

IMPACT OF MODERN IMAGING ON THE MANAGEMENT OF PROSTATE CANCER

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LIST OF ABBREVIATIONS

99mTC-BS: 99mTc-methylene diphosphonate bone scintigraphy

ADC: Apparent diffusion coefficient

ARPI: Androgen receptor pathway inhibitor

AsMRI: Magnetic resonance imaging of the axial skeleton

BCR: Biochemical recurrence

CI: Confidence interval

CT-TAP: Thoraco-abdominal-pelvic contrast-enhanced computed tomography

DWI: Diffusion-weighted imaging

ENRT: Elective nodal radiotherapy to the pelvis

ePLND: Extended pelvic lymph node dissection

FF: Bone marrow fat fraction

MDT: Metastasis-directed therapy

MET-RADS-P: METastasis Reporting and Data System for Prostate Cancer

MFS: Metastasis-free survival

mCRPC: Metastatic castration-resistant prostate cancer

mHSPC: Metastatic hormone-sensitive prostate cancer

MRI: Magnetic resonance imaging

NPV: Negative predictive value

PCa: Prostate cancer

PFS: Progression-free survival

PPV: Positive predictive value

PSA: Prostate-specific antigen

PSMA: Prostate-specific membrane antigen

RCT: Randomised controlled trial

SUVs: Standardised uptake values

tDV: Total diffusion volume

TNM: Tumour, node, metastases

WBMRI: Whole-body magnetic resonance imaging

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1. Introduction

1.1. Staging and classification of PCa

PCa (PCa) is the second most common malignancy among men and remains a leading cause of cancer-related mortality worldwide, with an estimated 1.467 million diagnoses and 397,000 deaths worldwide in 2022. In Europe, it is the most frequently diagnosed cancer in men and the third leading cause of cancer-related death in men ¹. Prostate cancer is the most common cancer in males in Belgium, with a lifetime risk of about 1 in 5, 12,435 new diagnoses in 2023, and 1,495 deaths in 2021, while 10-year net survival reaches 96.5%, and 5-year net survival for recent cohorts is around 99%, exceeding 100% for non-metastatic disease because net survival is estimated relative to background mortality². It shows that incidence is high and increases with age (median age at diagnosis 70 years), that distant metastases are more frequent in older patients, and that the risk of being diagnosed has been rising (average annual percentage change +3.3% from 2015-2023) whereas mortality risk has been declining (average annual percentage change -2.2%)

Despite significant therapeutic advances, PCa continues to account for a substantial proportion of global cancer deaths, underscoring the importance of screening and early detection, accurate staging, early detection of recurrence, and reliable assessment of treatment response.

The Tumour, Node, Metastasis (TNM) system is the internationally accepted framework for describing the anatomic extent of cancer at diagnosis and during follow-up (<https://www.uicc.org/>) ³. The European Association of Urology (EAU) risk group classification, which is essentially based on D'Amico's classification system for PCa, combines clinical information on tumour extent, prostate-specific antigen level (PSA), and pathology from prostate biopsy according to the International Society of Urological Pathology (ISUP) grade group classification ⁴. The objective of a tumour classification system is to group patients with similar

clinical outcomes. This enables discussions with patients about prognosis, the design of clinical trials in relatively homogeneous populations, comparisons of clinical and pathological data from different hospitals worldwide, and the development of recommendations for treating these patient populations.

Based on the EAU guidelines of PCa, patients with newly diagnosed PCa are categorised into⁵:

- **Low risk localised:** ISUP grade 1 and PSA < 10 ng/mL and cT1-2a
- **Favourable intermediate risk localised:** ISUP grade 2 and PSA <10 ng/ml and cT1-2b **or** ISUP grade 1 and PSA 10– 20 ng/ml and cT1-2b **or** ISUP grade 1 and PSA < 10 ng/ml and cT2b
- **Unfavourable intermediate risk localised:** ISUP grade 2 and PSA 10 – 20 ng/ml **and** cT1 2b **or** ISUP grade 3and cT1-2b
- **High risk localised:** ISUP grade 4/5 **or** PSA > 20 ng/ml **or** cT2c
- **Very high risk or locally advanced disease:** cT3-4 and/or N1, any ISUP grade, any PSA, N1, M0
- **Metastatic disease:** M1

The distinction between localised and metastatic PCa is vital, as prognosis and treatment plans differ fundamentally between these disease states. Patients diagnosed with localised disease may achieve long-term remission or even a cure following definitive local treatments such as radical prostatectomy or radiotherapy. However, the risk of biochemical recurrence varies by risk stratification category. In contrast, patients with metastatic PCa generally cannot be cured with current treatment options and instead receive systemic therapies aimed at delaying disease progression, relieving symptoms, and extending survival. This difference emphasises the importance of accurate initial staging in guiding therapeutic decisions.

For patients with metastatic disease, accurate quantification of tumour burden and reliable monitoring of treatment response are essential. Disease volume and distribution (lymph nodes, bone, and visceral organs) strongly influence prognosis and therapeutic selection, including decisions regarding systemic therapy intensification, the role of local consolidative therapy, and the use of metastasis-directed therapies (MDT) in oligometastatic states.

1.2. Natural History of PCa

Most patients present with clinically localised PCa, whereas fewer than 10% have de novo or synchronous metastatic disease at diagnosis.

Across large series, 20–40% of men develop biochemical recurrence (BCR) within 10 years after curative-intent therapy. The median time to recurrence is about 3 to 5 years, although late recurrences can occur even beyond 10 years^{6,7}. BCR is defined by a rising PSA in the absence of clinical or radiographic progression: ≥ 0.2 ng/mL after prostatectomy and >2 ng/mL above the nadir after definitive radiotherapy, by the Phoenix criterion (nadir + 2.0 ng/mL)^{5,8}. Whilst rising PSA levels universally precede metastatic progression, physicians must inform the patient that the natural history of PSA-only recurrence may be prolonged and that a measurable PSA may not necessarily lead to clinically apparent metastatic disease. At the BCR stage, PCa may still be amenable to salvage local approaches (e.g., postoperative salvage radiotherapy; salvage prostatectomy or focal ablation after radiotherapy), eventually combined with a short course of systemic hormonal therapy. Contemporary restaging with cross-sectional imaging is recommended during BCR to detect occult metastatic spread; detection of distant lesions following an initially localised course defines metachronous metastatic hormone-sensitive prostate cancer (mHSPC).

Androgen deprivation therapy (ADT) is the historical standard of care treatment for PCa. It is initiated at an early stage in association with radiotherapy, in case of rapid biochemical progression, or in the presence of metastases. In locally

advanced and metastatic disease, ADT is rarely curative. A substantial proportion of patients evolve to castration-resistant PCa (CRPC), characterised by rising PSA and/or radiographic or clinical progression despite castrate serum testosterone (<50 ng/dL). CRPC may emerge without detectable metastases (non-metastatic CRPC, nmCRPC) or with metastases (mCRPC), the latter representing the lethal phase of the disease⁵.

Patients were historically classified as metastatic or non-metastatic based on standard imaging techniques, including ^{99m}Tc-99m-methylene diphosphonate bone scintigraphy (^{99m}TC-BS), thoraco-abdominal-pelvic contrast-enhanced computed tomography (CT-TAP), or abdominal MRI. The emergence of newer imaging modalities and metastatic targeted therapy has been associated with the concept of **oligometastatic** disease, a stage characterised by a limited number of detectable metastases⁹. The implication of this concept, as proposed by Hellman and Weichselbaum, is that local cancer treatments are curative in some patients with metastases. Biologically, oligometastases may reflect reduced metastatic potential, with limited tumour cell dissemination and lower genomic heterogeneity than in widely metastatic disease¹⁰. In PCa, this concept has attracted increasing interest due to advances in imaging that enable earlier and more precise detection of small metastatic deposits¹¹. Definitions vary. Most often, oligometastatic disease refers to having 1 to 5 metastases, although the exact cutoff remains debated. Other factors, such as the metastatic site (bone, lymph node, visceral) and timing (synchronous vs. metachronous), are also considered.

Additionally, the oligometastatic condition across various clinical scenarios may exhibit distinct underlying biology and require different treatment strategies¹². In terms of patient management, identifying an oligometastatic state in PCa has significant implications: it enables metastasis-directed therapies (e.g., stereotactic body radiotherapy or surgical resection), local treatment of the primary tumour even in the presence of metastases, and the possibility of

delaying or modulating systemic therapy. However, despite growing clinical use, no universally accepted definition of oligometastatic PCa currently exists¹³.

1.3. Importance of Accurate Imaging in PCa

PCa displays a highly characteristic metastatic pattern, with a predominant predilection for the skeleton. Bone is by far the most common site of distant spread, involved in approximately 85-90% of men with advanced or castration-resistant disease. Metastases typically localise to the axial skeleton, including the spine, pelvis, and ribs¹⁴. They are classically osteoblastic on imaging, although mixed or lytic lesions may occur in late-stage or treatment-refractory cases. Bone involvement represents a significant source of morbidity, contributing to pain, fractures, and reduced quality of life¹⁵. Lymph node metastases represent the second most common pattern, affecting regional pelvic nodes early in disease progression and, less frequently, distant nodes such as para-aortic, mediastinal, or supraclavicular chains. Visceral metastases are less common and generally occur in the context of aggressive or castration-resistant phenotypes. The lung is the most frequent visceral site, present in approximately 10-20% of cases, while liver metastases occur in about 8-10%, often signifying a poor prognosis and frequent neuroendocrine differentiation. Brain, adrenal, and soft tissue metastases are rare and typically indicate advanced systemic spread. This hierarchical dissemination—from lymph nodes to bone and, later, to visceral organs—reflects the biological tropism of PCa cells and underpins current imaging and treatment paradigms, including the growing use of radioligands for detection and management of metastatic disease.

As previously mentioned, PCa's care pathway has historically relied on conventional imaging modalities, including CT-TAP, abdominal MRI, and ^{99m}Tc-BS⁵.

CT has limited sensitivity for detecting nodal metastases because it depends only on size criteria; micrometastatic disease in normal-sized nodes often goes

undetected. ^{99m}Tc -BS, while sensitive to osteoblastic activity, lacks specificity and offers little capacity to quantify tumour burden, especially at low PSA levels. Furthermore, bone metastases are not objectively measurable by RECIST on CT or by BS, which restricts the standardised assessment of response¹⁶.

Accurate initial staging, especially early detection of metastatic spread, enables risk stratification and guides therapeutic choices. In newly diagnosed cN1M0 PCa (characterised by pelvic nodal involvement on imaging without distant metastases), standard management includes definitive radiotherapy to the prostate and pelvic lymph nodes combined with long-term androgen deprivation therapy (ADT) and one androgen receptor pathway inhibitor (ARPI). Early detection of metastasis at biochemical recurrence (BCR) following definitive local treatment is vital, as salvage options can be curative when employed at low disease burden. For patients with metastatic disease, precise assessment of tumour burden is also crucial. Disease volume and distribution (lymph nodes, bones, and visceral organs) significantly influence prognosis and treatment decisions, including options for intensifying systemic therapy, the role of local consolidative therapy, and metastasis-directed approaches in oligometastatic states.

