPECT with ^{99m}Tc-labelled phosphates	Assessment of bone metastases prior to therapy with ^{223}Radium (XOFIGO®)	Useful for skeletal metastases only and with limited diagnostic yield. Useless for early biochemical recurrence.
	2. [^{18}F]FDG-PET/CT	FDG avidity in highly aggressive forms	Limited value in less aggressive PCa
	3. Choline-PET/CT	Many years of experience	Limited performance in early recurrence & in aggressive (high GS) tumors
	4. [^{18}F]NaF-PET/CT	High sensitivity for bone metastases	Limited to bone metastases only
	5. PSMA-PET/CT	Predominant imaging modality in both recurrent and primary PCa	Ineffective in rare case of PSMA-negative tumors
Theragnostics	PSMA-based radiotracers *e.g. [^{68}Ga]Ga-PSMA-617 (for diagnosis)* *[^{177}Lu]Lu-PSMA-617 (for therapy)*	Image-guided lymph-node dissection, or image-guided radiotherapy	Restricted by PSMA expression: -not completely specific for prostate -PSMA is also expressed in normal tissues -ineffective in rare de-differentiated PSMA-negative advanced tumors
Nuclear Therapy	1. ^{223}Radium	Palliative pain reduction, delay occurrence of first skeletal events	Limited to patients without visceral metastasis
	2. PSMA-labelled radioligand therapy *e.g.[^{177}Lu]Lu-PSMA-617,* *[^{177}Lu]Lu-PSMA-I&T*	Highly effective in 1/3 of the patients Possible alternative for patients whose standard therapeutic options have been exhausted	Currently approved for the third-line treatment of mCRPC only. There, not effective in ca. 60% of patients

Fig. 3. Overview of Imaging Tools in Bone Metastasis. Summary of the traditional imaging tools for the detection of bone metastasis and their evolution over the last few decades. The main advantages and unmet challenges of each imaging approach are highlighted, based on the applicability for diagnostic imaging, theragnostic and nuclear therapy. GS, Gleason Score; PET/CT, positron emission tomography–computed tomography; PSMA, prostate specific membrane antigen; SPECT, single photon emission computed tomography; FDG; 2-[fluorine-18]-fluoro-2-deoxy-D-glucose; [^{18}F], Fluorine-18; NaF; sodium fluoride; [^{68}Ga], Gallium-68; [^{177}Lu], Lutetium-177. Scheme created with BioRender.com.

radiotracers were introduced [158] and capitalize on the derangement in choline metabolism observed in malignant cells [159]. In many jurisdictions, choline PET/CT has become the standard of care imaging modality for advanced PCa, and in situations where other imaging modalities are not available, remains the recommended modality endorsed by the AUA/ASTRO/SUO guidelines [160]. However, although choline-based radiotracers for PET-imaging are a significant improvement on previous scintigraphy techniques, they still exhibit limited performance, particularly in early recurrence. [^{18}F]NaF is a long established PET-tracer for bone metastasis, having been first approved by the United States Food and Drug Administration (FDA) in 1972 [161]. It outperforms bone scintigraphy and choline and may have superior sensitivity for bone metastases compared to other radiotracers [162]. However, since it is limited to the detection of bone metastases, it has hitherto had a limited role in the staging of PCa.

The discovery in the 1980's of a novel antigenic marker in PCa led to a significant revolution in the imaging of PCa [163–165]. Initially, radiolabeled antibodies for SPECT imaging were introduced (e.g. ^{111}Indium-labelled capromab-pendetide, known as ProstaScint) [166]. However, it was the first clinical introduction of positron-emitting radiolabeled prostate specific membrane antigen (PSMA)-ligands with [^{68}Ga]Ga-PSMA-11 in 2011 (also known as PSMA-HBED or HBED-CC [167]) that revolutionized the imaging of PCa. PSMA, which is also known as Glutamate carboxypeptidase II (GCPII) or *N*-acetyl-L-aspartyl-L-glutamate peptidase I (NAALADase I) [168], is over-expressed on the majority of PCa cells [163–165]. Although a widely recognized term, PSMA is a misnomer, since the expression of this transmembrane protein is not restricted to PCa and can also be found in a variety of normal tissues. PET/CT using radioligands of PSMA has become the favored imaging modality for biochemical recurrence and the role of PSMA-PET/CT in high-risk primary PCa is also increasingly recognized [169,170]. However, although PSMA-PET/CT has been enthusiastically established as the predominant imaging modality in both recurrent and primary disease, overall evidence for its use is rated as weak [160]. In particular, while PSMA-based radiotracers clearly outperform previous generation tracers such as choline in early recurrence [171], this may not be the case for more advanced disease, where choline-positive and PSMA-negative disease is encountered [172] as a result of tumor de-differentiation and loss of PSMA-expression. For this reason, some authorities recommend additional 2-[^{18}F]FDG PET/CT at advanced stages of disease. Furthermore, there is only scant evidence as to whether performing PSMA-PET/CT translates into improved clinical outcomes. Although PSMA-PET/CT has been demonstrated to influence treatment planning, particularly radiotherapy [173,174], there are only limited data as to whether individuals undergoing PSMA-guided radiotherapy have better results [160]. Data from clinical trials are required to resolve this important question [175]. Finally, in the decade since the introduction of [^{68}Ga]Ga-PSMA-11 a plethora of other PSMA-radiotracers have been developed, each with important advantages and disadvantages. However, owing to the lack of formal comparative imaging trials for these tracers, no evidence-based recommendations can be made at present to favor one tracer over another [176].

5.2. Theragnostic imaging approaches

One advantage of using PSMA-based radiotracers for the detection of PCa metastases is the ability to perform a theragnostic assessment of the patient's disease. Theragnostics, a portmanteau of the words therapy and diagnostics [177] describes the use of PSMA-radioligands to both detect and treat PCa, which is achieved with either a diagnostic radiopharmaceutical such as the positron-emitting [^{68}Ga]Ga-PSMA-11, or treatment, such as the beta-emitting therapeutic radioligand [^{177}Lu]Lu-PSMA-617. The accurate identification of metastases can also guide image-guided lymph-node dissection, or image-guided radiotherapy. In cases where visceral metastases can be ruled out, the individual with symptomatic bone metastases may benefit from ^{223}Radium therapy [178]. In cases where standard therapeutic options have been exhausted, or where the patient is considered unsuitable, PSMA-radioligand therapy is an increasingly recognized option. In these cases, the degree of PSMA-expression by the metastatic lesions is an important consideration, where assessment by PET/CT to establish adequate uptake is recommended by extant guidelines [179].

5.3. Nuclear medicine therapies for bone metastases

A number of nuclear medicine therapeutic options are available for the management of bone metastases in PCa. However, it is important to note that these measures are palliative in nature and do not represent a cure. Historically, palliative therapy with bone targeting radiopharmaceuticals (^{186}Rhenium, ^{153}Samarium or ^{89}Strontium) has been performed [180,181]. Recently, ^{223}Radium therapy for bone metastasis has been introduced into the guidelines [182,183]. ^{223}Radium is substituted by osteoblasts for calcium in hydroxyapatite complexes within areas of metastatic bone formations [184] with reduction in pain reported in a majority of patients [182]. Trial data suggests that when ^{223}Radium therapy was performed after treatment with docetaxel, time to first skeletal events such as pathologic fractures is longer [185]. Side effects include diarrhea, nausea, vomiting and thrombocytopenia [183]. Significantly, pancytopenia can occur, particularly when performed after docetaxel treatment [185,186]. ^{223}Radium is only of use when visceral metastases are ruled out. In cases where solid organ or nodal metastases are present, PSMA-labelled radioligand therapy (e.g. with ^{177}Lutetium) represent a possible therapeutic option [187]. When using PSA as a surrogate marker for tumor-load, roughly one third of patients show therapeutic response, one third have transient stable-disease and one third regrettably do not respond to treatment [188]. Importantly, recent trial evidence shows that when compared to the standard second or third-line chemotherapeutic agent Cabazitaxel, [^{177}Lu]Lu-PSMA-617 results in improved PSA response and fewer adverse events, suggesting an increased role for this treatment and for its placement earlier in the management algorithm for these patients [189].

5.4. Microenvironment-directed treatment for PCa bone metastases

Treatment modalities targeting the interaction between tumor cells and their surrounding bone TME are increasingly reported. The tumor derived CXCR4 specifically interacts with CXCL12 on pericytes/bone marrow stromal cells around vascular structures of the bone marrow. Treatment with AMD3100 blocks the CXCR4-CXCL12 axis and sensitizes cancer cells to chemotherapy [190]. A recent clinical trial testing CXCR4 inhibitor in combination with granulocyte-colony-stimulating factor (G-CSF) and chemotherapy, aiming to target niche-occupancy, unfortunately did not have a promising outcome for PCa bone metastasis treatment [191]. Other possibilities include compounds that interfere with bone resorption and osteoclast activity, such as RANKL antibody denosumab and bisphosphonates [192]. Inhibition of AXL receptor kinase and its ligand growth arrest-specific 6 (expressed in osteoblasts) has been shown to modulate tumor cell dormancy and interaction with the TME in other cancer types, with possible implications also in PCa bone metastasis [193,194].

6. Conclusions and future directions

During the progression of PCa, the crosstalk with the TME supports tumor growth and mediates the selection of therapy-resistant and metastatic tumor cells. The tendency of PCa to metastasize to the bone is a multifactorial and not yet fully understood process that is facilitated by intrinsic malignant features of the tumor and bone marrow biology. The bone microenvironment provides stable structural support for aggressive tumor cells, promoting a feedforward loop of tissue remodeling to aid tumor cell colonization.

Currently available transgenic mouse models are still poorly able to adequately represent the bone metastatic phenotype after occurrence of orthotopic prostate tumor formation, as in the human disease. Spontaneous bone metastasis models are needed to allow delineation of the tumor-stromal interactions and their disease causality in a spatiotemporal manner. To better study bone-metastatic PCa, a characterization of stroma remodeling in PCa tissue microarrays in parallel to the genomic alterations would be relevant for improved clinical management of metastatic PCa. Due to the high degree of malignancy of PCa bone metastasis, early diagnosis and effective treatments are needed to improve prognosis. Advances in nuclear medicine-based diagnosis and therapy of bone metastasis include the development of more sensitive PSMA-PET/CT techniques, a widely used primary imaging modality for primary and recurrent disease. However, certain limitations such as actual clinical benefit or ineffectiveness in certain types (e.g. PSMA-negative NEPC) have yet to be resolved. Traditionally, much attention has been dedicated to understanding tumor evolution dynamics. However, multiple studies have recently highlighted the fundamental role of the tumor- supportive stroma, both at primary and metastatic sites, in disease progression and therapy resistance. Identifying the synergy of tumor and TME co-evolution, improving the accuracy of imaging diagnosis and reducing the side effects of nuclear medicine treatment will improve patients' risk stratification and treatment, overcoming the limitations of current one-fits-all clinical regime.

Author contributions

Juening Kang: Investigation, Writing-Original draft preparation; **Federico La Manna:** Conceptualization, Investigation, Writing-Original draft preparation; **Francesco Bonollo:** Writing-Original draft preparation**; Natalie Sampson:** Writing – review & editing, Funding acquisition; **Ian Alberts:** Writing-Original draft preparation, Writing – review & editing; **Clemens Mingels:** Writing-Original draft preparation, Writing – review & editing; **Ali Afshar-Oromieh:** Writing-Original draft preparation, Writing – review & editing; **George N. Thalmann:** Writing – review & editing, Funding acquisition; **Sofia Karkampouna:** Conceptualization, Supervision, Writing-Original draft preparation, Writing – review & editing.

Financial support

This project has received funding from the Swiss National Science Foundation (320030L_189369 to G.N.Thalmann) and Austrian Science Fund (FWF, I-4565 to N. Sampson).

Declaration of competing interest

The authors declare no conflict of interest.

Acknowledgements

The authors would like to thank Marta De Menna and Peter C. Gray for discussions and proofreading of the manuscript.

References

[1] R.L. Siegel, K.D. Miller, H.E. Fuchs, A. Jemal, Cancer statistics, CA A Cancer J. Clin. 71 (2021) (2021) 7–33.
[2] M. Eiber, M. Kroenke, A. Wurzer, L. Ulbrich, L. Jooß, T. Maurer, T. Horn, K. Schiller, T. Langbein, G. Buschner, H.J. Wester, W. Weber, 18)F-rhPSMA-7 PET for the detection of biochemical recurrence of prostate cancer after radical prostatectomy, J. Nucl. Med. 61 (2020) 696–701.
[3] U. Swami, T.R. McFarland, R. Nussenzveig, N. Agarwal, Advanced prostate cancer: treatment advances and future directions, Trends Canc. 6 (2020) 702–715.
[4] G. Wang, D. Zhao, D.J. Spring, R.A. DePinho, Genetics and biology of prostate cancer, Genes Dev. 32 (2018) 1105–1140.
[5] D.A. Siegel, M.E. O'Neil, T.B. Richards, N.F. Dowling, W. Hk, Prostate cancer incidence and survival, by stage and race/ethnicity — United States, 2001–2017, MMWR Morb. Mortal. Wkly. Rep. 69 (2020) (2020) 1473–1480.
[6] D.C. Grossman, S.J. Curry, D.K. Owens, K. Bibbins-Domingo, A.B. Caughey, K. W. Davidson, C.A. Doubeni, M. Ebell, J.W. Epling Jr., A.R. Kemper, A.H. Krist, M. Kubik, C.S. Landefeld, C.M. Mangione, M. Silverstein, M.A. Simon, A.L. Siu, C. W. Tseng, Screening for prostate cancer: US preventive services task force recommendation statement, JAMA 319 (2018) 1901–1913.
[7] R. Ge, Z. Wang, R. Montironi, Z. Jiang, M. Cheng, M. Santoni, K. Huang, F. Massari, X. Lu, A. Cimadamore, A. Lopez-Beltran, L. Cheng, Epigenetic modulations and lineage plasticity in advanced prostate cancer, Ann. Oncol. 31 (2020) 470–479.
[8] G. Gandaglia, F. Abdollah, J. Schiffmann, V. Trudeau, S.F. Shariat, S.P. Kim, P. Perrotte, F. Montorsi, A. Briganti, Q.D. Trinh, P.I. Karakiewicz, M. Sun, Distribution of metastatic sites in patients with prostate cancer: a population-based analysis, Prostate 74 (2014) 210–216.
[9] M. Riihimäki, H. Thomsen, K. Sundquist, J. Sundquist, K. Hemminki, Clinical landscape of cancer metastases, Cancer Med. 7 (2018) 5534–5542.
[10] C. Pezaro, A. Omlin, D. Lorente, D.N. Rodrigues, R. Ferraldeschi, D. Bianchini, D. Mukherji, R. Riisnaes, A. Altavilla, M. Crespo, N. Tunariu, J. de Bono, G. Attard, Visceral disease in castration-resistant prostate cancer, Eur. Urol. 65 (2014) 270–273.
[11] Y. Loriot, K. Fizazi, J.S. de Bono, D. Forer, M. Hirmand, H.I. Scher, Enzalutamide in castration-resistant prostate cancer patients with visceral disease in the liver and/or lung: outcomes from the randomized controlled phase 3 AFFIRM trial, Cancer 123 (2017) 253–262.
[12] I.W. Tremont-Lukats, G. Bobustuc, G.K. Lagos, K. Lolas, A.P. Kyritsis, V. K. Puduvalli, Brain metastasis from prostate carcinoma: the M. D. Anderson Cancer Center experience, Cancer 98 (2003) 363–368.
[13] H.P. Bhambhvani, D.R. Greenberg, S. Srinivas, M. Hayden Gephart, Prostate cancer brain metastases: a single-institution experience, World Neurosurg. 138 (2020) e445–e449.
[14] F. Macedo, K. Ladeira, F. Pinho, N. Saraiva, N. Bonito, L. Pinto, F. Goncalves, Bone metastases: an overview, Onco Rev. 11 (2017) 321.
[15] C.J. Logothetis, S.H. Lin, Osteoblasts in prostate cancer metastasis to bone, Nat. Rev. Cancer 5 (2005) 21–28.
[16] G. Sgouros, L. Bodei, M.R. McDevitt, J.R. Nedrow, Radiopharmaceutical therapy in cancer: clinical advances and challenges, Nat. Rev. Drug Discov. 19 (2020) 589–608.
[17] F.X. Li, J.J. Liu, F. Xu, X. Lin, J.Y. Zhong, F. Wu, L.Q. Yuan, Role of tumor-derived exosomes in bone metastasis, Oncol. Lett. 18 (2019) 3935–3945.
[18] S. Das, S.S. Salami, D.E. Spratt, S.D. Kaffenberger, M.F. Jacobs, T.M. Morgan, Bringing prostate cancer germline genetics into clinical practice, J. Urol. 202 (2019) 223–230.
[19] M.A. Rubin, C.A. Maher, A.M. Chinnaiyan, Common gene rearrangements in prostate cancer, J. Clin. Oncol. 29 (2011) 3659–3668.
[20] C.E. Barbieri, S.C. Baca, M.S. Lawrence, F. Demichelis, M. Blattner, J. P. Theurillat, T.A. White, P. Stojanov, E. Van Allen, N. Stransky, E. Nickerson, S. S. Chae, G. Boysen, D. Auclair, R.C. Onofrio, K. Park, N. Kitabayashi, T. Y. MacDonald, K. Sheikh, T. Vuong, C. Guiducci, K. Cibulskis, A. Sivachenko, S. L. Carter, G. Saksena, D. Voet, W.M. Hussain, A.H. Ramos, W. Winckler, M. C. Redman, K. Ardlie, A.K. Tewari, J.M. Mosquera, N. Rupp, P.J. Wild, H. Moch, C. Morrissey, P.S. Nelson, P.W. Kantoff, S.B. Gabriel, T.R. Golub, M. Meyerson, E. S. Lander, G. Getz, M.A. Rubin, L.A. Garraway, Exome sequencing identifies recurrent SPOP, FOXA1 and MED12 mutations in prostate cancer, Nat. Genet. 44 (2012) 685–689.
[21] D. Robinson, E.M. Van Allen, Y.M. Wu, N. Schultz, R.J. Lonigro, J.M. Mosquera, B. Montgomery, M.E. Taplin, C.C. Pritchard, G. Attard, H. Beltran, W. Abida, R. K. Bradley, J. Vinson, X. Cao, P. Vats, L.P. Kunju, M. Hussain, F.Y. Feng, S. A. Tomlins, K.A. Cooney, D.C. Smith, C. Brennan, J. Siddiqui, R. Mehra, Y. Chen, D.E. Rathkopf, M.J. Morris, S.B. Solomon, J.C. Durack, V.E. Reuter, A. Gopalan, J. Gao, M. Loda, R.T. Lis, M. Bowden, S.P. Balk, G. Gaviola, C. Sougnez, M. Gupta, E.Y. Yu, E.A. Mostaghel, H.H. Cheng, H. Mulcahy, L.D. True, S.R. Plymate, H. Dvinge, R. Ferraldeschi, P. Flohr, S. Miranda, Z. Zafeiriou, N. Tunariu, J. Mateo, R. Perez-Lopez, F. Demichelis, B.D. Robinson, M. Schiffman, D. M. Nanus, S.T. Tagawa, A. Sigaras, K.W. Eng, O. Elemento, A. Sboner, E.I. Heath, H.I. Scher, K.J. Pienta, P. Kantoff, J.S. de Bono, M.A. Rubin, P.S. Nelson, L. A. Garraway, C.L. Sawyers, A.M. Chinnaiyan, Integrative clinical genomics of advanced prostate cancer, Cell 161 (2015) 1215–1228.
[22] P.S. Nelson, Beyond the Androgen Receptor: Targeting Actionable Drivers of Prostate Cancer, JCO Precision Oncology, 2017, pp. 1–3.
[23] B.S. Taylor, N. Schultz, H. Hieronymus, A. Gopalan, Y. Xiao, B.S. Carver, V. K. Arora, P. Kaushik, E. Cerami, B. Reva, Y. Antipin, N. Mitsiades, T. Landers, I. Dolgalev, J.E. Major, M. Wilson, N.D. Socci, A.E. Lash, A. Heguy, J.A. Eastham, H.I. Scher, V.E. Reuter, P.T. Scardino, C. Sander, C.L. Sawyers, W.L. Gerald, Integrative genomic profiling of human prostate cancer, Cancer Cell 18 (2010) 11–22.
[24] M.C. Haffner, T. Mosbruger, D.M. Esopi, H. Fedor, C.M. Heaphy, D.A. Walker, N. Adejola, M. Gürel, J. Hicks, A.K. Meeker, M.K. Halushka, J.W. Simons, W. B. Isaacs, A.M. De Marzo, W.G. Nelson, S. Yegnasubramanian, Tracking the clonal origin of lethal prostate cancer, J. Clin. Invest. 123 (2013) 4918–4922.
[25] S.C. Baca, D. Prandi, M.S. Lawrence, J.M. Mosquera, A. Romanel, Y. Drier, K. Park, N. Kitabayashi, T.Y. MacDonald, M. Ghandi, E. Van Allen, G.V. Kryukov, A. Sboner, J.P. Theurillat, T.D. Soong, E. Nickerson, D. Auclair, A. Tewari, H. Beltran, R.C. Onofrio, G. Boysen, C. Guiducci, C.E. Barbieri, K. Cibulskis, A. Sivachenko, S.L. Carter, G. Saksena, D. Voet, A.H. Ramos, W. Winckler,