1.4. Modern Imaging in PCa

1.4.1. Whole Body Magnetic Resonance Imaging (WB-MRI)

Since the early 1990s, bone marrow MRI has been developed to overcome the limitations of bone scintigraphy and CT in assessing metastatic bone disease, demonstrating unmatched sensitivity to marrow replacement by tumour cells¹⁷. Axial skeleton MRI (AsMRI), covering the spine, pelvis, and proximal femurs, was initially used to detect and quantify neoplastic infiltration, already encompassing over 80% of red marrow regions where metastases are most frequently observed, with limited risk of missing peripheral lesions^{18,19}. Whole-body MRI (WB-MRI) was later introduced for comprehensive assessment of the

skeleton and for a one-step “all-organ” approach to metastatic disease, first relying on morphologic T1 and T2/STIR sequences and later incorporating functional diffusion-weighted imaging (DWI)^{18,20}. More recently, a fast (<30 min) “All-In-One” WB-MRI protocol has been proposed to integrate prostate imaging²¹.

Dixon-based T2 sequences are now preferred, as they provide both water-only and fat-only images, improving focal lesion detection in fatty marrow while also offering T1-like information, questioning the need for separate T1 images²². This approach can be extended to WB-MRI, significantly reducing acquisition times and enabling quantification of marrow fat fraction (FF), which, together with apparent diffusion coefficient (ADC) measurements, is gaining recognition as a biomarker for treatment response^{23,24}.

Classic morphologic anatomical MRI sequences detect bone metastases by identifying the replacement of normal marrow fat by tumour tissue, which alters biochemical composition and may influence adjacent bone structure²⁵. Bone metastatic deposits are characterised by significantly low FF% compared to normal bone. Several studies have highlighted the diagnostic utility of FF% in detecting bone malignancies, with a threshold value of 20% generally regarded as a reliable discriminator²⁶.

In contrast, DWI detects restricted water diffusion caused by tumour infiltration, resulting in decreased ADC values. It offers a functional perspective by examining membrane integrity, cell viability, and tissue density, enabling quantitative analysis²⁷. The significance of quantitatively assessing ADC values has been demonstrated, and although it is not possible to define a single, definitive threshold—partly due to variability related to the choice of b values—lesions with intermediate to low ADC values, whether in bone marrow or soft tissues, are more likely to be malignant²⁸. Specifically, MET-RADs guidelines state that ADC values characterize viable lesions between 600–700 $\mu\text{m}^2/\text{s}$ and 1400 $\mu\text{m}^2/\text{s}$ ²⁹.

MRI does not depend on osteoblastic/osteoclastic reactions, unlike radiographs, CT, and scintigraphy, thus avoiding diagnostic delays³⁰. Unlike PET, MRI is independent of tracer avidity, which can vary by tumour type and stage, giving MRI a “universal” role in assessing metastases. MRI also allows detailed morphological analysis to differentiate benign from malignant fractures, evaluate extra osseous spread, and monitor neurological complications following treatment³¹. Limitations include the possibility that benign lesions may mimic metastases, requiring correlation of DWI, morphological sequences, and ADC values^{32,33}. In advanced disease, treated lesions and scar tissue may hinder detection and measurement of active metastases, making DWI and ADC maps crucial for response assessment^{34,35}. Furthermore, therapy-related benign increases in marrow cellularity may lead to diffuse “pseudo-progression”³⁶.

Bone marrow MRI is now widely applied in clinical practice and trials to evaluate treatment response in bone-predominant disease³⁷. Efforts have been made to standardise acquisition protocols and response criteria, including harmonisation of quantitative DWI and ADC mapping by the UK Quantitative WB-DWI Technical Workgroup^{23,35}. Response assessment combines quantitative and qualitative markers. The appearance of new lesions, growth of existing lesions, or extra osseous extension defines disease progression. In contrast, response corresponds to reductions in lesion size or number and to the reappearance of a normal marrow signature³⁸. Qualitative signs include the “fatty halo” on T1 images as a marker of regression, and disappearance of high T2 signal in aggressive lesions as an early indicator of response, with reappearance suggesting relapse. Conversely, new malignant vertebral fractures or epidural spread unambiguously indicate progression³⁸. Quantitatively, ADC values rise early during the response, then decrease as marrow is recolonised, with concurrent reductions in high-b-value signal and sclerotic transformation of treated lesions³⁹. Global disease burden can be monitored through total diffusion volume (tDV) derived from WB-DWI^{40,41}.

Increases in FF also reflect treatment-induced regression of marrow infiltration²⁴.

Finally, multiparametric WB-MRI combines anatomical T1 and STIR (or Dixon) with DWI/ADC and FF mapping, offering a comprehensive approach for assessing bone metastases and monitoring treatment response.

1.4.2. PSMA-PET/CT

Positron emission tomography (PET) has traditionally been used for staging a wide range of malignancies due to its high sensitivity in visualising metastatic disease, most often using ¹⁸F-FDG as the radiotracer. In 2009, new qualitative and quantitative frameworks for assessing metabolic tumour response, designed explicitly for ¹⁸F-FDG PET, were introduced under the name PERCIST (PET Response Criteria in Solid Tumours)⁴². The aim of developing these criteria was to address the inherent limitations of morphology-based imaging systems such as RECIST and RECIST 1.1, which depend solely on measuring size changes, and to leverage the additional benefits of PET in tracking therapeutic success—especially with newer systemic anticancer therapies^{42,43}.

The quantitative potential of PET imaging remains vastly underutilised. This is particularly relevant in the evaluation of bone metastases, which are considered non-measurable according to RECIST 1.1. In such settings, quantification of radiotracer uptake may play a pivotal role in assessing bone disease by capturing changes in tumour cell viability or molecular activity, rather than relying solely on morphologic alterations. An additional advantage is that quantitative PET analysis can be applied at both the individual lesion level and across the whole body, thereby enabling a more comprehensive assessment of disease burden. Parameters that can be extracted from routinely acquired static whole-body PET images have been validated for many tracers in different cancer types. In general, these parameters can be divided into those based on tracer uptake intensity (e.g. standardised uptake values, SUVs),

metabolically active tumour volumes (MATV), and a combination of both, representing the total tracer uptake in a tumour. Typical SUV metrics are the mean SUV uptake (SUV_{mean}), the maximum SUV uptake (highest voxel value; SUV_{max}), or the peak uptake (highest average value of a 1cm^3 sphere; SUV_{peak}) within an identified lesion. Depending on the radiotracer's pharmacokinetics, normalisation of uptake to background activity in reference tissues such as liver or blood may be required ⁴⁴.

Positron emission tomography (PET) targeting the ***prostate-specific membrane antigen (PSMA)*** has transformed the imaging landscape of PCa. PSMA (Prostate-Specific Membrane Antigen) is a type II transmembrane glycoprotein enzyme highly expressed on the surface of prostate epithelial cells and significantly overexpressed in PCa, especially in advanced or metastatic disease⁴⁵. PSMA is composed of three main domains — a short cytoplasmic tail (19 amino acids), a transmembrane region (24 amino acids), and a large extracellular domain (707 amino acids)⁴⁵. PSMA acts as a glutamate carboxypeptidase/folate hydrolase, cleaving substrates such as N-acetylaspartylglutamate and polyglutamated folates. In normal tissue, PSMA is found in the prostate epithelium, proximal renal tubules, small intestine, and salivary glands⁴⁶. In malignant tissue, PSMA is upregulated in nearly all prostate adenocarcinomas, with expression increasing with tumour aggressiveness, androgen independence, and metastatic potential⁴⁶. PSMA is also expressed in the neo vasculature of many non-prostatic solid tumours (such as renal cell or colon carcinoma), making it a broader angiogenic marker.

Multiple PSMA ligands are now established for PET imaging in PCa, including ^{68}Ga -PSMA-11, ^{18}F -DCFPyL, and ^{18}F -PSMA-1007, with newer fluorine-18-labelled agents such as ^{18}F -rhPSMA-7.3 emerging^{47,48}. All bind with high affinity to the extracellular domain of PSMA, which is overexpressed in most PCa cells, and all provide excellent lesion detection across disease stages. ^{68}Ga -PSMA-11 is the gold standard but lacks the sensitivity and resolution of ^{18}F -tracers. ^{18}F -PSMA-1007 excels in low-PSA settings but risks false positives, while ^{18}F -DCFPyL

offers high detection and flexibility⁴⁹. Tailored tracer selection is crucial, with further studies needed to refine application.

In biochemical recurrence, detection rates range from 75% to 90%, depending mainly on PSA level and disease burden rather than the ligand itself. Nevertheless, the tracers differ in pharmacokinetics and biodistribution, which can influence interpretation in specific settings. ⁶⁸Ga-PSMA-11, the first widely used agent, offers robust tumour-to-background contrast but is limited by its short half-life (68 min) and generator-based production. ¹⁸F-labelled ligands benefit from a longer half-life (110 min), higher positron yield, and broader distribution capacity. Among these, ¹⁸F-PSMA-1007 shows minimal urinary excretion, improving visualisation of local recurrence near the prostate bed, though it exhibits higher hepatic uptake that may obscure small liver metastases. ¹⁸F-DCFPyL provides high-resolution images with low urinary background. Overall, all major PSMA ligands demonstrate comparable diagnostic accuracy, and ligand selection should be guided primarily by availability, clinical indication, and local production logistics rather than intrinsic differences in tumour detection performance.

The PCa molecular imaging standardised evaluation (PROMISE) criteria have been proposed as a framework for whole-body staging (molecular imaging TNM staging, denoted miTNM) to describe the extent of PCa on PSMA-PET⁵⁰. The updated PROMISE V2 offers standardised reporting of disease extent for clinical routine and research. Parameters recorded within clinical trials also facilitate objective response assessment⁵¹. A multicentre retrospective study has compared the prognostic value of PSMA-PET by PROMISE stage with that of established clinical nomograms in a large PCa dataset with follow-up data on OS. They have also designed and validated a nomogram to stratify patients into high- and low-risk groups for overall survival at early and late stages of PCa, yielding predictive accuracy equal to or superior to that of established clinical risk tools⁵². In parallel, **Rowe et al.** have proposed a structured reporting and data system, called PSMA-RADS version 1.0, for PSMA-targeted PET imaging

studies to standardise how imaging specialists interpret PSMA PET scan⁵³. This system aims to facilitate data collection for large prospective trials and to provide an accurate and efficient way to communicate findings to referring clinicians. PSMA-RADS is expressed on a scale from 1 to 5, with PSMA-RADS 1 indicating a lesion most likely benign, and PSMA-RADS 5 representing a lesion most probably consistent with PCa.

1.4.3. The Physiopathology of Bone Metastases in Prostate Cancer, a modern imaging perspective

The development of metastasis involves a multistep cascade comprising local invasion, intravasation, survival in the circulation, extravasation, and colonisation of the bone marrow niche. Prostate cancer cells exhibit specific molecular characteristics that favour skeletal dissemination. As first described by Stephen Paget, the preferential dissemination of prostate cancer cells to bone is partially explained by the “seed and soil” hypothesis. Prostate cancer cells (the “seed”) exhibit molecular adaptations that favor survival and colonization within the bone marrow niche (the “soil”).^{54,55}

Bone marrow endothelial cells, osteoblasts, and stromal cells secrete chemokines such as CXCL12 (stromal-derived factor-1), which interact with CXCR4 and CXCR7 expressed on prostate cancer cells, facilitating homing and extravasation into the bone marrow. Additionally, adhesion molecules, including integrins (e.g., $\alpha\text{v}\beta 3$), annexin II, and cadherins, mediate the stable anchoring of tumour cells to the endosteal surface. Following homing, disseminated tumor cells may persist in a dormant state for prolonged periods. Dormancy is regulated by microenvironmental cues, including TGF- β , bone morphogenetic proteins (BMPs), and GAS6/AXL signalling, which can enforce cell cycle arrest and promote survival without proliferation. The balance between dormancy and reactivation is influenced by bone remodelling activity, inflammatory signals, angiogenic switching, and systemic therapies⁵⁶.

Physiological bone remodelling is a tightly coordinated process involving osteoclast-mediated bone resorption followed by osteoblast-mediated bone formation ⁵⁷. This coupling ensures maintenance of skeletal integrity and mineral homeostasis. The receptor activator of nuclear factor κ B (RANK), its ligand RANKL, and the decoy receptor osteoprotegerin (OPG) form a central regulatory axis that controls osteoclast differentiation and activity ⁵⁸.

Prostate cancer metastases take over normal bone remodelling to support tumour growth, establishing a self-sustaining “vicious cycle.” Tumour cells secrete osteotropic factors that alter osteoblast and osteoclast function, leading to excessive and unbalanced bone turnover.

Although prostate cancer metastases are classically osteoblastic, osteoclast activity is essential for their initiation and progression. Tumour cells indirectly stimulate osteoclastogenesis by increasing RANKL expression and suppressing OPG production by osteoblasts and stromal cells. Osteoclast-mediated bone resorption releases growth factors embedded in the bone matrix, including TGF- β , insulin-like growth factors (IGFs), and fibroblast growth factors (FGFs), which, in turn, promote tumour cell proliferation, survival, and the further secretion of osteogenic mediators. This “vicious cycle” promotes osteoblast proliferation and inhibits osteoclast function, thereby favouring net bone formation ⁵⁹.

However, the newly formed bone is structurally abnormal, consisting largely of immature woven bone with impaired mineralisation and mechanical properties. This pathological bone contributes to skeletal fragility and clinical complications despite increased bone density on Androgen receptor (AR) signalling further modulates tumour–bone interactions. AR-regulated transcription influences the expression of osteogenic and osteoclast-modulating factors, linking androgen deprivation therapy to alterations in the bone metastatic niche and contributing to bone density loss ⁵⁶.

The molecular understanding of prostate cancer bone metastases has led to the development of bone-targeted therapies. Bisphosphonates and RANKL inhibitors reduce skeletal-related events by inhibiting osteoclast activity and disrupting the vicious cycle of bone resorption and tumour growth ⁶⁰. Radiopharmaceuticals such as radium-223 selectively target osteoblastic lesions, delivering localized cytotoxic radiation ⁶¹.

1.4.4. Physiological response of bone metastases and MRI imaging biomarkers

Prostate cancer bone metastases produce lesions that are radiologically osteoblastic (sclerotic) but biologically heterogeneous, with variable tumour cell density, woven bone, necrosis and fibrosis within a reactive microenvironment ⁵⁶. These features explain why CT shows dense sclerosis, ^{99m}Tc bone scintigraphy shows intense osteoblastic turnover, PSMA-PET/CT directly depicts viable tumour cell burden, and WB-MRI shows marrow replacement and cellularity rather than bone mineral ⁶².

Under systemic therapy or local stereotactic radiotherapy, prostate bone metastases show a complex, regionally heterogeneous response that involves a reduction in the viable tumour cell fraction, the replacement of tumour by fatty marrow and/or fibrous tissue, variable secondary osteoblastic repair and sclerosis, and changes in vascular permeability and edema ^{30,38,39}.

1.4.4.1. The Fat Fraction

Successful treatment reduces tumour cellularity and allows reconversion to fatty yellow marrow; conversely, an active tumour replaces fat with cellular and edematous tissue.

Dixon-based MR techniques quantify the fat fraction (FF) within lesions and background marrow. Responding lesions show an increase in FF over time, often paralleling T1 hyperintensity and a decrease in ADC signal; non-responding or progressing lesions maintain a low FF ^{24,63}.

1.4.4.2.The ADC (diffusion weighted MRI)

ADC reflects water mobility constrained by cell membranes, extracellular matrix and oedema. Highly cellular tumours with intact membranes have low ADC; necrosis, fibrosis, and fatty replacement increase ADC by expanding extracellular or less-restricted compartments.

At baseline, most active marrow metastases are hyperintense on high b-value DWI and hypointense on ADC maps (low ADC) ^{39,64}.

Under effective therapy, several studies report a decrease in DWI highbvalue signal and an increase in mean ADC and “slow” ADC components, consistent with reduced cellular density and increased extracellular space. Also, a reduction in tDV (diffusiondefined tumor volume) combined with an increase in global ADC correlates with PSA decline and improved survival ⁶⁴.

However, in some responding lesions, oedema or necrosis may increase both T2 signal and ADC, resulting in a persistently high DWI signal despite a biological response. Correlation with ADC maps and T1/fat fraction is therefore essential ⁶⁵.

1.4.4.3.Calcification / sclerosis

Osteoblastic repair and woven bone formation often intensify following effective treatment, independent of immediate tumour kill ³⁹.

On CT, increasing sclerosis or new sclerotic foci early after systemic or radionuclide therapy may represent a “flare” phenomenon rather than true progression. This is analogous to the flare seen on a bone scan.

On MRI, dense sclerosis appears as a very low signal on all sequences and may be indistinguishable from inactive scar tissue. DWI often shows low signal with a relatively high ADC, reflecting reduced marrow space.

Therefore, increased calcification/sclerosis with concurrent PSA decrease and improving DWI/ADC/fat fraction parameters is usually considered a healing response, whereas new mixed lytic-sclerotic lesions with persistent low ADC are more concerning ³⁸.

1.4.4.4.Fibrosis

Late treatment response typically involves replacement of both tumour and reactive stroma with collagen-rich fibrous tissue, which has low cellularity and low free water.

On T1weighted images, fibrosis may remain lowtointermediate signal, lacking the bright hyperintensity of pure fatty marrow, and can be hard to distinguish from a lowcellularity tumour without functional imaging ³⁰.

On DWI/ADC, fibrotic tissue generally shows low or absent highbvalue signal and intermediatetohigh ADC compared with baseline tumour. ADC values may plateau at levels reflecting low but stable cellular density.

Areas of pure fibrosis are usually interpreted as treated, inactive disease. METRADSP emphasises integrating lesion morphology, ADC changes and fat content to avoid overcalling such areas as persistent tumour ³⁵.

1.4.4.5.Dehydration/edema changes

Active metastases often display increased extracellular water (oedema, hyperemia), whereas responding or late-stage sclerotic/fibrotic lesions may become relatively dehydrated.

Oedema increases T2/STIR signal and can reduce ADC initially (if tightly packed) or increase ADC (if necrotic), contributing to complex DWI behaviour ³⁸.

Loss of oedema with therapy reduces STIR signal and may further normalise ADC or reduce residual high DWI signal, especially when combined with fat replacement.

Changes in hydration state modulate DWI and ADC, and must be read together with T2/STIR and fat fraction to distinguish necrotic/edematous response from true progression ³⁸.

In practice, the biology–imaging links in prostate bone metastases can be summarized as follows:

An active bone metastasis will show as a high tumour cell density, a preserved PSMA expression, low fat, high osteoblastic activity, intense PSMA uptake, positive BS, low T1 marrow signal, high STIR and DWI signal, a low ADC, and low fat fraction.

An Effective systemic or focal therapy will show a reduction in viable tumour cells, a transient flare in osteoblastic reaction, then increasing marrow fat fraction, rising ADC, decreasing DWI and STIR signal, with CT/MRI sclerosis and sometimes calcification representing healing rather than progression.

A Late or incomplete response with predominant fibrosis and sclerosis will show as a structurally dense lesion on CT, low signal on most MRI sequences, low osteoblastic turnover on bone scan, minimal DWI signal and intermediate ADC, corresponding to low but possibly residual tumour burden.

2. Imaging Modalities for Detecting Metastases at Various Stages of PCa

The imaging workup at initial diagnosis must distinguish localised/locally advanced from metastatic PCa and evaluate the metastatic tumour load.

- The European Association of Urology (EAU) recommend using PSMA-PET/CT if available, or at least cross-sectional abdominopelvic imaging and a bone scan, for metastatic screening in patients with unfavourable intermediate- or high-risk localised or locally advanced disease⁵.
- The National Comprehensive Cancer Network (NCCN) guidelines recommend performing abdominopelvic imaging only if nomograms based on clinical features predict a >10% probability of pelvic lymph node involvement and performing bone imaging in patients with unfavourable intermediate- and high-risk localised PCa⁶⁶. PSMA-PET/CT or PET/MRI can be considered an alternative to CT-TAP, MRI, or ^{99m}Tc-BS in patients with intermediate-, high-, or very-high-risk disease.

It has been abundantly demonstrated that WB-MRI and PET/CT can more accurately define the extent of the disease, locally and remotely, and help tailor a more personalised treatment plan for patients. It is, however, important to mention that the benefit of this has not yet been demonstrated in a prospective clinical trial. It has not been shown to reduce unnecessary treatment, improve progression-free survival, overall survival (OS), or improve quality of life.

The stage migration resulting from more advanced imaging is a typical “Will Rogers” effect. Named after the humorist Will Rogers’s quip that “when the Okies left Oklahoma and moved to California, they raised the average intelligence in both states,” the effect arises when improved diagnostic techniques detect disease earlier or more accurately. In cancer staging, patients who would previously have been classified as “low stage” may now be reassigned to a “higher stage” due to more sensitive imaging. This reclassification makes the remaining low-stage group appear to have better survival (since the worst cases were

removed) and the high-stage group also appear to have better survival (since it now includes less advanced cases), even though overall survival for all patients is unchanged. With the adoption of PSMA PET/CT and WB-MRI, PCa patients who were once labelled cN0M0 on CT-TAP or ^{99m}Tc -BS are now frequently upstaged to N1 or M1, often with low-volume/oligometastatic disease. So, the remaining “localised” group becomes biologically more favourable, while the newly defined mHSPC cohort contains earlier, lower-burden metastases; survival can appear to improve in both groups, even in the absence of therapeutic advances. This stage migration can confuse cross-trial comparisons between pre- and post-modern imaging techniques’ eras and emphasises the importance of reporting imaging modality and considering lead-time and length biases when interpreting outcomes.