M. Cipicchio, K. Ardlie, P.W. Kantoff, M.F. Berger, S.B. Gabriel, T.R. Golub, M. Meyerson, E.S. Lander, O. Elemento, G. Getz, F. Demichelis, M.A. Rubin, L. A. Garraway, Punctuated evolution of prostate cancer genomes, Cell 153 (2013) 666–677.
[26] H. Hieronymus, C.L. Sawyers, Traversing the genomic landscape of prostate cancer from diagnosis to death, Nat. Genet. 44 (2012) 613–614.
[27] J. Mateo, G. Seed, C. Bertan, P. Rescigno, D. Dolling, I. Figueiredo, S. Miranda, D. Nava Rodrigues, B. Gurel, M. Clarke, M. Atkin, R. Chandler, C. Messina, S. Sumanasuriya, D. Bianchini, M. Barrero, A. Petermolo, Z. Zafeiriou, M. Fontes, R. Perez-Lopez, N. Tunariu, B. Fulton, R. Jones, U. McGovern, C. Ralph, M. Varughese, O. Parikh, S. Jain, T. Elliott, S. Sandhu, N. Porta, E. Hall, W. Yuan, S. Carreira, J.S. de Bono, Genomics of lethal prostate cancer at diagnosis and castration resistance, J. Clin. Invest. 130 (2020) 1743–1751.
[28] G. Gundem, P. Van Loo, B. Kremeyer, L.B. Alexandrov, J.M.C. Tubio, E. Papaemmanuil, D.S. Brewer, H.M.L. Kallio, G. Högnäs, M. Annala, K. Kivinummi, V. Goody, C. Latimer, S. O'Meara, K.J. Dawson, W. Isaacs, M. R. Emmert-Buck, M. Nykter, C. Foster, Z. Kote-Jarai, D. Easton, H.C. Whitaker, D. E. Neal, C.S. Cooper, R.A. Eeles, T. Visakorpi, P.J. Campbell, U. McDermott, D. C. Wedge, G.S. Bova, The evolutionary history of lethal metastatic prostate cancer, Nature 520 (2015) 353–357.
[29] C.S. Grasso, Y.M. Wu, D.R. Robinson, X. Cao, S.M. Dhanasekaran, A.P. Khan, M. J. Quist, X. Jing, R.J. Lonigro, J.C. Brenner, I.A. Asangani, B. Ateeq, S.Y. Chun, J. Siddiqui, L. Sam, M. Anstett, R. Mehra, J.R. Prensner, N. Palanisamy, G. A. Ryslik, F. Vandin, B.J. Raphael, L.P. Kunju, D.R. Rhodes, K.J. Pienta, A. M. Chinnaiyan, S.A. Tomlins, The mutational landscape of lethal castration-resistant prostate cancer, Nature 487 (2012) 239–243.
[30] W. Abida, J. Armenia, A. Gopalan, R. Brennan, M. Walsh, D. Barron, D. Danila, D. Rathkopf, M. Morris, S. Slovin, B. McLaughlin, K. Curtis, D.M. Hyman, J. C. Durack, S.B. Solomon, M.E. Arcila, A. Zehir, A. Syed, J. Gao, D. Chakravarty, H. A. Vargas, M.E. Robson, V. Joseph, K. Offit, M.T.A. Donoghue, A.A. Abeshouse, R. Kundra, Z.J. Heins, A.V. Penson, C. Harris, B.S. Taylor, M. Ladanyi, D. Mandelker, L. Zhang, V.E. Reuter, P.W. Kantoff, D.B. Solit, M.F. Berger, C. L. Sawyers, N. Schultz, H.I. Scher, Prospective Genomic Profiling of Prostate Cancer across Disease States Reveals Germline and Somatic Alterations that May Affect Clinical Decision Making, JCO Precis Oncol, 2017, p. 2017.
[31] H. Beltran, D. Prandi, J.M. Mosquera, M. Benelli, L. Puca, J. Cyrta, C. Marotz, E. Giannopoulou, B.V. Chakravarthi, S. Varambally, S.A. Tomlins, D.M. Nanus, S. T. Tagawa, E.M. Van Allen, O. Elemento, A. Sboner, L.A. Garraway, M.A. Rubin, F. Demichelis, Divergent clonal evolution of castration-resistant neuroendocrine prostate cancer, Nat. Med. 22 (2016) 298–305.
[32] K.H. Stopsack, C.A. Whittaker, T.A. Gerke, M. Loda, P.W. Kantoff, L.A. Mucci, A. Amon, Aneuploidy drives lethal progression in prostate cancer, Proc. Natl. Acad. Sci. U. S. A. 116 (2019) 11390–11395.
[33] H. Hieronymus, R. Murali, A. Tin, K. Yadav, W. Abida, H. Moller, D. Berney, H. Scher, B. Carver, P. Scardino, N. Schultz, B. Taylor, A. Vickers, J. Cuzick, C. L. Sawyers, Tumor copy number alteration burden is a pan-cancer prognostic factor associated with recurrence and death, Elife 7 (2018).
[34] H. Hieronymus, N. Schultz, A. Gopalan, B.S. Carver, M.T. Chang, Y. Xiao, A. Heguy, K. Huberman, M. Bernstein, M. Assel, R. Murali, A. Vickers, P. T. Scardino, C. Sander, V. Reuter, B.S. Taylor, C.L. Sawyers, Copy number alteration burdeInt. J. Endocr. Oncol.n predicts prostate cancer relapse, Proc. Natl. Acad. Sci. U. S. A. 111 (2014) 11139–11144.
[35] P.-L. Clermont, X. Ci, H. Pandha, Y. Wang, F. Crea, Treatment-emergent neuroendocrine prostate cancer: molecularly driven clinical guidelines, Int. J. Endocr. Oncol. 6 (2019).
[36] S.Y. Ku, S. Rosario, Y. Wang, P. Mu, M. Seshadri, Z.W. Goodrich, M.M. Goodrich, D.P. Labbé, E.C. Gomez, J. Wang, H.W. Long, B. Xu, M. Brown, M. Loda, C. L. Sawyers, L. Ellis, D.W. Goodrich, Rb1 and Trp53 cooperate to suppress prostate cancer lineage plasticity, metastasis, and antiandrogen resistance, Science 355 (2017) 78–83.
[37] A. Berger, N.J. Brady, R. Bareja, B. Robinson, V. Conteduca, M.A. Augello, L. Puca, A. Ahmed, E. Dardenne, X. Lu, I. Hwang, A.M. Bagadion, A. Sboner, O. Elemento, J. Paik, J. Yu, C.E. Barbieri, N. Dephoure, H. Beltran, D.S. Rickman, N-Myc-mediated epigenetic reprogramming drives lineage plasticity in advanced prostate cancer, J. Clin. Invest. 129 (2019) 3924–3940.
[38] R.B. Shah, K.T. Shore, J. Yoon, S. Mendrinos, J.K. McKenney, W. Tian, PTEN loss in prostatic adenocarcinoma correlates with specific adverse histologic features (intraductal carcinoma, cribriform Gleason pattern 4 and stromogenic carcinoma), Prostate 79 (2019) 1267–1273.
[39] C.W.D. Armstrong, P.J. Maxwell, C.W. Ong, K.M. Redmond, C. McCann, J. Neisen, G.A. Ward, G. Chessari, C. Johnson, N.T. Crawford, M.J. LaBonte, K. M. Prise, T. Robson, M. Salto-Tellez, D.B. Longley, D.J.J. Waugh, PTEN deficiency promotes macrophage infiltration and hypersensitivity of prostate cancer to IAP antagonist/radiation combination therapy, Oncotarget 7 (2016) 7885–7898.
[40] J. Zhang, X. Bu, H. Wang, Y. Zhu, Y. Geng, N.T. Nihira, Y. Tan, Y. Ci, F. Wu, X. Dai, J. Guo, Y.-H. Huang, C. Fan, S. Ren, Y. Sun, G.J. Freeman, P. Sicinski, W. Wei, Cyclin D-CDK4 kinase destabilizes PD-L1 via cullin 3-SPOP to control cancer immune surveillance, Nature 553 (2018) 91–95.
[41] C. Calagua, M. Ficial, C.S. Jansen, T. Hirz, L. Del Balzo, S. Wilkinson, R. Lake, A. T. Ku, O. Voznesensky, D.B. Sykes, P.J. Saylor, H. Ye, S. Signoretti, H. Kissick, A. G. Sowalsky, S.P. Balk, D.J. Einstein, A subset of localized prostate cancer displays an immunogenic phenotype Associated with losses of key tumor suppressor genes, Clin. Cancer Res. 27 (2021) 4836–4847.