2.1. Newly Diagnosed PCa

2.1.1. Bone metastases detection

Standard imaging modalities, ^{99m}Tc -BS and CT-TAP, have poor diagnostic accuracy for metastatic staging. CT has a modest pooled sensitivity of 72.9% and specificity of 94.8% for detecting bone metastases ⁶⁷. ^{99m}Tc -BS is a highly sensitive conventional imaging technique for bones but has demonstrated up to 40% false-positive results, as it detects osteoblastic activity that can be seen in both metastasis and benign conditions such as inflammation or fractures ⁶⁸. A meta-analysis showed combined sensitivity and specificity of 79% (95% confidence interval (CI) 73–83%) and 82% (95% CI 78–85%) at the patient level ⁶⁹. ^{99m}Tc -BS positivity is significantly influenced by a high PSA level (≥ 20 ng/ml) and a high tumour Gleason score (≥ 8) ⁷⁰.

Single Photon Emission Computed Tomography (SPECT)–CT improves the specificity and positive predictive value of ^{99m}Tc -BS, allowing downstaging of metastatic disease in 29.5% of PCa patients ⁷¹. In a multicentre Canadian phase 3 trial in patients with high-risk prostate or breast cancer, SPECT demonstrated

sensitivities of 63.3%, specificities of 87.5%, and positive predictive values (PPVs) of 78.4% for the detection of osseous metastases⁷².

Numerous studies have demonstrated that AsMRI, WB-MRI and PSMA-PET/CT outperform ^{99m}Tc-BS for bone metastatic screening. For almost two decades, our group, led by Prof. F. Lecouvet and Prof. B. Tombal, has demonstrated that MRI is more sensitive than BS plus targeted X-Ray (TXR) in detecting bone metastases in high-risk PCa patients ¹⁷. In their seminal study on sixty-six consecutive patients with high-risk PCa, they reported sensitivity of 46% for ^{99m}Tc-BS alone, 63% for ^{99m}Tc-BS complemented with targeted X-Rays, and 100% for AsMRI. The corresponding specificities were 32%, 64%, 100%, and 88%, respectively. AsMRI identified metastases in 7/23 (30%) patients considered M0 and in 8/17 (47%) patients deemed equivocal by other strategies.

PSMA PET imaging has demonstrated very high diagnostic accuracy for detecting bone metastases in PCa, owing to the high and specific expression of PSMA on PCa cells and their osseous deposits. Across multiple studies and meta-analyses, sensitivity and specificity typically exceed 95%, substantially higher than with traditional imaging modalities. In a large meta-analysis by **Perera et al.** that included over 4,700 patients, pooled sensitivity and specificity of PSMA PET for metastatic disease were 0.97 (95% CI 0.95–0.98) and 0.97 (95% CI 0.96–0.98), respectively, with similarly excellent performance for bone lesions⁷³. Head-to-head comparative trials have confirmed this superiority: in the proPSMA randomised trial, ⁶⁸Ga-PSMA-11 PET/CT achieved an accuracy of 92% for detecting pelvic nodal and distant metastases (including bone), compared to 65% with conventional CT and bone scan ⁷⁴. PSMA PET showed both higher sensitivity (85% vs 38%) and specificity (98% vs 91%) in this context.

2.1.2. *Lymph node staging*

2.1.2.1. Extended lymph node dissection as a standard of care

Lymph node staging has always been a challenge in PCa; no imaging technique has demonstrated optimal performance in detecting metastatic lymph nodes. Extended surgical pelvic lymph node dissection (ePLND) is used as a gold standard and is still routinely performed during radical surgery in high-risk PCa ^{5,75}. Several predictive nomograms are available to estimate the risk of lymph node invasion and inform the indication for ePLND. For example, based on the Briganti 2019 nomogram, with a 7% risk of lymph node invasion, 56% of ePLNDs would be spared, and only 2.6% lymph node invasion would be missed ⁷⁶.

There is, however, a caveat. ePLND involves removing the nodes over the external iliac artery and vein, the nodes within the obturator fossa situated cranially and caudally to the obturator nerve, and the nodes medial and lateral to the internal iliac artery. Consequently, ePLND offers precise information for staging and prognosis in the pelvis, mainly ⁷⁷. Several studies utilising modern imaging have shown that initial lymph node spread may occur outside the pelvis ⁷⁸. In a series of 270 patients with BCR and a PSA < 1 ng/mL who underwent ⁶⁸Ga-PSMA-11 PET/CT, 12% harboured extra-pelvic PSMA-positive lesions, while 7% exhibited intrapelvic PSMA-positive disease outside the planned radiation field⁷⁹.

In addition, the exact benefit of ePLND on oncological outcomes is still disputed. A recent systematic review found that ePLND did not improve oncological outcomes⁸⁰. Two randomised controlled trials have been unable to show a benefit of an extended approach vs. a limited PLND on early oncologic outcomes⁸¹. Only one prospective study has demonstrated a significant improvement in metastasis-free survival (MFS) with comparable biochemical-recurrence-free survival⁸².

ePLND is not an innocuous procedure. The overall complication rate ranges from 10% to 25%, with major complications, Clavien–Dindo grade ≥ 3 , occurring in approximately 1–5% of patients⁷⁷. The most frequent adverse event is lymphocele formation, reported in up to 15% of cases, though only 2–5% are clinically significant and require intervention. Other complications include infection or wound issues (2–8%), venous thromboembolism (1–3%), lymphorrhea or lymphedema (<5%), and rarely vascular, nerve, or ureteric injury (<1%). The risk of morbidity increases with larger dissection templates, open surgical approaches, obesity, and anticoagulant use.

Sentinel lymph node dissection techniques have been developed to better identify which patients need an ePLND. The prospective SENTINELLE study has compared the diagnostic accuracy of sentinel lymph node biopsy-guided lymph node dissection following intraprostatic injection of ^{99m}Tc-nanocolloid with that of ePLND in patients with intermediate- or high-risk PCa. The sensitivity, specificity, negative predictive value, and positive predictive value for detecting patients with at least one LN metastasis were 95.4%, 100%, 99.2%, and 100%, respectively⁸³. An emerging alternative to sentinel node removal following intraprostatic injections is PSMA-guided lymph node dissection after intravenous radioisotope injection, with intraoperative radio or optical guidance⁸⁴. Initial studies report high specificity approaching 100%, although limited sensitivity and the associated poor negative predictive value limit the functional value at this point.

2.1.2.2. MRI-based imaging in lymph node detection

MRI without specific contrast is not particularly sensitive. ADC values have been investigated as a potential parameter for distinguishing benign from malignant lymph nodes, particularly in cases where nodes exhibit equivocal morphologic or dimensional features.²⁶ Although multiple studies have demonstrated lower ADC values in malignant lymphadenopathies compared

to benign nodes, considerable overlap between the two populations persists, thereby limiting reliable differentiation.

One way to improve MRI diagnostic accuracy is to use superparamagnetic or ultrasmall superparamagnetic iron oxide (SPIO/USPIO) nanoparticles. USPIOs act as potent MRI contrast agents for lymph node imaging. After intravenous or interstitial injection, these particles are taken up by macrophages in normal lymph nodes, producing T_2/T_2^* signal loss. Metastatic deposits, lacking normal macrophage function, show relative preservation of signal, allowing indirect visualisation of tumour infiltration.

Clinical studies have demonstrated high sensitivity of USPIO-enhanced MRI for detecting small nodal metastases, particularly in prostate, bladder and head-and-neck cancers^{85,86}. Recent studies have confirmed excellent subnodal correspondence between PSMA expression and USPIO-MRI in pelvic lymph nodes in PC⁸⁷. However, widespread clinical adoption has been limited by restricted agent availability and the technical demands of high-resolution imaging. The key advantages include non-radioactive operation, prolonged nodal retention, and compatibility with quantitative magnetic particle imaging. Limitations involve susceptibility artefacts, heterogeneous uptake, and a lack of standardised imaging protocols.

2.1.2.3. PSMA-PET/CT is the modern gold standard for detecting lymph node metastases.

⁶⁸Ga-PSMA-PET/CT, because of its rapid development and promising detection rates in other disease stages, has been proposed for primary lymph node staging.

The largest prospective phase III imaging trial has enrolled 764 men with intermediate- and high-risk PCa who underwent ⁶⁸Ga-PSMA-11 PET scans before prostatectomy and ePLND⁸⁸. Sensitivity, specificity, positive

predictive value, and negative predictive value for pelvic nodal metastases were 40%, 95%, 75%, and 81%, respectively.

These results are consistent with previous findings from prospective, multicentre studies evaluating the accuracy of ¹⁸F-DCFPyL PET/CT for LN staging in patients with newly diagnosed PCa.

- In the **SALT** trial, the sensitivity, specificity, positive predictive value, and negative predictive value for ¹⁸F-DCFPyL PET/CT detection of pelvic lymph node metastases at the patient level were 41.2%, 94.0%, 53.8%, and 90.4%, respectively⁸⁹.
- In the **OSPREY** study, ¹⁸F-DCFPyL-PET/CT had a median specificity of 97.9% and a median sensitivity of 40.3% for pelvic nodal involvement; the median positive predictive value and negative predictive value were 86.7% and 83.2%, respectively⁹⁰.
- A recent meta-analysis by **Wu et al.** found higher sensitivity (65% vs. 41%) and specificity (94% vs. 92%) for ⁶⁸Ga-PSMA PET compared with mpMRI in detecting pelvic pathological nodes⁹¹.
- Finally, an analysis of 20 intermediate- and high-risk patients with PCa who underwent ⁶⁸Ga-PSMA-11 PET/CT, anatomical MRI or contrast-enhanced CT, and DWI-MRI before laparoscopic, template-based, extended LND showed that the sensitivity and specificity for detecting lymph node metastases were, respectively, 39% and 100% with ⁶⁸Ga-PSMA PET/CT, 8% and 100% with MRI/CT, and 36% and 83% with DWI-MRI⁹².

In summary, PSMA PET/CT is more sensitive for N-staging compared to MRI, CT-TAP, or choline PET/CT. Due to its limited sensitivity, especially for small lymph node metastases within PET's spatial resolution, PSMA PET/CT cannot replace diagnostic ePLND, for the pelvis.

During the APCCC24 meeting, there was no consensus on omitting ePLND or pelvic RT in patients with negative PSMA PET/ CT undergoing definitive surgery or RT⁹³.

2.1.2.4. Direct comparison of WB-MRI and PSMA-PET/CT

Although WB-MRI and PSMA-PET/CT outperform ^{99m}Tc-BS and CT-TAP for detecting distant metastases, few studies have directly compared the two methods.

One study prospectively evaluated the diagnostic accuracy of ⁶⁸Ga-PSMA-PET/CT compared with ¹⁸F-fluoride-PET/CT and WB-MRI for detecting bone metastases in patients with PCa⁹⁴. More than two-thirds of the 55-patient cohort were under ADT or had CRPC. The patient-based diagnostic sensitivity, specificity, and overall accuracy were, respectively, 100%, 100%, and 100% for PSMA-PET/CT; 95%, 97%, and 96% for NaF-PET/CT; and 80%, 83%, and 82% for WB-MRI; the overall diagnostic accuracy of PSMA-PET/ CT was significantly superior to that of WBMRI ($p = 0.004$) but not to NaF-PET/ CT ($p = 0.48$).

The PROSTAGE trial found higher sensitivity (90%–96%) but lower specificity (70%–90%) for ¹⁸F-PSMA-PET/CT compared to WB-MRI (sensitivity 43%–80%; specificity 80%–96%). Important to note that in this study, ¹⁸F-PSMA-1007 PET-CT showed a relatively high number of false-positive bone lesions (15%)⁹⁵.

2.2. Biochemical Recurrence (BCR) after Radical Treatment

BCR is a highly heterogeneous disease, with most patients presenting a slow evolution. It is thus critical to first estimate the risk of metastases and death before treating the patient to limit exposure to side effects.

2.2.1. BCR management in the era of conventional imaging techniques

Efforts have been made to stratify that population. The disease trajectory can be estimated by combining the Gleason score, the interval between the local treatment and the BCR, and, more importantly, the PSA doubling time (PSADT). The Johns Hopkins series is the most extensive series of patients monitored after surgery for a BCR without initiating treatment before developing metastases^{96,97}. In Freedland's landmark publication, the HR for the time to PCa-specific death after BCR following radical prostatectomy was 3.53 ($p = 0.002$) for interval ≤ 3 vs. > 3 years, 2.26 ($p = 0.002$) for a pathological Gleason score ≥ 8 vs. < 8 , and 8.76 ($p < 0.0013$) for a PSADT between 3.0 and 8.9 vs. ≥ 15 months⁹⁷. Similar observations have been made after radiotherapy⁹⁸. There have been many attempts to define optimal high- and low-risk BCRs by integrating PSA kinetic and pathological characteristics, leading to several definitions with varying prognostic value⁹⁸.

A systematic review by **Van den Broeck et al.** led to the introduction of the concept of BCR risk stratification in the European Association of Urology (EAU) guidelines⁷. The EAU guidelines stratify BCR patients into low and high risk, the latter being the patients with PSADT < 1 year or a pathological ISUP grade 4–5 after radical prostatectomy and an interval to biochemical failure < 18 months or a biopsy ISUP grade 4–5 after radiotherapy⁵.

Because of the limited diagnostic accuracy of conventional imaging, most patients developing a BCR would be classified as non-metastatic (NOM0). The questions then became simple: is there a role for salvage local treatment, and when should ADT be initiated? These questions have been debated for years.

In case of BCR after surgery, the EAU guidelines recommend salvage radiotherapy for NOM0 and for N1M0 patients. Of note, no adequately designed randomised controlled trial (RCT) has demonstrated that salvage radiotherapy (early or late) delays PFS, metastasis-free survival (MFS), or OS versus surveillance. Three RCTs have demonstrated that adjuvant RT delays PSA

PFS⁹⁹⁻¹⁰¹. Only one showed that it increases MFS by 10% at 10 years from 61% to 71% and OS by 8% at 10 years from 66% to 74%⁹⁹. To spare some patients unnecessary salvage RT, 3 RCTs, RADICALS RT¹⁰², RAVES¹⁰³, and GETUG-AFU-17¹⁰⁴, and a meta-analysis, ARTISTIC¹⁰⁵ have compared early salvage vs. adjuvant RT with respect to oncological outcomes and toxicity. Adjuvant RT was not superior to salvage RT for PFS, and it was associated with increased genitourinary (GU) toxicity, as approximately 2/3 of patients in the salvage RT group did not receive RT. Considering these results, PSA monitoring and early salvage RT are currently the most widely adopted practices. The optimal timing for salvage radiotherapy remains a matter of debate, although it is usually recommended to irradiate before the PSA reaches 0,7 ng/ml to avoid co-administration with ADT. *In fine*, the status of salvage radiotherapy as the “standard of care” is based on ambispective series demonstrating that selected patients, with a PSA <0,7 ng/mL, an ISUP 1-3, and a slow PSADT may experience prolonged PSA response¹⁰⁶⁻¹⁰⁸.

Following definitive radiotherapy, available local salvage options include salvage radical prostatectomy, re-irradiation using brachytherapy or stereotactic body radiotherapy, and ablative therapies such as high-intensity focused ultrasound (HIFU) and cryotherapy. The optimal approach depends on tumour location, the extent of recurrence, comorbidities, and patient preference. Salvage re-irradiation through brachytherapy or external beam radiotherapy offers the most durable oncologic control, with 5-year biochemical-free survival rates of approximately 60%, but is associated with significant morbidity, including near-universal erectile dysfunction and increased risks of urinary incontinence, rectal injury, and anastomotic stricture due to prior radiation¹⁰⁹. Careful patient selection is crucial: the best outcomes are observed in those with organ-confined disease, Gleason ≤ 7 , and pre-salvage PSA <10 ng/mL. Re-irradiation, delivered via low- or high-dose-rate brachytherapy or SBRT, represents a less invasive option that achieves local control rates of 60–80%, albeit with a moderate risk of genitourinary and

gastrointestinal toxicity. Ablative therapies, including HIFU and cryotherapy, aim to destroy residual tumour tissue while minimising treatment morbidity, although long-term oncologic data remain limited. Across modalities, lower PSA at the time of salvage is consistently associated with improved biochemical control and survival outcomes.

The only systemic treatment to decide on for many years was ADT. No study has definitively shown that immediately starting ADT improves OS. The largest trial so far randomised 293 men between immediate and delayed ADT¹¹⁰. Interestingly, the definition of delayed included a decrease in PSADT ≤ 6 months. Five-year OS were 86.4% and 91.2% in the delayed and immediate ADT arms, respectively (HR 0.55, $p = 0.050$). ADT also has side effects, including hot flashes, loss of libido, and cognitive decline. Administered over a long period, ADT induces metabolic changes that can lead to an increased risk of cardiovascular events and decreased bone mineral density, leading to an increased risk of fracture¹¹¹. Consequently, physicians usually consider that the risk of ADT outweighs its benefits and generally agree that strategies aiming at delaying ADT are acceptable. The guidelines are more prudent, stating that immediate ADT should not be offered to low-risk patients.

2.2.2. Diagnostic performance of modern imaging technologies

EAU guidelines recommend performing PSMA-PET/CT in patients with relapse PSA > 0.2 ng/mL after RP, or, if PSMA-PET/CT is unavailable and PSA ≥ 1 ng/mL, fluciclovine or choline PET/CT is used. After RT, guidelines recommend performing prostate gland mpMRI to localise abnormal areas and guide further biopsies and performing a PSMA-PET/CT or fluciclovine or choline PET/CT in patients fit for curative salvage treatment⁵.

2.2.2.1. PSMA-PET/CT

PSMA-PET/CT has been proven more sensitive than choline PET/CT in two prospective study, especially for PSA levels < 1 ng/ ml^{112,113}.

In a systematic review and meta-analysis involving 1309 patients by **Perera et al.**, the percentage of patients with positive ^{68}Ga -PSMA-PET for BCR was 76% (95% CI 66-85%) for BCR¹¹⁴. Positive ^{68}Ga -PSMA-PET scans for BCR patients increased with pre-PET PSA. For the PSA categories 0-0.2, 0.2-1, 1-2, and >2 ng/ml, 42%, 58%, 76%, and 95% scans, respectively, were positive. A shorter PSA doubling time was associated with increased ^{68}Ga -PSMA-PET positivity. On per-patient analysis, the summary sensitivity and specificity were both 86%. On per-lesion analysis, the summary sensitivity and specificity were 80% and 97%, respectively.

- A recent systematic review and meta-analysis by **Mazzone et al.** reported substantial variability in PSMA PET positivity rates for BCR, driven by significant study heterogeneity, primarily due to differences in treatment type, PSA, and anatomic sites¹¹⁵. In post-RP BCR, approximately half of patients undergoing PSMA PET had positive findings, even at low PSA (0.2–0.5 ng/ml). In the post-RT setting, PSMA PET use was generally aligned with the Phoenix criterion for BCR, with most studies performing PSMA PET at PSA ≥ 2 ng/ml. PSMA PET positivity by anatomic location was 23% for local recurrence, 32% for pelvic nodes, 14% for extra pelvic nodes, 16% for bone metastases, and just 1% for visceral metastases
- In a prospective study by **Fendler et al.**, 635 patients with BCR following RP, RT, or combined modalities underwent ^{68}Ga -PSMA-11 PET/CT¹¹⁶. On a per-patient basis, the PPV was 0.84 when validated against histopathology and 0.92 when using a composite reference standard. Overall, ^{68}Ga -PSMA-11 PET localised recurrent disease in 475 of 635 patients (75%). The detection rates were strongly associated with PSA level: 38% for <0.5 ng/ml (n = 136), 57% for 0.5 to <1.0 ng/ml (n = 79), 84% for 1.0 to <2.0 ng/ml (n = 89), 86% for 2.0 to <5.0 ng/ml (n = 158), and 97% for ≥ 5.0 ng/ml.

- The prospective **CONDOR** study has evaluated the diagnostic performance of ^{18}F -DCFPyL in 208 men with BCR after RP or RT¹¹⁷. The correct localisation rate was 84.8%-87.0% (95% CI 77.8-80.4), demonstrating positive findings on ^{18}F -DCFPyL PET/CT in the setting of negative standard conventional imaging
- Two prospective cross-over trials have demonstrated the superiority of ^{18}F -DCFPyL over ^{18}F -fluoromethylcholine PET/CT in patients with BCR. In the PYTHON trial, ^{18}F -DCFPyL achieved significantly higher detection rates than ^{18}F -fluoromethylcholine (58% vs. 40%; $p < 0.0001$) in 201 high-risk BCR patients after radical therapy ¹¹⁸. Similarly, a phase III multicenter trial showed higher correct detection rates with ^{18}F -PSMA-1007 compared to ^{18}F -fluorocholine (0.82 vs. 0.65; $p < 0.0001$), particularly when equivocal findings were considered malignant¹¹⁹.
- The diagnostic performance of ^{18}F -PSMA PET/ CT in patients with BCR has been reported in systematic reviews and meta-analyses¹²⁰. The pooled sensitivity, specificity, and AUC values for ^{18}F -PSMA PET/CT in the diagnosis of prostate recurrence and/ or metastasis were 92%, 94%, and 96%, respectively. The per-patient pooled sensitivity and specificity values were 92% and 83%, respectively. The per-lesion pooled sensitivity and specificity values were identical, 91%.