[42] R. Deplus, C. Delliaux, N. Marchand, A. Flourens, N. Vanpouille, X. Leroy, Y. de Launoit, M. Duterque-Coquillaud, TMPRSS2-ERG fusion promotes prostate cancer metastases in bone, Oncotarget 8 (2017) 11827–11840.
[43] C.-C. Weng, P.-Y. Ding, Y.-H. Liu, J.R. Hawse, M. Subramaniam, C.-C. Wu, Y.-C. Lin, C.-Y. Chen, W.-C. Hung, K.-H. Cheng, Mutant Kras-induced upregulation of CD24 enhances prostate cancer stemness and bone metastasis, Oncogene 38 (2019) 2005–2019.
[44] E. Stankiewicz, X. Mao, D.C. Mangham, L. Xu, M. Yeste-Velasco, G. Fisher, B. North, T. Chaplin, B. Young, Y. Wang, J. Kaur Bansal, S. Kudahetti, L. Spencer, C.S. Foster, H. Møller, P. Scardino, R.T. Oliver, J. Shamash, J. Cuzick, C.S. Cooper, D.M. Berney, Y.-J. Lu, Identification of FBXL4 as a metastasis associated gene in prostate cancer, Sci. Rep. 7 (2017) 5124.
[45] L.F. van Dessel, J. van Riet, M. Smits, Y. Zhu, P. Hamberg, M.S. van der Heijden, A.M. Bergman, I.M. van Oort, R. de Wit, E.E. Voest, N. Steeghs, T.N. Yamaguchi, J. Livingstone, P.C. Boutros, J.W.M. Martens, S. Sleijfer, E. Cuppen, W. Zwart, H. J.G. van de Werken, N. Mehra, M.P. Lolkema, The genomic landscape of metastatic castration-resistant prostate cancers reveals multiple distinct genotypes with potential clinical impact, Nat. Commun. 10 (2019) 5251.
[48] S.L. Shiao, G.C. Chu, L.W. Chung, Regulation of prostate cancer progression by the tumor microenvironment, Cancer Lett. 380 (2016) 340–348.
[49] F. Bonollo, G.N. Thalmann, M. Kruithof-de Julio, S. Karkampouna, The role of cancer-associated fibroblasts in prostate cancer tumorigenesis, Cancers 12 (2020).
[50] P. Chiarugi, P. Paoli, P. Cirri, Tumor microenvironment and metabolism in prostate cancer, Semin. Oncol. 41 (2014) 267–280.
[51] J.A. Tuxhorn, G.E. Ayala, M.J. Smith, V.C. Smith, T.D. Dang, D.R. Rowley, Reactive stroma in human prostate cancer: induction of myofibroblast phenotype and extracellular matrix remodeling, Clin. Cancer Res. 8 (2002) 2912–2923.
[52] A.F. Olumi, G.D. Grossfeld, S.W. Hayward, P.R. Carroll, T.D. Tlsty, G.R. Cunha, Carcinoma-associated fibroblasts direct tumor progression of initiated human prostatic epithelium, Cancer Res. 59 (1999) 5002–5011.
[53] G.N. Thalmann, H. Rhee, R.A. Sikes, S. Pathak, A. Multani, H.E. Zhau, F. F. Marshall, L.W. Chung, Human prostate fibroblasts induce growth and confer castration resistance and metastatic potential in LNCaP Cells, Eur. Urol. 58 (2010) 162–171.
[54] G. Gabbiani, The myofibroblast in wound healing and fibrocontractive diseases, J. Pathol. 200 (2003) 500–503.
[55] C. Levesque, P.S. Nelson, Cellular constituents of the prostate stroma: key contributors to prostate cancer progression and therapy resistance, Cold Spring Harb. Perspect. Med. 8 (2018).
[56] T. Alkasalias, L. Moyano-Galceran, M. Arsenian-Henriksson, K. Lehti, Fibroblasts in the tumor microenvironment: shield or spear? Int. J. Mol. Sci. 19 (2018) 1532.
[57] Z. Yang, Y.C. Peng, A. Gopalan, D. Gao, Y. Chen, A.L. Joyner, Stromal hedgehog signaling maintains smooth muscle and hampers micro-invasive prostate cancer, Dis. Model. Mech. 10 (2017) 39–52.
[58] S. Chen, G. Zhu, Y. Yang, F. Wang, Y.T. Xiao, N. Zhang, X. Bian, Y. Zhu, Y. Yu, F. Liu, K. Dong, J. Mariscal, Y. Liu, F. Soares, H. Loo Yau, B. Zhang, W. Chen, C. Wang, D. Chen, Q. Guo, Z. Yi, M. Liu, M. Fraser, D.D. De Carvalho, P. C. Boutros, D. Di Vizio, Z. Jiang, T. van der Kwast, A. Berlin, S. Wu, J. Wang, H. H. He, S. Ren, Single-cell analysis reveals transcriptomic remodellings in distinct cell types that contribute to human prostate cancer progression, Nat. Cell Biol. 23 (2021) 87–98.
[59] M.V. Blagosklonny, Oncogenic resistance to growth-limiting conditions, Nat. Rev. Cancer 2 (2002) 221–225.
[60] K. Polyak, I. Haviv, I.G. Campbell, Co-evolution of tumor cells and their microenvironment, Trends Genet. 25 (2009) 30–38.
[61] S. Josson, Y. Matsuoka, L.W. Chung, H.E. Zhau, R. Wang, Tumor-stroma co-evolution in prostate cancer progression and metastasis, Semin. Cell Dev. Biol. 21 (2010) 26–32.
[62] S.Y. Sung, C.L. Hsieh, A. Law, H.E. Zhau, S. Pathak, A.S. Multani, S. Lim, I. M. Coleman, L.C. Wu, W.D. Figg, W.L. Dahut, P. Nelson, J.K. Lee, M.B. Amin, R. Lyles, P.A. Johnstone, F.F. Marshall, L.W. Chung, Coevolution of prostate cancer and bone stroma in three-dimensional coculture: implications for cancer growth and metastasis, Cancer Res. 68 (2008) 9996–10003.
[63] A. DiNatale, A. Fatatis, The bone microenvironment in prostate cancer metastasis, Adv. Exp. Med. Biol. 1210 (2019) 171–184.
[64] X. Lin, S. Patil, Y.G. Gao, A. Qian, The bone extracellular matrix in bone formation and regeneration, Front. Pharmacol. 11 (2020) 757.
[65] S.S. Deville, N. Cordes, The extracellular, cellular, and nuclear stiffness, a trinity in the cancer resistome-a review, Front. Oncol. 9 (2019) 1376.
[66] X. Pang, R. Xie, Z. Zhang, Q. Liu, S. Wu, Y. Cui, Identification of SPP1 as an extracellular matrix signature for metastatic castration-resistant prostate cancer, Front. Oncol. 9 (2019) 924.
[67] L. Tang, M. Xu, L. Zhang, L. Qu, X. Liu, Role of αVβ3 in prostate cancer: metastasis initiator and important therapeutic target, OncoTargets Ther. 13 (2020) 7411–7422.
[68] C.L. Hall, C.W. Dubyk, T.A. Riesenberger, D. Shein, E.T. Keller, K.L. van Golen, Type I collagen receptor (alpha2beta1) signaling promotes prostate cancer invasion through RhoC GTPase, Neoplasia 10 (2008) 797–803.
[69] R. San Martin, R. Pathak, A. Jain, S.Y. Jung, S.G. Hilsenbeck, M.C. Piña-Barba, A. G. Sikora, K.J. Pienta, D.R. Rowley, Tenascin-C and integrin α9 mediate interactions of prostate cancer with the bone microenvironment, Cancer Res. 77 (2017) 5977–5988.
[70] T. Yoshida, T. Akatsuka, K. Imanaka-Yoshida, Tenascin-C and integrins in cancer, Cell Adhes. Migrat. 9 (2015) 96–104.
[71] S. Karkampouna, M.R. De Filippo, C.K.Y. Ng, I. Klima, E. Zoni, M. Spahn, F. Stein, P. Haberkant, G.N. Thalmann, M. Kruithof de Julio, Stroma transcriptomic and proteomic profile of prostate cancer metastasis xenograft models reveals prognostic value of stroma signatures, Cancers 12 (2020).