2.2.2.2. Whole-Body MRI

WB-MRI has not been extensively evaluated in BCR because of its limited ability to detect early metastatic spread in normal-sized lymph nodes. However, whole-body MRI protocols that include DWI are technically reliable in assessing recurrent PCa. Since DWI offers a higher contrast-to-noise ratio than conventional T1-weighted and T2-weighted STIR imaging, it generally improves lesion detection, although sclerotic bone metastases remain difficult to identify¹²¹.

- **Zacho et al** have compared the diagnostic performance of DWI-MRI, ^{68}Ga -PSMA-PET/CT and ^{18}NaF -PET/CT in a prospective series of 68 patients with BCR. The performance of WB-MRI was significantly lower¹²². On a patient level, sensitivity, specificity and the area under the curve (AUC) by receiver operating characteristic analysis were, respectively, 0.80, 0.98-1.00 and 0.89-0.90 for ^{68}Ga -PSMA PET/CT (n = 68 patients); 0.90, 0.90-0.98 and 0.90-0.94 for ^{18}NaF PET/CT (n = 67 patients); and 0.25-0.38, 0.87-0.92 and 0.59-0.62 for DW₆₀₀-MRI (n = 60 patients). Additionally, no significant difference in the AUC was seen between ^{68}Ga -PSMA PET/CT and ^{18}NaF PET/CT (p = 0.65).
- In a prospective trial of 28 patients with BCR after RP by **Sawicki et al.**, ^{68}Ga -PSMA-PET/CT detected all lesions (56/56) in 20 patients, whereas WB-MRI detected only 23.2% (13/56) in 11 patients¹²³. The higher detection rate with ^{68}Ga -PSMA-PET/CT was statistically significant on both a per-lesion basis (p < 0.001) and a per-patient basis (p = 0.0167). ^{68}Ga -PSMA PET/CT also detected all lesions detected by WB-MRI.
- The **LOCATE** trial is an ongoing prospective, multi-centre diagnostic accuracy study evaluating WB-MRI for re-staging PCa patients with BCR after radiotherapy. Patients undergo WB-MRI plus standard imaging at baseline and 12 months¹²⁴. Diagnostic accuracy, cost-effectiveness, and exploratory biomarker analysis will be assessed to determine whether WB-MRI provides a more efficient imaging pathway.

2.2.2.3. Pelvic mpMRI

Pelvic mpMRI is the most effective imaging method for identifying local recurrences, either in the prostatic bed after RP or within the prostate to guide biopsy. The PSA threshold for MRI positivity is estimated to be between 0.3 and 0.5 ng/mL, and PSA kinetics also influence detection even at low levels ¹²⁴.

The Prostate Imaging for Recurrence Reporting (PI-RR) system was recently introduced to standardise MRI interpretation in patients with BCR after RP or RT¹²⁵. It reduces variability by applying a structured 5-point scale for overall suspicion of recurrence, derived from DWI and dynamic contrast-enhanced (DCE) assessments. Separate scales are used after RT and RP, accounting for the relation between abnormalities and the primary tumour site on pretreatment imaging. T2WI is also graded on a 5-point scale for anatomic assessment, but this grading does not influence the final score. Initial retrospective studies show promising reproducibility and accuracy of PI-RR in detecting local recurrence¹²⁶.

Combining ⁶⁸Ga-PSMA-PET or WB-MRI with pelvic mpMRI may improve the detection of local recurrences compared with ⁶⁸Ga-PSMA-PET/CT or WB-MRI alone¹²⁷.

The EMPIRE-1 study, a single-centre, open-label, phase II/III RCT, included 165 patients with detectable PSA after RP but negative conventional imaging results¹²⁸. They were randomised to receive radiotherapy guided by conventional imaging alone or by conventional imaging plus ¹⁸F-fluciclovine-PET/CT. In the ¹⁸F-fluciclovine-PET/CT group, radiotherapy decisions were strictly based on PET findings, which also guided target delineation. Patients with M1 disease in the PET/CT group (n = 4) were excluded. Patients with cN1 were irradiated to the pelvic nodes without a boost to the metastases. After a median follow-up of 3.5 years, the PET/CT group showed a significant association with longer event-free survival (HR: 2.04, 95% CI: 1.06–3.93, p = 0.0327).

A retrospective study evaluated the use of WB-MRI combined with mpMRI in 76 patients with BCR after RP and low PSA levels (median 0.36 ng/ml). Recurrence was detected in 21% of cases, with local recurrence identified in 9%. MRI proved feasible for clinical practice and offered incremental information compared with conventional imaging¹²⁹.

2.2.3. *The impact of modern imaging technologies on the management of BCR, a case of “conventional wisdom”*

In the setting of BCR, PET/CT with diverse radioligands has been shown to outperform ^{99m}Tc -BS and CT-TAP scans and to robustly identify metastatic deposits earlier, usually at the stage of a few metastases¹³⁰⁻¹³².

2.2.3.1. Salvage local and pelvic treatment

The incorporation of new imaging technologies into the management of patients with BCR has led to the identification of many oligometastatic deposits.

After treatment of the primary, oligorecurrent pelvic nodal disease is a frequent situation. In a cohort of 270 patients with BCR after RP and a PSA below 1 ng/ml, **Calais et al.** reported that 30.5% of patients had a pelvic nodal recurrence on ^{68}Ga -PSMA-11-PET/CT⁷⁹. Considering the frequency of oligorecurrent pelvic nodal disease and the better overall prognosis of these patients, they have attracted a lot of therapeutic attention. Radical salvage treatment, including salvage lymph node dissection or RT, has been implemented with the hope of “curing” patients. Several groups have offered systematic salvage lymph node dissections in patients with oligorecurrent nodal disease with disappointing long-term outcomes. **Bravi et al.** recently reported on 189 patients who underwent salvage lymph node dissection after diagnosis by ^{11}C -choline or ^{68}Ga -PSMA PET/CT^{133,134}. The clinical and biochemical recurrence-free survival at 10 years are 31% and 11%, respectively. A total of 145 patients received ADT, with a median time to ADT of 41 months.

The optimal RT regimen for nodal oligorecurrent PCa patients is not yet defined, with substantial treatment variability between centres and no consensus on volumes, doses, or techniques. Salvage RT for nodal recurrences can be delivered either by covering prophylactically the

bilateral pelvic drainage regions (elective nodal RT) or by treating focally the nodal relapse using SBRT.

- The **PEACE V-STORM** phase 2 trial compared metastasis-directed therapy (MDT) versus elective nodal radiotherapy to the pelvis (ENRT) in 190 patients with PET-detected pelvic nodal oligorecurrence (up to 5 nodes) after local treatment¹³⁵. Patients in the MDT group had salvage lymph node dissection or stereotactic body radiotherapy (30 Gy in three fractions every other day), with 6 months of ADT. Patients in the ENRT group received a 45 Gy dose in 25 fractions to the pelvis with a simultaneous integrated boost of 65 Gy to the PET-positive nodes or salvage lymph node dissection, with 6 months of ADT. At a median follow-up of 50 months, 4-year MFS was higher with ENRT (76%) compared to MDT (63%) (HR 0.62; p=0.063). These results suggest ENRT, combined with short-term ADT, provides superior disease control and could become a standard approach pending phase 3 confirmation.
- The phase-II trial **GETUG P07-OLIGOPELVIS** is investigating the clinical outcome of ENRT+ADT in 67 patients with oligorecurrent (<5) pelvic node relapses on fluorocholine PET/CT¹³⁶. Sixty-one percent of patients had only one positive node. The 5-year PFS, biochemical relapse-free (BFS), and ADT-free rates were 39%, 31%, and 64%, respectively, after elective RT of the PLN and 6 months of ADT. At 5 years, one-third of patients had not relapsed biochemically.

2.2.3.2. Salvage treatment of oligometastatic deposits

The new imaging techniques have become fertile ground for developing MDT strategies. MDT was adopted as standard treatment because these metastases were technically amenable to targeted therapy, typically stereotactic radiotherapy.

However, the evidence needs to be stronger. There is no properly designed randomised phase III trial aiming to impact robust oncological endpoints such as MFS, OS, and health-related quality of life (HR-QoL). Small, short-term phase II trials currently drive the field.

- **STOMP** was the first randomised phase 2 trial to compare MDT (surgery ± SABR) vs. surveillance in 62 men with oligorecurrent PCa (<3 lesions on choline-PET/CT) ¹³⁷. Most patients had nodal-only disease. The primary endpoint was ADT-free survival, which was prolonged with MDT compared to surveillance.
- The **ORIOLE** phase 2 trial has randomised 54 men with BCR and one to three metastases detectable by conventional imaging to receive systemic treatment alone or in combination with SABR ¹³⁸. PFS was significantly lower with SABR than with surveillance (19% vs. 61%, $p = 0.005$). The most interesting observation was that total consolidation of PSMA radiotracer decreased the risk of new lesions at 6 months (16% vs. 63%; $p = 0.006$), thus confirming the importance of accurate imaging staging by PSMA-PET/CT.
- These two studies have been combined to confirm the significant improvement in PFS in favour of MDT (HR: 0.44, $p < 0.001$)¹³⁹. However, these trials failed to demonstrate that MDT prolonged MFS or OS, or improved HR-QoL. At best, they suggest that ADT can be postponed.
- The individual patient data (IPD) from five randomised trials (**WOLVERINE**) were released with preliminary results at ASCO GU 2025¹⁴⁰. It reported a significant benefit of MDT for longer-term endpoints, including rPFS and castration-resistant-free survival (CRFS), and a near-significant association with OS.

It can be concluded that new imaging technologies and MDT have thus occupied the field of BCR treatment, challenging the “conventional wisdom” concept described by the economist JK. Galbraith as “the ideas that are

esteemed at any time for their acceptability” in his 1958 book “The Affluent Society”.

2.2.4. The role of modern imaging technologies after EMBARK

The phase 3 **EMBARK** trial has evaluated enzalutamide, alone or in combination with leuprolide, in men with high-risk biochemically recurrent PCa, defined by a PSA doubling time ≤ 9 months and no radiographic metastases^{141,142}. Patients were adjudicated as non-metastatic (N0M0) by conventional imaging. A total of 1068 patients were randomised to enzalutamide + leuprolide, leuprolide alone, or enzalutamide monotherapy. The primary endpoint was MFS, assessed by blinded central review. After a median follow-up of 60.7 months, combination therapy significantly improved outcomes: 5-year MFS was 87.3% versus 71.4% with leuprolide alone (HR 0.42; 95% CI 0.30–0.61; $P < 0.001$). Enzalutamide monotherapy was also superior (5-year MFS 80.0%; HR 0.63; 95% CI 0.46–0.87; $P = 0.005$). Both regimens delayed PSA progression, the need for next-line antineoplastic therapy, and the development of castration resistance. Treatment was suspended at week 37 in patients with undetectable PSA; 90.9% in the combination group and 85.9% in the monotherapy group achieved this threshold. The 8-year overall survival is 78.9% (95% CI, 73.9 to 83.1) in the combination group and 69.5% (95% CI, 64.0 to 74.3) in the leuprolide-alone group; the hazard ratio for death was 0.60 (95% CI, 0.44 to 0.80; $P < 0.001$). The 8-year overall survival with monotherapy was 73.1% (95% CI, 67.6 to 77.9), which did not differ significantly from that with leuprolide alone (hazard ratio, 0.83; 95% CI, 0.63 to 1.10; $P = 0.19$).

EMBARK profoundly changes the management of high-risk BCR. Is it still acceptable to delay systemic treatment now that we have potent AR pathway inhibitors (ARPI) that significantly delay MFS and OS? Delaying ADT may have been sufficient, but delaying enzalutamide for high-risk BCR is no longer permissible unless we have strong evidence. EMBARK establishes ARPI as the new standard of care for patients with high-risk BCR. A rapid rise in PSA,

especially in the context of an ISUP 4–5 cancer or a short interval to BCR, may now serve as a trigger to treat rather than just to scan to determine if treatment is needed. Whether a patient has metastases or not, whether few or many, he needs enzalutamide immediately. As the standard of care evolves, new questions will arise, involving emerging imaging technologies.

So, what is the future role of modern imaging technologies in these patients? Certainly not to identify patients as candidates for salvage local treatment or MDT, but rather to enhance the effect of systemic therapy, increase the response rate, and prolong the eventual intermittent treatment phase. This concept has been developed in the **EXTEND** phase II trial¹⁴³. EXTEND evaluated the impact of adding MDT to standard hormonal therapy in oligometastatic PCa (≤ 5 lesions). A planned break in hormone therapy occurred 6 months after enrolment, after which hormone therapy was withheld until progression. Among 87 randomised patients, most had only 1–2 metastases. Fifty-one received ADT alone, and 66 received ADT plus an ARPi. MDT significantly improved PFS (15.8 months vs not reached; HR 0.25, $p < 0.001$) and eugonadal, treatment-free, PFS (6.1 months vs not reached; HR 0.32, $p = 0.03$). The benefit was consistent across both ADT-alone and ADT+ARPI subgroups.

2.3. Metastatic PCa

Therapeutic strategies for metastatic PCa continue to evolve but remain primarily based on ADT combined with one of the ARPI (enzalutamide, abiraterone, darolutamide, apalutamide), chemotherapy (docetaxel, cabazitaxel), PARP inhibitors, bone-targeted therapies (radium-223) and PSMA-targeted radioligand therapy^{93,111}.

Imaging is essential for defining metastatic disease (M1), whether PSA rises in men with normal testosterone levels (hormone- or castration-sensitive) or in those with suppressed testosterone levels (castration-resistant). It is also

required during treatment to assess response and to identify the onset of primary or secondary resistance.

Several prognostic factors for survival in M1 PCa have been suggested, including the number and location of bone metastases, presence of visceral metastases, ISUP Grade Group, performance status, and initial PSA and alkaline phosphatase levels¹⁴⁴. In the CHAARTED trial, the metastatic burden was defined as high volume by conventional imaging when patients had visceral metastases and/or ≥ 4 bone lesions, with at least one beyond the vertebral bodies or pelvis. At the same time, all other cases were considered low volume¹⁴⁵. Metachronous metastatic disease (after radical local treatment) also has a better prognosis than synchronous (or de novo) metastatic disease¹⁴⁶.

Nevertheless, all prospective data in M1 PCa were based on conventional imaging modalities: CT, MRI, or BS. The effect of modern imaging, such as WB-MRI or PSMA-PET/CT, on treatment selection and outcomes has not yet been evaluated in prospective randomised trials.

To monitor progression, clinicians mainly rely on PSA kinetics as surrogate indicators of treatment efficacy¹⁴⁷⁻¹⁴⁹. The most accepted definition of progression on ADT is based on PSA increases, following the PCa Working Group (PCWG3) consensus: a 25% increase from the nadir (starting at 1.0 ng/ml), with a minimum rise of 2 ng/ml, in the context of castrate testosterone levels (<50 ng/dl)¹⁵⁰. In patients with CRPC who show no clinical evidence of metastases on ^{99m}Tc -BS or CT, baseline PSA, PSA velocity, and PSA doubling time have been associated with the time until first bone metastasis, MFS, and overall survival¹⁵¹.

The PCa Radiographic Assessments for Detection of Advanced Recurrence (RADAR) group issued a consensus statement recommending a bone scan and CT when PSA reaches 2 ng/mL¹⁵². If results are negative, imaging should be repeated at 5 ng/mL, and again at every subsequent PSA doubling, based on PSA testing every three months in asymptomatic men. Symptomatic patients, however, should undergo appropriate investigations regardless of PSA level.

3. Imaging modalities for assessing therapeutic response in advanced PCa

Monitoring tumour response is a cornerstone of modern oncology, providing essential information about the biological and clinical effectiveness of cancer therapy. Assessing how a tumour responds to treatment allows clinicians to determine whether a given intervention achieves meaningful disease control, to identify treatment resistance early, and to tailor subsequent therapy accordingly. Advances in imaging, molecular biomarkers, and functional assays have improved the precision of response evaluation, moving beyond simple measurements of tumour size to include biological indicators of viability and proliferation. Accurate response assessment is also critical for predicting survival outcomes and optimising the balance between therapeutic efficacy and toxicity. Moreover, in an era of personalised medicine, dynamic monitoring helps align treatment decisions with the individual patient's disease trajectory. Therefore, integrating robust, standardised methods for tumour response assessment is fundamental to improve clinical outcomes and advancing evidence-based cancer care.

Quantitative measurement tools have been validated for assessing the effectiveness of cancer therapy in soft-tissue lesions using CT¹⁵³. Lymph nodes and visceral metastasis detected by abdominopelvic CT or MRI must be recorded, quantified, and followed per RECIST⁴³. According to PCWG3, nodes are considered pathological when they are 10-15 mm on the short axis and are subject to clinical discretion. Still, they are only considered measurable when they exceed 15 mm¹⁵⁰.

Precise measurement of tumour response in advanced PCa is impeded by the "osteophilic" nature of PCa, which is characterised by an exquisite tropism for bone that results in a high incidence of bone metastases¹⁵⁴. In clinical trials and routine clinics, bone metastases is exclusively followed using ^{99m}Tc-BS. Metastatic deposits in the bone marrow cause various skeletal responses that depend on the type of malignancy, leading to sclerotic, lytic, or mixed lesions. These lesions may

also change their appearance due to treatment or secondary bone remodelling. An example of this phenomenon is the so-called “flare phenomenon” (pseudo-progression), characterised by the appearance of new uptake foci on an early follow-up ^{99m}Tc -BS, which are caused by osteoblastic reaction and can occur within 8–12 weeks of starting treatment¹⁵⁵.

As a result, conventional morphological imaging is considered inadequate for assessing treatment response in bone metastases, and the RECIST 1.1 guidelines classify such lesions as unmeasurable⁴³. Bone scintigraphy, however, remains recommended by practice guidelines and regulators to assess bone disease response in patients with metastatic PCa, although it suffers from significant limitations¹⁵⁶. To overcome these limitations, the PCWG3 defines imaging progression in mCRPC based on bone scan as the appearance of ≥ 2 lesions during treatment continuation and confirmed 6 weeks later by a second ^{99m}Tc -BS¹⁵⁰. This considerably lengthens decision times and can cause the continuation of ineffective and potentially toxic treatment. Finally, in patients with diffuse metastatic bone disease on ^{99m}Tc -BS (so-called superscans), tumour response cannot be adequately monitored because new lesions cannot be distinguished against a background of diffusely elevated tracer uptake⁶².

3.1. PSA as a universal marker to measure tumour response in advanced PCa

In the setting of advanced PCa, PSA monitoring remains essential, although it is an indirect biomarker of tumour activity. Nevertheless, it is critical to emphasise the limitations of PSA in this context. Declines in PSA levels have not universally been validated as a reliable surrogate endpoint for survival outcomes, and reductions in AR signalling activity cannot be assumed to reflect actual tumour cell eradication. This distinction is critical, as biological heterogeneity in PCa means that AR signalling is not universally representative of disease dynamics. In fact, some aggressive tumour phenotypes are characterised by minimal PSA secretion, potentially leading to underestimation of disease activity when PSA alone is used for monitoring. Thus, while PSA remains a useful and widely

accessible marker for assessing AR-driven disease biology in advanced PCa, its interpretation requires caution. In the **CHAARTED** trial, 25% of patients, regardless of docetaxel exposure, experienced clinical progression without a concomitant rise in PSA, including 1 in 8 men who progressed despite PSA levels below 2 ng/mL¹⁵⁷. In the **TITAN** study evaluating ADT combined with apalutamide in mHSPC, nearly half of patients developed radiographic progression despite no PSA progression¹⁵⁸. Finally, the **PREVAIL** trial reported that approximately one-quarter of mCRPC patients treated with enzalutamide experienced radiographic progression without concurrent PSA increase¹⁵⁹. Thus, while PSA remains a useful and widely accessible marker for assessing AR-driven disease biology in advanced Pca, its interpretation requires caution.

The discordance between PSA and imaging responses supports the clonal theory of castration resistance, which assumes that PCa comprises two pools of AR-dependent and AR-independent cells. ADT and ARPIs selectively eradicate the AR-dependent PSA-expressing cells. This induces selective outgrowth of AR-independent cells, leading to further progression¹⁶⁰.

To address these issues, **PCWG3** emphasises a composite approach integrating clinical, biochemical, and imaging endpoints. PCWG3 explicitly recognises the limitations of conventional imaging and the need to interpret early changes across multiple domains to inform therapy continuation or modification.

Achieving a PSA level < 0.2 ng/mL during initial systemic therapy has emerged as a robust prognostic marker in metastatic hormone-sensitive PCa (mHSPC). Early studies in men treated with ADT alone demonstrated that a 7-month PSA $\leq$ 0.2 ng/mL strongly predicted prolonged overall survival compared with higher nadirs, establishing this cutoff as a benchmark for deep biochemical response¹⁴⁹. Subsequent analyses in the era of treatment intensification have confirmed its prognostic value¹⁶¹. A recent systematic review identified 14 studies comprising 8883 patients. Among the four studies in metastatic hormone-sensitive PC (n = 2197), achieving an undetectable PSA level was associated with better OS (HR

0.33, 95% confidence interval [CI] 0.23-0.49). Among four studies in metastatic castration-resistant PC (n = 3728), PSA reductions of $\geq 90\%$ (HR 0.22, 95% CI 0.14-0.34) and $\geq 50\%$ (HR 0.29, 95% CI 0.20-0.41) were associated with better OS. Similar findings were reported in the multinational **IRONMAN** registry, where failure to achieve PSA ≤ 0.2 ng/mL at 6–12 months was associated with inferior outcomes, regardless of disease volume or treatment regimen¹⁶². Deep PSA suppression likely reflects a highly androgen-sensitive tumour phenotype and effective systemic control, whereas incomplete suppression may indicate early resistance or heterogeneous tumour biology. Although the optimal timing and threshold remain under investigation, consistent evidence supports PSA < 0.2 ng/mL as a simple, reproducible, and clinically meaningful early surrogate of long-term benefit.