[72] A. Gupta, W. Cao, M.A. Chellaiah, Integrin αvβ3 and CD44 pathways in metastatic prostate cancer cells support osteoclastogenesis via a Runx2/Smad 5/receptor activator of NF-κB ligand signaling axis, Mol. Cancer 11 (2012) 66.
[73] G.P. Gupta, J. Massagué, Cancer metastasis: building a framework, Cell 127 (2006) 679–695.
[74] B.J. Grindel, J.R. Martinez, T.V. Tellman, D.A. Harrington, H. Zafar, L. Nakhleh, L.W. Chung, M.C. Farach-Carson, Matrilysin/MMP-7 cleavage of perlecan/HSPG2 complexed with semaphorin 3A supports FAK-mediated stromal invasion by prostate cancer cells, Sci. Rep. 8 (2018) 7262.
[75] R.B. Berish, A.N. Ali, P.G. Telmer, J.A. Ronald, H.S. Leong, Translational models of prostate cancer bone metastasis, Nat. Rev. Urol. 15 (2018) 403–421.
[76] J. Fornetti, A.L. Welm, S.A. Stewart, Understanding the bone in cancer metastasis, J. Bone Miner. Res. 33 (2018) 2099–2113.
[77] S. Helo, J.P. Manger, T.L. Krupski, Role of denosumab in prostate cancer, Prostate Cancer Prostatic Dis. 15 (2012) 231–236.
[78] B.A. Gartrell, R. Coleman, E. Efstathiou, K. Fizazi, C.J. Logothetis, M.R. Smith, G. Sonpavde, O. Sartor, F. Saad, Metastatic prostate cancer and the bone: significance and therapeutic options, Eur. Urol. 68 (2015) 850–858.
[79] S.S. Ganguly, X. Li, C.K. Miranti, The host microenvironment influences prostate cancer invasion, systemic spread, bone colonization, and osteoblastic metastasis, Front. Oncol. 4 (2014) 364.
[80] K.N. Weilbaecher, T.A. Guise, L.K. McCauley, Cancer to bone: a fatal attraction, Nat. Rev. Cancer 11 (2011) 411–425.
[81] I. Roato, R. Ferracini, Solid tumours show osteotropism: mechanisms of bone metastases, Clin. Rev. Bone Miner. Metabol. 11 (2013).
[82] R.E. Coleman, P.I. Croucher, A.R. Padhani, P. Clézardin, E. Chow, M. Fallon, T. Guise, S. Colangeli, R. Capanna, L. Costa, Bone metastases, Nat. Rev. Dis. Prim. 6 (2020) 83.
[83] G. Furesi, M. Rauner, L.C. Hofbauer, Emerging players in prostate cancer–bone niche communication, Trends Canc. 7 (2021) 112–121.
[84] I. Moreno-Jiménez, A. Cipitria, A. Sánchez-Herrero, A.F. van Tol, A. Roschger, C. A. Lahr, J.A. McGovern, D.W. Hutmacher, P. Fratzl, Human and mouse bones physiologically integrate in a humanized mouse model while maintaining species-specific ultrastructure, Sci. Adv. 6 (2020), eabb9265.
[85] B. Meza-León, D. Gratzinger, A.G. Aguilar-Navarro, F.G. Juárez-Aguilar, V. I. Rebel, E. Torlakovic, L.E. Purton, E.M. Dorantes-Acosta, A. Escobar-Sánchez, J. E. Dick, E. Flores-Figueroa, Human, Mouse, and Dog Bone Marrow Show Similar Mesenchymal Stromal Cells within a Distinctive Microenvironment, Experimental Hematology, 2021.
[86] H. Peinado, H. Zhang, I.R. Matei, B. Costa-Silva, A. Hoshino, G. Rodrigues, B. Psaila, R.N. Kaplan, J.F. Bromberg, Y. Kang, M.J. Bissell, T.R. Cox, A.J. Giaccia, J.T. Erler, S. Hiratsuka, C.M. Ghajar, D. Lyden, Pre-metastatic niches: organ-specific homes for metastases, Nat. Rev. Cancer 17 (2017) 302–317.
[87] C.J. Logothetis, S.-H. Lin, Osteoblasts in prostate cancer metastasis to bone, Nat. Rev. Cancer 5 (2005) 21–28.
[88] P.D. Ottewell, The role of osteoblasts in bone metastasis, J. Oncol. 5 (2016) 124–127.
[89] B.C. Özdemir, J. Hensel, C. Secondini, A. Wetterwald, R. Schwaninger, A. Fleischmann, W. Raffelsberger, O. Poch, M. Delorenzi, R. Temanni, I.G. Mills, G. van der Pluijm, G.N. Thalmann, M.G. Cecchini, The molecular signature of the stroma response in prostate cancer-induced osteoblastic bone metastasis highlights expansion of hematopoietic and prostate epithelial stem cell niches, PLoS One 9 (2014), e114530.
[90] J. Hensel, A. Wetterwald, R. Temanni, I. Keller, C. Riether, G. van der Pluijm, M. G. Cecchini, G.N. Thalmann, Osteolytic cancer cells induce vascular/axon guidance processes in the bone/bone marrow stroma, Oncotarget 9 (No 48) (2018).
[91] K.R. Stone, D.D. Mickey, H. Wunderli, G.H. Mickey, D.F. Paulson, Isolation of a human prostate carcinoma cell line (DU 145), Int. J. Cancer 21 (1978) 274–281.
[92] J. Yin, C. Pollock, K. Tracy, M. Chock, P. Martin, M. Oberst, K. Kelly, Activation of the RalGEF/Ral pathway promotes prostate cancer metastasis to bone, Mol. Cell Biol. 27 (2007) 7538–7550.
[93] V. Vlaeminck-Guillem, Extracellular vesicles in prostate cancer carcinogenesis, diagnosis, and management, Front. Oncol. 8 (2018) 222.
[94] T. Lorenc, K. Klimczyk, I. Michalczewska, M. Słomka, G. Kubiak-Tomaszewska, W. Olejarz, Exosomes in prostate cancer diagnosis, prognosis and therapy, Int. J. Mol. Sci. 21 (2020).
[95] T.O. Adekoya, R.M. Richardson, Cytokines and chemokines as mediators of prostate cancer metastasis, Int. J. Mol. Sci. 21 (2020).
[96] T. Bellido, V.Z. Borba, P. Roberson, S.C. Manolagas, Activation of the Janus kinase/STAT (signal transducer and activator of transcription) signal transduction pathway by interleukin-6-type cytokines promotes osteoblast differentiation, Endocrinology 138 (1997) 3666–3676.
[97] J. Dai, J. Keller, J. Zhang, Y. Lu, Z. Yao, E.T. Keller, Bone morphogenetic protein-6 promotes osteoblastic prostate cancer bone metastases through a dual mechanism, Cancer Res. 65 (2005) 8274–8285.
[98] C.L. Hall, S. Kang, O.A. MacDougald, E.T. Keller, Role of Wnts in prostate cancer bone metastases, J. Cell. Biochem. 97 (2006) 661–672.
[99] R.E. Vickman, M.M. Broman, N.A. Lanman, O.E. Franco, P.A.G. Sudyanti, Y. Ni, Y. Ji, B.T. Helfand, J. Petkewicz, M.C. Paterakos, S.E. Crawford, T.L. Ratliff, S. W. Hayward, Heterogeneity of human prostate carcinoma-associated fibroblasts implicates a role for subpopulations in myeloid cell recruitment, Prostate 80 (2020) 173–185.
[100] R.D. Loberg, C. Ying, M. Craig, L.L. Day, E. Sargent, C. Neeley, K. Wojno, L. A. Snyder, L. Yan, K.J. Pienta, Targeting CCL2 with systemic delivery of neutralizing antibodies induces prostate cancer tumor regression in vivo, Cancer Res. 67 (2007) 9417–9424.
[101] R.D. Loberg, L.L. Day, J. Harwood, C. Ying, L.N. St John, R. Giles, C.K. Neeley, K. J. Pienta, CCL2 is a potent regulator of prostate cancer cell migration and proliferation, Neoplasia 8 (2006) 578–586.
[102] C. Probert, T. Dottorini, A. Speakman, S. Hunt, T. Nafee, A. Fazeli, S. Wood, J. E. Brown, V. James, Communication of prostate cancer cells with bone cells via extracellular vesicle RNA; a potential mechanism of metastasis, Oncogene 38 (2019) 1751–1763.
[103] C.M. Liu, C.L. Hsieh, C.N. Shen, C.C. Lin, K. Shigemura, S.Y. Sung, Exosomes from the tumor microenvironment as reciprocal regulators that enhance prostate cancer progression, Int. J. Urol. 23 (2016) 734–744.
[104] K. Hashimoto, H. Ochi, S. Sunamura, N. Kosaka, Y. Mabuchi, T. Fukuda, K. Yao, H. Kanda, K. Ae, A. Okawa, C. Akazawa, T. Ochiya, M. Futakuchi, S. Takeda, S. Sato, Cancer-secreted hsa-miR-940 induces an osteoblastic phenotype in the bone metastatic microenvironment via targeting ARHGAP1 and FAM134A, Proc. Natl. Acad. Sci. U. S. A. 115 (2018) 2204–2209.
[105] J. Morhayim, J. van de Peppel, J.A. Demmers, G. Kocer, A.L. Nigg, M. van Driel, H. Chiba, J.P. van Leeuwen, Proteomic signatures of extracellular vesicles secreted by nonmineralizing and mineralizing human osteoblasts and stimulation of tumor cell growth, Faseb. J. 29 (2015) 274–285.
[106] S.E. Henrich, K.M. McMahon, M.P. Plebanek, A.E. Calvert, T.J. Feliciano, S. Parrish, F. Tavora, A. Mega, A. De Souza, B.A. Carneiro, C.S. Thaxton, Prostate cancer extracellular vesicles mediate intercellular communication with bone marrow cells and promote metastasis in a cholesterol-dependent manner, J. Extracell. Vesicles 10 (2020), e12042.
[107] A. Hoshino, B. Costa-Silva, T.L. Shen, G. Rodrigues, A. Hashimoto, M. Tesic Mark, H. Molina, S. Kohsaka, A. Di Giannatale, S. Ceder, S. Singh, C. Williams, N. Soplop, K. Uryu, L. Pharmer, T. King, L. Bojmar, A.E. Davies, Y. Ararso, T. Zhang, H. Zhang, J. Hernandez, J.M. Weiss, V.D. Dumont-Cole, K. Kramer, L. H. Wexler, A. Narendran, G.K. Schwartz, J.H. Healey, P. Sandstrom, K.J. Labori, E.H. Kure, P.M. Grandgenett, M.A. Hollingsworth, M. de Sousa, S. Kaur, M. Jain, K. Mallya, S.K. Batra, W.R. Jarnagin, M.S. Brady, O. Fodstad, V. Muller, K. Pantel, A.J. Minn, M.J. Bissell, B.A. Garcia, Y. Kang, V.K. Rajasekhar, C.M. Ghajar, I. Matei, H. Peinado, J. Bromberg, D. Lyden, Tumour exosome integrins determine organotropic metastasis, Nature 527 (2015) 329–335.
[108] G. Deep, A. Jain, A. Kumar, C. Agarwal, S. Kim, W.M. Leevy, R. Agarwal, Exosomes secreted by prostate cancer cells under hypoxia promote matrix metalloproteinases activity at pre-metastatic niches, Mol. Carcinog. 59 (2020) 323–332.
[109] J. Dai, J. Escara-Wilke, J.M. Keller, Y. Jung, R.S. Taichman, K.J. Pienta, E. T. Keller, Primary prostate cancer educates bone stroma through exosomal pyruvate kinase M2 to promote bone metastasis, J. Exp. Med. 216 (2019) 2883–2899.
[110] M. Zayzafoon, S.A. Abdulkadir, J.M. McDonald, Notch signaling and ERK activation are important for the osteomimetic properties of prostate cancer bone metastatic cell lines, J. Biol. Chem. 279 (2004) 3662–3670.
[111] S. Tyekucheva, M. Bowden, C. Bango, F. Giunchi, Y. Huang, C. Zhou, A. Bondi, R. Lis, M. Van Hemelrijck, O. Andrén, S.-O. Andersson, R.W. Watson, S. Pennington, S.P. Finn, N.E. Martin, M.J. Stampfer, G. Parmigiani, K.L. Penney, M. Fiorentino, L.A. Mucci, M. Loda, Stromal and epithelial transcriptional map of initiation progression and metastatic potential of human prostate cancer, Nat. Commun. 8 (2017) 420.
[112] T. Tsunoda, B. Furusato, Y. Takashima, S. Ravulapalli, A. Dobi, S. Srivastava, D. G. McLeod, I.A. Sesterhenn, D.K. Ornstein, S. Shirasawa, The increased expression of periostin during early stages of prostate cancer and advanced stages of cancer stroma, Prostate 69 (2009) 1398–1403.
[113] M. Singh, R. Jha, J. Melamed, E. Shapiro, S.W. Hayward, P. Lee, Stromal androgen receptor in prostate development and cancer, Am. J. Pathol. 184 (2014) 2598–2607.
[114] P. Wikström, J. Marusic, P. Stattin, A. Bergh, Low stroma androgen receptor level in normal and tumor prostate tissue is related to poor outcome in prostate cancer patients, Prostate 69 (2009) 799–809.
[115] C. Ricciardelli, C.S. Choong, G. Buchanan, S. Vivekanandan, P. Neufing, J. Stahl, V.R. Marshall, D.J. Horsfall, W.D. Tilley, Androgen receptor levels in prostate cancer epithelial and peritumoral stromal cells identify non-organ confined disease, Prostate 63 (2005) 19–28.
[116] D.A. Leach, E.F. Need, R. Toivanen, A.P. Trotta, H.M. Palethorpe, D.J. Tamblyn, T. Kopsaftis, G.M. England, E. Smith, P.A. Drew, C.B. Pinnock, P. Lee, J. Holst, G. P. Risbridger, S. Chopra, D.B. DeFranco, R.A. Taylor, G. Buchanan, Stromal androgen receptor regulates the composition of the microenvironment to influence prostate cancer outcome, Oncotarget 6 (2015) 16135–16150.
[117] A. Mantalaris, N. Panoskaltsis, Y. Sakai, P. Bourne, C. Chang, E.M. Messing, J. H. David Wu, Localization of androgen receptor expression in human bone marrow, J. Pathol. 193 (2001) 361–366.
[118] T. Gevaert, Y.R. Van Eycke, T. Vanden Broeck, H. Van Poppel, I. Salmon, S. Rorive, T. Muilwijk, F. Claessens, D. De Ridder, S. Joniau, C. Decaestecker, The potential of tumour microenvironment markers to stratify the risk of recurrence in prostate cancer patients, PLoS One 15 (2020), e0244663.
[119] M.A. Kiebish, J. Cullen, P. Mishra, A. Ali, E. Milliman, L.O. Rodrigues, E.Y. Chen, V. Tolstikov, L. Zhang, K. Panagopoulos, P. Shah, Y. Chen, G. Petrovics, I. L. Rosner, I.A. Sesterhenn, D.G. McLeod, E. Granger, R. Sarangarajan, V. Akmaev, A. Srinivasan, S. Srivastava, N.R. Narain, A. Dobi, Multi-omic serum biomarkers for prognosis of disease progression in prostate cancer, J. Transl. Med. 18 (2020) 10.

[120] K. Ishii, S. Takahashi, Y. Sugimura, M. Watanabe, Role of stromal paracrine signals in proliferative diseases of the aging human prostate, J. Clin. Med. 7 (2018) 68.
[121] S. Kajiwara, K. Ishii, T. Sasaki, M. Kato, K. Nishikawa, H. Kanda, K. Arima, M. Watanabe, Y. Sugimura, Castration-induced stromal remodeling disrupts the reconstituted prostate epithelial structure, Lab. Invest. 100 (2020) 670–681.
[122] Z. Zhang, W.R. Karthaus, Y.S. Lee, V.R. Gao, C. Wu, J.W. Russo, M. Liu, J. M. Mota, W. Abida, E. Linton, E. Lee, S.D. Barnes, H.-A. Chen, N. Mao, J. Wongvipat, D. Choi, X. Chen, H. Zhao, K. Manova-Todorova, E. de Stanchina, M.-E. Taplin, S.P. Balk, D.E. Rathkopf, A. Gopalan, B.S. Carver, P. Mu, X. Jiang, P. A. Watson, C.L. Sawyers, Tumor microenvironment-derived NRG1 promotes antiandrogen resistance in prostate cancer, Cancer Cell 38 (2020) 279–296, e279.
[123] B. Cioni, E. Nevedomskaya, M.H.M. Melis, J. van Burgsteden, S. Stelloo, E. Hodel, D. Spinozzi, J. de Jong, H. van der Poel, J.P. de Boer, L.F.A. Wessels, W. Zwart, A. M. Bergman, Loss of androgen receptor signaling in prostate cancer-associated fibroblasts (CAFs) promotes CCL2- and CXCL8-mediated cancer cell migration, Mol. Oncol. 12 (2018) 1308–1323.
[124] V.R. Placencio, A.R. Sharif-Afshar, X. Li, H. Huang, C. Uwamariya, E.G. Neilson, M.M. Shen, R.J. Matusik, S.W. Hayward, N.A. Bhowmick, Stromal transforming growth factor-beta signaling mediates prostatic response to androgen ablation by paracrine Wnt activity, Cancer Res. 68 (2008) 4709–4718.
[125] P.D. Ottewell, N. Wang, J. Meek, C.A. Fowles, P.I. Croucher, C.L. Eaton, I. Holen, Castration-induced bone loss triggers growth of disseminated prostate cancer cells in bone, Endocr. Relat. Cancer 21 (2014) 769–781.
[126] G. van der Pluijm, I. Que, B. Sijmons, J.T. Buijs, C.W. Löwik, A. Wetterwald, G. N. Thalmann, S.E. Papapoulos, M.G. Cecchini, Interference with the microenvironmental support impairs the de novo formation of bone metastases in vivo, Cancer Res. 65 (2005) 7682–7690.
[127] M.X. He, M.S. Cuoco, J. Crowdis, A. Bosma-Moody, Z. Zhang, K. Bi, A. Kanodia, M.J. Su, S.Y. Ku, M.M. Garcia, A.R. Sweet, C. Rodman, L. DelloStritto, R. Silver, J. Steinharter, P. Shah, B. Izar, N.C. Walk, K.P. Burke, Z. Bakouny, A.K. Tewari, D. Liu, S.Y. Camp, N.I. Vokes, K. Salari, J. Park, S. Vigneau, L. Fong, J.W. Russo, X. Yuan, S.P. Balk, H. Beltran, O. Rozenblatt-Rosen, A. Regev, A. Rotem, M. E. Taplin, E.M. Van Allen, Transcriptional mediators of treatment resistance in lethal prostate cancer, Nat. Med. 27 (2021) 426–433.
[128] Y. Sun, J. Campisi, C. Higano, T.M. Beer, P. Porter, I. Coleman, L. True, P. S. Nelson, Treatment-induced damage to the tumor microenvironment promotes prostate cancer therapy resistance through WNT16B, Nat. Med. 18 (2012) 1359–1368.
[129] J.R. Gingrich, R.J. Barrios, R.A. Morton, B.F. Boyce, F.J. DeMayo, M.J. Finegold, R. Angelopoulou, J.M. Rosen, N.M. Greenberg, Metastatic prostate cancer in a transgenic mouse, Cancer Res. 56 (1996) 4096–4102.
[130] P.J. Kaplan-Lefko, T.M. Chen, M.M. Ittmann, R.J. Barrios, G.E. Ayala, W.J. Huss, L.A. Maddison, B.A. Foster, N.M. Greenberg, Pathobiology of autochthonous prostate cancer in a pre-clinical transgenic mouse model, Prostate 55 (2003) 219–237.
[131] E.M. Garabedian, P.A. Humphrey, J.I. Gordon, A transgenic mouse model of metastatic prostate cancer originating from neuroendocrine cells, Proc. Natl. Acad. Sci. Unit. States Am. 95 (1998) 15382–15387.
[132] N. Masumori, T.Z. Thomas, P. Chaurand, T. Case, M. Paul, S. Kasper, R. M. Caprioli, T. Tsukamoto, S.B. Shappell, R.J. Matusik, A probasin-large T antigen transgenic mouse line develops prostate adenocarcinoma and neuroendocrine carcinoma with metastatic potential, Cancer Res. 61 (2001) 2239–2249.
[133] C. Perez-Stable, N.H. Altman, P.P. Mehta, L.J. Deftos, B.A. Roos, Prostate cancer progression, metastasis, and gene expression in transgenic mice, Cancer Res. 57 (1997) 900–906.
[134] N. Yanagisawa, R. Li, D. Rowley, H. Liu, D. Kadmon, B.J. Miles, T.M. Wheeler, G. E. Ayala, Stromogenic prostatic carcinoma pattern (carcinomas with reactive stromal grade 3) in needle biopsies predicts biochemical recurrence-free survival in patients after radical prostatectomy, Hum. Pathol. 38 (2007) 1611–1620.
[135] M. Bezzi, N. Seitzer, T. Ishikawa, M. Reschke, M. Chen, G. Wang, C. Mitchell, C. Ng, J. Katon, A. Lunardi, S. Signoretti, J.G. Clohessy, J. Zhang, P.P. Pandolfi, Diverse genetic-driven immune landscapes dictate tumor progression through distinct mechanisms, Nat. Med. 24 (2018) 165–175.
[136] T.M. Morgan, P.H. Lange, M.P. Porter, D.W. Lin, W.J. Ellis, I.S. Gallaher, R. L. Vessella, Disseminated tumor cells in prostate cancer patients after radical prostatectomy and without evidence of disease predicts biochemical recurrence, Clin. Cancer Res. 15 (2009) 677–683.
[137] J.M. Arriaga, S. Panja, M. Alshalalfa, J. Zhao, M. Zou, A. Giacobbe, C. J. Madubata, J. Yeji Kim, A. Rodriguez, I. Coleman, R.K. Virk, H. Hibshoosh, O. Ertunc, B. Ozbek, J. Fountain, R.J. Karnes, J. Luo, E.S. Antonarakis, P. S. Nelson, F.Y. Feng, M.A. Rubin, A.M. De Marzo, R. Rabadan, P.A. Sims, A. Mitrofanova, C. Abate-Shen, A MYC and RAS co-activation signature in localized prostate cancer drives bone metastasis and castration resistance, Nat. Can. 1 (2020) 1082–1096.
[138] A. Aytes, A. Mitrofanova, C.W. Kinkade, C. Lefebvre, M. Lei, V. Phelan, H. C. LeKaye, J.A. Koutcher, R.D. Cardiff, A. Califano, M.M. Shen, C. Abate-Shen, ETV4 promotes metastasis in response to activation of PI3-kinase and Ras signaling in a mouse model of advanced prostate cancer, Proc. Natl. Acad. Sci. U. S. A 110 (2013) E3506–E3515.
[139] J.M. Arriaga, C. Abate-Shen, Genetically engineered mouse models of prostate cancer in the postgenomic era, Cold Spring Harb. Perspect. Med. 9 (2019).
[140] Z. Ding, C.J. Wu, M. Jaskelioff, E. Ivanova, M. Kost-Alimova, A. Protopopov, G. C. Chu, G. Wang, X. Lu, E.S. Labrot, J. Hu, W. Wang, Y. Xiao, H. Zhang, J. Zhang, J. Zhang, B. Gan, S.R. Perry, S. Jiang, L. Li, J.W. Horner, Y.A. Wang, L. Chin, R. A. DePinho, Telomerase reactivation following telomere dysfunction yields murine prostate tumors with bone metastases, Cell 148 (2012) 896–907.
[141] M. Ittmann, J. Huang, E. Radaelli, P. Martin, S. Signoretti, R. Sullivan, B. W. Simons, J.M. Ward, B.D. Robinson, G.C. Chu, M. Loda, G. Thomas, A. Borowsky, R.D. Cardiff, Animal models of human prostate cancer: the consensus report of the New York meeting of the mouse models of human cancers consortium prostate pathology committee, Cancer Res. 73 (2013) 2718–2736.
[142] Z. Ding, C.J. Wu, G.C. Chu, Y. Xiao, D. Ho, J. Zhang, S.R. Perry, E.S. Labrot, X. Wu, R. Lis, Y. Hoshida, D. Hiller, B. Hu, S. Jiang, H. Zheng, A.H. Stegh, K. L. Scott, S. Signoretti, N. Bardeesy, Y.A. Wang, D.E. Hill, T.R. Golub, M. J. Stampfer, W.H. Wong, M. Loda, L. Mucci, L. Chin, R.A. Depinho, SMAD4-dependent barrier constrains prostate cancer growth and metastatic progression, Nature 470 (2011) 269–276.
[143] A. Lunardi, U. Ala, M.T. Epping, L. Salmena, J.G. Clohessy, K.A. Webster, G. Wang, R. Mazzucchelli, M. Bianconi, E.C. Stack, R. Lis, A. Patnaik, L.C. Cantley, G. Bubley, C. Cordon-Cardo, W.L. Gerald, R. Montironi, S. Signoretti, M. Loda, C. Nardella, P.P. Pandolfi, A co-clinical approach identifies mechanisms and potential therapies for androgen deprivation resistance in prostate cancer, Nat. Genet. 45 (2013) 747–755.
[144] J. Kim, M. Roh, I. Doubinskaia, G.N. Algarroba, I.E.A. Eltoum, S.A. Abdulkadir, A mouse model of heterogeneous, c-MYC-initiated prostate cancer with loss of Pten and p53, Oncogene 31 (2012) 322–332.
[145] K. Ellwood-Yen, T.G. Graeber, J. Wongvipat, M.L. Iruela-Arispe, J. Zhang, R. Matusik, G.V. Thomas, C.L. Sawyers, Myc-driven murine prostate cancer shares molecular features with human prostate tumors, Cancer Cell 4 (2003) 223–238.
[146] B.W. Simons, V. Kothari, B. Benzon, K. Ghabili, R. Hughes, J.C. Zarif, A.E. Ross, P. J. Hurley, E.M. Schaeffer, A mouse model of prostate cancer bone metastasis in a syngeneic immunocompetent host, Oncotarget 10 (2019) 6845–6854.
[147] G.K. Hubbard, L.N. Mutton, M. Khalili, R.P. McMullin, J.L. Hicks, D. Bianchi-Frias, L.A. Horn, I. Kulac, M.S. Moubarek, P.S. Nelson, S. Yegnasubramanian, A. M. De Marzo, C.J. Bieberich, Combined MYC activation and Pten loss are sufficient to create genomic instability and lethal metastatic prostate cancer, Cancer Res. 76 (2016) 283–292.
[148] J. Mestas, C.C.W. Hughes, Of mice and not men: differences between mouse and human immunology, J. Immunol. 172 (2004) 2731–2738.
[149] M. Kerschnitzki, W. Wagermaier, P. Roschger, J. Seto, R. Shahar, G.N. Duda, S. Mundlos, P. Fratzl, The organization of the osteocyte network mirrors the extracellular matrix orientation in bone, J. Struct. Biol. 173 (2011) 303–311.
[150] L.C. Martine, B.M. Holzapfel, J.A. McGovern, F. Wagner, V.M. Quent, P. Hesami, F.M. Wunner, C. Vaquette, E.M. De-Juan-Pardo, T.D. Brown, B. Nowlan, D.J. Wu, C.O. Hutmacher, D. Moi, T. Oussenko, E. Piccinini, P.W. Zandstra, R. Mazzieri, J. P. Lévesque, P.D. Dalton, A.V. Taubenberger, D.W. Hutmacher, Engineering a humanized bone organ model in mice to study bone metastases, Nat. Protoc. 12 (2017) 639–663.
[151] J.A. McGovern, N. Bock, A. Shafiee, L.C. Martine, F. Wagner, J.G. Baldwin, M. Landgraf, C.A. Lahr, C. Meinert, E.D. Williams, P.M. Pollock, J. Denham, P. J. Russell, G.P. Risbridger, J.A. Clements, D. Loessner, B.M. Holzapfel, D. W. Hutmacher, A humanized orthotopic tumor microenvironment alters the bone metastatic tropism of prostate cancer cells, Commun. Biol. (2021) 1014.
[152] N. Bock, T. Kryza, A. Shokoohmand, J. Röhl, A. Ravichandran, M.-L. Wille, C. C. Nelson, D.W. Hutmacher, J.A. Clements, In vitro engineering of a bone metastases model allows for study of the effects of antiandrogen therapies in advanced prostate cancer, Sci. Adv. 7 (2021).
[153] J.A. McGovern, A. Shafiee, F. Wagner, C.A. Lahr, M. Landgraf, C. Meinert, E. D. Williams, P.J. Russell, J.A. Clements, D. Loessner, B.M. Holzapfel, G. P. Risbridger, D.W. Hutmacher, Humanization of the prostate microenvironment reduces homing of PC3 prostate cancer cells to human tissue-engineered bone, Cancers 10 (2018).
[154] D.J. Mulholland, N. Kobayashi, M. Ruscetti, A. Zhi, L.M. Tran, J. Huang, M. Gleave, H. Wu, Pten loss and RAS/MAPK activation cooperate to promote EMT and metastasis initiated from prostate cancer stem/progenitor cells, Cancer Res. 72 (2012) 1878–1889.
[155] J. Wang, T. Kobayashi, N. Floc'h, C.W. Kinkade, A. Aytes, D. Dankort, C. Lefebvre, A. Mitrofanova, R.D. Cardiff, M. McMahon, A. Califano, M.M. Shen, C. Abate-Shen, B-Raf activation cooperates with PTEN loss to drive c-Myc expression in advanced prostate cancer, Cancer Res. 72 (2012) 4765–4776.
[156] C.J. Kane, C.L. Amling, P.A.S. Johnstone, N. Pak, R.S. Lance, J.B. Thrasher, J. P. Foley, R.H. Riffenburgh, J.W. Moul, Limited value of bone scintigraphy and computed tomography in assessing biochemical failure after radical prostatectomy, Urology 61 (2003) 607–611.
[157] T. Beyer, D.W. Townsend, T. Brun, P.E. Kinahan, M. Charron, R. Roddy, J. Jerin, J. Young, L. Byars, R. Nutt, A combined PET/CT scanner for clinical oncology, J. Nucl. Med. 41 (2000) 1369.
[158] T. Hara, N. Kosaka, H. Kishi, PET imaging of prostate cancer using carbon-11-choline, J. Nucl. Med. 39 (1998) 990–995.
[159] K. Glunde, Z.M. Bhujwalla, S.M. Ronen, Choline metabolism in malignant transformation, Nat. Rev. Cancer 11 (2011) 835–848.
[160] T. Lowrance William, H. Breau Rodney, R. Chou, F. Chapin Brian, T. Crispino, R. Dreicer, F. Jarrard David, S. Kibel Adam, M. Morgan Todd, K. Morgans Alicia, K. Oh William, J. Resnick Matthew, L. Zietman Anthony, S. Cookson Michael, Advanced prostate cancer: AUA/ASTRO/SUO guideline PART I, J. Urol. 205 (2021) 14–21.
[161] S. Bastawrous, P. Bhargava, F. Behnia, D.S.W. Djang, D.R. Haseley, Newer PET application with an old tracer: role of 18F-NaF skeletal PET/CT in oncologic practice, Radiographics 34 (2014) 1295–1316.

[162] C. Uprimny, A. Svirydenka, J. Fritz, A.S. Kroiss, B. Nilica, C. Decristoforo, R. Haubner, E. von Guggenberg, S. Buxbaum, W. Horninger, I.J. Virgolini, Comparison of [68Ga]Ga-PSMA-11 PET/CT with [18F]NaF PET/CT in the evaluation of bone metastases in metastatic prostate cancer patients prior to radionuclide therapy, Eur. J. Nucl. Med. Mol. Imag. 45 (2018) 1873–1883.
[163] J.S. Horoszewicz, G.P. Kawinski, E Fau - Murphy, G.P. Murphy, Monoclonal antibodies to a new antigenic marker in epithelial prostatic cells and serum of prostatic cancer patients, Anticancer Res. 7 (5B) (1987) 927–935.
[164] R.S. Israeli, C.T. Powell, J.G. Corr, W.R. Fair, W.D.W. Heston, Expression of the prostate-specific membrane antigen, Cancer Res. 54 (1994) 1807.
[165] R.S. Israeli, C.T. Powell, W.R. Fair, W.D.W. Heston, Molecular cloning of a complementary DNA encoding a prostate-specific membrane antigen, Cancer Res. 53 (1993) 227.
[166] K.A.-O. Rahbar, A. Afshar-Oromieh, H. Jadvar, H. Ahmadzadehfar, PSMA Theranostics: Current Status and Future Directions.
[167] A. Afshar-Oromieh, A. Malcher, M. Eder, M. Eisenhut, H.G. Linhart, B. A. Hadaschik, T. Holland-Letz, F.L. Giesel, C. Kratochwil, S. Haufe, U. Haberkorn, C.M. Zechmann, PET imaging with a [68Ga]gallium-labelled PSMA ligand for the diagnosis of prostate cancer: biodistribution in humans and first evaluation of tumour lesions, Eur. J. Nucl. Med. Mol. Imag. 40 (2013) 486–495.
[168] W.J.L.R.A. Shimkets, The Oncogenomics Handbook, Humana Press, Totowa, New Jersey, 2005.
[169] C. Sachpekidis, K. Kopka, M. Eder, B.A. Hadaschik, M.T. Freitag, L. Pan, U. Haberkorn, A. Dimitrakopoulou-Strauss, 68Ga-PSMA-11 dynamic PET/CT imaging in primary prostate cancer, Clin. Nucl. Med. 41 (2016).
[170] M.S. Hofman, N. Lawrentschuk, R.J. Francis, C. Tang, I. Vela, P. Thomas, N. Rutherford, J.M. Martin, M. Frydenberg, R. Shakher, L.-M. Wong, K. Taubman, S. Ting Lee, E. Hsiao, P. Roach, M. Nottage, I. Kirkwood, D. Hayne, E. Link, P. Marusic, A. Matera, A. Herschtal, A. Iravani, R.J. Hicks, S. Williams, D. G. Murphy, Prostate-specific membrane antigen PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA): a prospective, randomised, multicentre study, Lancet 395 (2020) 1208–1216.
[171] J. Calais, F. Ceci, M. Eiber, T.A. Hope, M.S. Hofman, C. Rischpler, T. Bach-Gansmo, C. Nanni, B. Savir-Baruch, D. Elashoff, T. Grogan, M. Dahlbom, R. Slavik, J. Gartmann, K. Nguyen, V. Lok, H. Jadvar, A.U. Kishan, M.B. Rettig, R. E. Reiter, W.P. Fendler, J. Czernin, 18F-fluciclovine PET-CT and 68Ga-PSMA-11 PET-CT in patients with early biochemical recurrence after prostatectomy: a prospective, single-centre, single-arm, comparative imaging trial, Lancet Oncol. 20 (2019) 1286–1294.
[172] I. Alberts, C. Sachpekidis, V. Fech, A. Rominger, A. Afshar-Oromieh, PSMA-negative prostate cancer and the continued value of choline-PET/CT, Nuklearmedizin, Nucl. Med. 59 (2020) 1.
[173] J. Calais, J. Czernin, M. Cao, A.U. Kishan, J.V. Hegde, N. Shaverdian, K. Sandler, F.I. Chu, C.R. King, M.L. Steinberg, I. Rauscher, N.S. Schmidt-Hegemann, T. Poeppel, P. Hetkamp, F. Ceci, K. Herrmann, W.P. Fendler, M. Eiber, N. G. Nickols, 68)Ga-PSMA-11 PET/CT mapping of prostate cancer biochemical recurrence after radical prostatectomy in 270 patients with a PSA level of less than 1.0 ng/mL: impact on salvage radiotherapy planning, J. Nucl. Med. 59 (2018) 230–237.
[174] B. Grubmuller, P. Baltzer, D. D'Andrea, S. Korn, A.R. Haug, M. Hacker, K. H. Grubmuller, G.M. Goldner, W. Wadsak, S. Pfaff, J. Babich, C. Seitz, H. Fajkovic, M. Susani, P. Mazal, G. Kramer, S.F. Shariat, M. Hartenbach, 68)Ga-PSMA 11 ligand PET imaging in patients with biochemical recurrence after radical prostatectomy - diagnostic performance and impact on therapeutic decision-making, Eur. J. Nucl. Med. Mol. Imag. 45 (2018) 235–242.
[175] J. Calais, J. Czernin, W.P. Fendler, D. Elashoff, N.G. Nickols, Randomized prospective phase III trial of (68)Ga-PSMA-11 PET/CT molecular imaging for prostate cancer salvage radiotherapy planning [PSMA-SRT], BMC Cancer 19 (2019) 18.
[176] I.L. Alberts, S.E. Seide, C. Mingels, K.P. Bohn, K. Shi, H.D. Zacho, A. Rominger, A. Afshar-Oromieh, Comparing the diagnostic performance of radiotracers in recurrent prostate cancer: a systematic review and network meta-analysis, Eur. J. Nucl. Med. Mol. Imag. 48 (9) (2021) 2978–2989.
[177] S. Frangos, J.R. Buscombe, Why should we be concerned about a "g", Eur. J. Nucl. Med. Mol. Imag. 46 (2019) 519. -519.
[178] O. Sartor, R. Coleman, S. Nilsson, D. Heinrich, S.I. Helle, J.M. O'Sullivan, S. D. Fosså, A. Chodacki, P. Wiechno, J. Logue, A. Widmark, D.C. Johannessen, P. Hoskin, N.D. James, A. Solberg, I. Syndikus, N.J. Vogelzang, C.G. O'Bryan-Tear, M. Shan, Ø.S. Bruland, C. Parker, Effect of radium-223 dichloride on symptomatic skeletal events in patients with castration-resistant prostate cancer and bone metastases: results from a phase 3, double-blind, randomised trial, Lancet Oncol. 15 (2014) 738–746.
[179] C. Kratochwil, W.P. Fendler, M. Eiber, R. Baum, M.F. Bozkurt, J. Czernin, R. C. Delgado Bolton, S. Ezziddin, F. Forrer, R.J. Hicks, T.A. Hope, L. Kabasakal, M. Konijnenberg, K. Kopka, M. Lassmann, F.M. Mottaghy, W. Oyen, K. Rahbar, H. Schöder, I. Virgolini, H.-J. Wester, L. Bodei, S. Fanti, U. Haberkorn, K. Herrmann, EANM procedure guidelines for radionuclide therapy with 177Lu-labelled PSMA-ligands (177Lu-PSMA-RLT), Eur. J. Nucl. Med. Mol. Imag. 46 (2019) 2536–2544.
[180] S. Fanti, S. Minozzi, G. Antoch, I. Banks, A. Briganti, I. Carrio, A. Chiti, N. Clarke, M. Eiber, J. De Bono, K. Fizazi, S. Gillessen, S. Gledhill, U. Haberkorn, K. Herrmann, R.J. Hicks, F. Lecouvet, R. Montironi, P. Ost, J.M. O'Sullivan, A. R. Padhani, J.A. Schalken, H.I. Scher, B. Tombal, R.J.A. van Moorselaar, H. Van Poppel, H.A. Vargas, J. Walz, W.A. Weber, H.-J. Wester, W.J.G. Oyen, Consensus on molecular imaging and theranostics in prostate cancer, Lancet Oncol. 19 (2018) e696–e708.
[181] R. Gallicchio, S. Giacomobono, A. Nardelli, T. Pellegrino, V. Simeon, D. Gattozzi, F. Maddalena, P. Mainenti, G. Storto, Palliative treatment of bone metastases with samarium-153 EDTMP at onset of pain, J. Bone Miner. Metabol. 32 (2014) 434–440.
[182] S. Nilsson, P. Strang, A.K. Aksnes, L. Franzèn, P. Olivier, A. Pecking, J. Staffurth, S. Vasanthan, C. Andersson, Ø.S. Bruland, A randomized, dose–response, multicenter phase II study of radium-223 chloride for the palliation of painful bone metastases in patients with castration-resistant prostate cancer, Eur. J. Cancer 48 (2012) 678–686.
[183] T.D. Poeppel, D. Handkiewicz-Junak, M. Andreeff, A. Becherer, A. Bockisch, E. Fricke, L. Geworski, A. Heinzel, B.J. Krause, T. Krause, M. Mitterhauser, W. Sonnenschein, L. Bodei, R.C. Delgado-Bolton, M. Gabriel, EANM guideline for radionuclide therapy with radium-223 of metastatic castration-resistant prostate cancer, Eur. J. Nucl. Med. Mol. Imag. 45 (2018) 824–845.
[184] M.J. Morris, E. Corey, T.A. Guise, J.L. Gulley, W. Kevin Kelly, D.I. Quinn, A. Scholz, G. Sgouros, Radium-223 mechanism of action: implications for use in treatment combinations, Nat. Rev. Urol. 16 (2019) 745–756.
[185] P. Hoskin, O. Sartor, J.M. O'Sullivan, D.C. Johannessen, S.I. Helle, J. Logue, D. Bottomley, S. Nilsson, N.J. Vogelzang, F. Fang, M. Wahba, A.K. Aksnes, C. Parker, Efficacy and safety of radium-223 dichloride in patients with castration-resistant prostate cancer and symptomatic bone metastases, with or without previous docetaxel use: a prespecified subgroup analysis from the randomised, double-blind, phase 3 ALSYMPCA trial, Lancet Oncol. 15 (2014) 1397–1406.
[186] W.P.t. Skelton, S.W. Dibenedetto, S.S. Pang, K. Pan, J.L. Barish, A. Nwosu-Iheme, L. Dang, A single-center retrospective analysis of the effect of radium-223 (Xofigo) on pancytopenia in patients with metastatic castration-resistant prostate cancer, Cureus 12 (2020) e6806. -e6806.
[187] A. Afshar-Oromieh, U. Haberkorn, C. Zechmann, T. Armor, W. Mier, F. Spohn, N. Debus, T. Holland-Letz, J. Babich, C. Kratochwil, Repeated PSMA-targeting radioligand therapy of metastatic prostate cancer with 131I-MIP-1095, Eur. J. Nucl. Med. Mol. Imag. 44 (2017) 950–959.
[188] K. Rahbar, H. Ahmadzadehfar, C. Kratochwil, U. Haberkorn, M. Schäfers, M. Essler, R.P. Baum, H.R. Kulkarni, M. Schmidt, A. Drzezga, P. Bartenstein, A. Pfestroff, M. Luster, U. Lützen, M. Marx, V. Prasad, W. Brenner, A. Heinzel, F. M. Mottaghy, J. Ruf, P.T. Meyer, M. Heuschkel, M. Eveslage, M. Bögemann, W. P. Fendler, B.J. Krause, German multicenter study investigating 177Lu-PSMA-617 radioligand therapy in advanced prostate cancer patients, J. Nucl. Med. 58 (2017) 85.
[189] M.S. Hofman, L. Emmett, S. Sandhu, A. Iravani, A.M. Joshua, J.C. Goh, D. A. Pattison, T.H. Tan, I.D. Kirkwood, S. Ng, R.J. Francis, C. Gedye, N. K. Rutherford, A. Weickhardt, A.M. Scott, S.-T. Lee, E.M. Kwan, A.A. Azad, S. Ramdave, A.D. Redfern, W. Macdonald, A. Guminski, E. Hsiao, W. Chua, P. Lin, A.Y. Zhang, M.M. McJannett, M.R. Stockler, J.A. Violet, S.G. Williams, A. J. Martin, I.D. Davis, A.A. Azad, W. Chua, I.D. Davis, N. Dhiantravan, L. Emmett, K. Ford, M.S. Hofman, R.J. Francis, C. Gedye, J.C. Goh, A. Guminski, E. Hsiao, A. Iravani, A.M. Joshua, I.D. Kirkwood, A. Langford, N. Lawrence, S.-T. Lee, P. Lin, A.J. Martin, W. McDonald, M.M. McJannett, S. Ng, D.A. Pattison, S. Ramdave, N. Rana, A.D. Redfern, N.K. Rutherford, S. Sandhu, A.M. Scott, M. R. Stockler, S. Subramaniam, T.H. Tan, J.A. Violet, A. Weickhardt, S.G. Williams, S. Yip, A.Y. Zhang, [177Lu]Lu-PSMA-617 versus cabazitaxel in patients with metastatic castration-resistant prostate cancer (TheraP): a randomised, open-label, phase 2 trial, Lancet 397 (2021) 797–804.
[190] B. Nervi, P. Ramirez, M.P. Rettig, G.L. Uy, M.S. Holt, J.K. Ritchey, J.L. Prior, D. Piwnica-Worms, G. Bridger, T.J. Ley, J.F. DiPersio, Chemosensitization of acute myeloid leukemia (AML) following mobilization by the CXCR4 antagonist AMD3100, Blood 113 (2009) 6206–6214.
[191] US National Library of Medicine, ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02478125.
[192] K. Fizazi, M. Carducci, M. Smith, R. Damião, J. Brown, L. Karsh, P. Milecki, N. Shore, M. Rader, H. Wang, Q. Jiang, S. Tadros, R. Dansey, C. Goessl, Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study, Lancet 377 (2011) 813–822.
[193] US National Library of Medicine, ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02488408.
[194] K. Yumoto, M.R. Eber, J. Wang, F.C. Cackowski, A.M. Decker, E. Lee, A.R. Nobre, J.A. Aguirre-Ghiso, Y. Jung, R.S. Taichman, Axl is required for TGF-β2-induced dormancy of prostate cancer cells in the bone marrow, Sci. Rep. 6 (2016) 36520. -36520.
[195] N. Rucci, A. Tetti, Osteomimicry: how the seed grows in the soil, Calcif. Tissue Int. (2018).