3.2. Objective measurement of tumour response in advanced PCa, with a focus on bone metastases

3.2.1. Whole-body MRI

MRI enables evaluation of treatment response in bone lesions, which are the most frequent metastatic sites in mCRPC and are poorly assessed with conventional imaging techniques³⁰. The feasibility and clinical value of AsMRI using size-based criteria to quantify bone metastases and monitor therapy response were already reported 10 years ago¹⁶³. WB-MRI response assessment relies on a multiparametric approach that combines anatomical and functional sequences. Quantitatively, treatment response may be indicated by reductions in the number and size of detectable lesions. At the same time, qualitatively it may be reflected by the replacement of the peripheral lesion zone with fat tissue producing a “fatty halo sign” and eventual restoration of normal bone marrow³⁸. Limitations of anatomical sequences include the challenging interpretation of residual low-signal tissue on T1-weighted images, which may represent inactive lesions (fibrosis or necrosis), the rare occurrence of post-

therapy “flare phenomena” due to oedema, and reconversion of yellow to red marrow leading to diffuse “pseudo progression”¹⁶⁴. Consequently, functional DWI-MRI and quantitative measurements, such as total diffusion volume (tDV), are recommended¹⁶⁵. A decline in lesion signal intensity on high b-value DWI and increased ADC values may suggest response; however, some responding lesions can paradoxically show increased signal intensity and ADC due to the “T2 shine-through effect” from necrosis or oedema. An ADC decrease in responding lesions is possible and is thought to be associated with the development of sclerosis or the reemergence of fatty marrow within the treated lesion, underscoring the importance of evaluating ADC maps alongside anatomical images, especially T1-weighted sequences and their derived relative FF% maps.

ADC increases within PCa metastases treated with ARPI may be detected as early as 1 month after the start of treatment and is correlated with a PSA level decrease ¹⁶⁶. Quantitative evaluation can be performed using mean ADC (ADC_{mean}) or slow ADC (ADC_{slow}), excluding perfusion effects, and global ADC (gADC) in total DWI settings ³⁹.

Changes in the ADC value have been investigated as an objective response criterion. Several studies have found a significant increase in the ADC of bone marrow lesions in patients responding to therapy.

- **Messiou et al.** found that the mean ADC and slow ADC of bone lesions increased in both responders and progressors following chemotherapy¹⁶⁷. However, the magnitude of the ADC increase was greater in responders, with an overall ADC increase of more than 25%, and 75% were sensitive and 66.6% specific for response. The heterogeneity of changes in ADC was likely to be related to the composition of bone marrow with changes that have opposing effects on ADC.
- **Perez-Lopez et al.** demonstrated in a prospective phase II study that decreases in volume and increases in median ADC of bone metastases can

serve as indicators of response to PARP inhibitor Olaparib in mCRPC⁶⁴. A positive association was detected between changes in tDV and the best percentage change in PSA level and circulating cell count ($r = 0.63$ [95% CI: 0.27, 0.83] and $r = 0.77$ [95% CI: 0.51, 0.90], respectively). When assessing five target lesions, decreases in volume were associated with response (odds ratio for volume increase, 0.89; 95% CI: 0.80, 0.99; $P = .037$). Similarly, increases in median ADC were associated with increased odds of response (odds ratio, 1.08; 95% confidence interval [CI]: 1.00, 1.15; $P = .04$).

- In the Bonenza study, **Dalla Volta et al.** used WB-MRI to evaluate bone response rates in 126 patients with mHSPC treated with ADT + enzalutamide, with or without zoledronic acid¹⁶⁸. The WBMRI response was defined based on lesion size, ADC, b800 DWI signal, and fat fraction. Complete response (CR) on WB-DW-MRI was correlated with a lower risk of death (HR 0.16, 95% CI 0.06–0.48; $p < 0.001$), as was partial response (PR) (HR 0.14, 95% CI 0.06–0.32; $p < 0.001$) and CR/PR versus stable disease (SD)/ progressive disease (PD) (HR 0.15, 95% CI 0.07–0.30; $p < 0.001$). The authors did not evaluate the correlation between imaging and other parameters, such as PSA, for response assessment.
- The **iPROMET** study initially evaluated the correlation between changes in MRI parameters and response or time to progression in 55 patients with mCRPC treated with ARPIs⁶⁵. Response was defined as either RECIST version 1.1 criteria or a 50% decrease in PSA. A decrease in tumour volume and an increase in fat fraction in lesions on WBMRI after treatment were the most significant indicators of a more extended response. Multivariate analysis revealed that higher-volume bone disease, lower fat fraction, and lower ADC were associated with a higher risk of progression. Conversely, a decrease in bone metastasis volume and higher FF were linked to response to therapy. On multivariable analysis, the addition of ctDNA to the imaging variables increased the C index from

0.68 to 0.78. The iPROMET study also indicates that ADC changes alone remain difficult to assess therapeutically. Some patients showed increased ADC, while others exhibited decreased ADC. The association between ADC and outcome improved after adjusting for FF at the individual-patient level. They hypothesised that low ADC at follow-up in some responding patients resulted from an increase in fat infiltration in responding bones, concluding that fat infiltration should be considered when interpreting ADC results.

To standardise response assessment, **the MET-RADS-P framework** has defined mpMRI-based criteria using a 5-point Likert-like scale, where 1 indicates a very high likelihood of response, 3 indicates stable disease, and 5 indicates progression²⁹. Bone disease response is categorised into progression, stability, response, or discordance, while soft-tissue lesions are assessed according to RECIST 1.1. In clinical applications, MET-RADS-P has demonstrated utility for patient management in advanced PCa, including a study of 72 mCRPC patients, in which a higher burden of bone (≥ 10) and visceral metastases was significantly correlated with shorter cancer-specific survival, highlighting the prognostic relevance of the MET-RADS-P volume score¹⁶⁹. MET-RADS-P accommodates these heterogeneous findings by allowing classification of discordant responses, in which some lesions progress while others remain stable or respond.

- **Tunariu et al.** have retrospectively compared METRADS-P vs. RECIST/PCWG criteria to detect disease progression in 100 mCRPC cases¹⁷⁰. They found that MET-RADS-P detects progression earlier than RECIST at 4.2% of time points. Regarding soft-tissue disease, it detects progression earlier than PCWG at 51.9% of time-points. Also, WB-MRI can better classify patients without a progression on bone scan into PR, SD and PD. They also showed that response evaluation based on WB-MRI is a prognostic factor in mCRPC.

- **Pricolo et al.** have underlined the ability to identify metastases with expertise to identify metastases with WB-MRI using the MET-RADS-P guidelines¹⁷¹. For the primary/dominant RAC pattern, the agreement between readers was excellent for the metastatic findings in cervical, dorsal, and lumbosacral spine, pelvis, limbs, lungs and other sites (K:0.81-1.0), substantial for thorax, retroperitoneal nodes, other nodes and liver (K:0.61-0.80), moderate for pelvic nodes (K:0.56), fair for primary soft tissue and not assessable for skull due to the absence of findings.
- **Garcia-Ruiz A et al.** have reanalysed the iPROMET data and classified the 55 participating patients according to MET-RADS criteria¹⁷². They found some criteria difficult to apply consistently and objectively, such as the “evolution of diffuse neoplastic pattern to focal lesions” and “emergence of intra/peritumoural fat within/around lesions” to define responses, as no objective thresholds were determined. Therefore, their assessment was limited to RECIST, absolute ADC, and relative ADC changes and did not include other subjective criteria specified in the MET-RADS publication. In summary, 42/55 patients were classified as RAC 1–2 (likely responding), 9/55 as RAC 3 (no change), and 4/55 as RAC 4–5 (likely progressing). Classification according to the response in soft tissue revealed that 19 patients achieved a CR or PR per RECIST, of whom 14 were also classified as RAC 1–2, indicating high concordance between response in soft-tissue metastases (evaluable by RECIST) and bone metastases, captured via WB-MRI. Based on ADC distribution, only three patients (7.3%) were classified as RAC 1. In contrast, 36 (65.5%) met the RAC 2 criteria (likely responders) due to an increase in ADC in bone metastases of 25–40% or from $<1000 \mu\text{m}^2/\text{s}$ at baseline to $1000\text{--}1400 \mu\text{m}^2/\text{s}$ after 12 weeks of treatment. Thirteen patients (23.6%) were classified as RAC 3 (no change), and three patients as RAC 4–5 (progression). Although the differences did not reach statistical significance, variations in time to progression (TTP) were observed among the different RAC categories. Specifically, the median TTP

was 15.21 mo (95% confidence interval [CI] 9.82–26.21) for RAC 1–2, 8.83 mo (95% CI 2.89–33.11) for RAC 3, and 8.28 mo (95% CI 2.53–unbounded) for RAC 4–5. In addition, the 12-mo probability of progression varied significantly across the groups: no patients progressed in the RAC 1 group, in comparison to 40% in the RAC 2 group, 66% in the RAC 3 group, and 67% in the RAC 4–5 group.

3.2.2. PSMA-PET/CT

Although its primary clinical utility has been in staging and restaging, PSMA PET is increasingly being explored as a tool for monitoring treatment response across disease stages, particularly in metastatic castration-resistant PCa (mCRPC) and in the context of PSMA-targeted radioligand therapy. However, despite its growing use, standardised criteria for response assessment on PSMA PET are still evolving.

3.2.2.1. PSMA-PET/CT to monitor PCa progression and response to therapy

PSMA PET differs fundamentally from conventional imaging. Unlike computed tomography (CT) or bone scans, which rely on morphologic or osteoblastic changes, PSMA PET reflects changes in PSMA expression and viable tumour burden. This molecular specificity allows earlier and potentially more accurate detection of therapeutic effects. Still, it introduces complexity: PSMA expression can be modulated by AR signalling, and thus by therapies such as ADT or ARPIs¹⁷³. Consequently, increases or decreases in tracer uptake may not directly correspond to changes in tumour size or number. Flares, PSMA upregulation and discordant results compared with PSA response or progression on ARPI have indeed been described. A prospective study evaluated changes in ⁶⁸Ga-PSMA-11 PET uptake after initiation of ARPI in eight patients with metastatic PCa¹⁷⁴. Serial PET scans showed that six of seven patients who later achieved >50% PSA declines exhibited early increases in PSMA uptake in at least one lesion,

consistent with a flare effect rather than disease progression. Overall, 49% of metastatic lesions demonstrated this transient increase in uptake, with substantial intra- and interpatient variability.

Several quantitative parameters have been proposed to measure response. The maximum or mean standardised uptake value (SUV_{max}/SUV_{mean}) reflects the intensity of tracer uptake, whereas PSMA tumour volume (PSMA-TV) quantifies the total extent of PSMA-avid disease. The total lesion PSMA (TLP), which multiplies tumour volume by mean uptake, serves as a composite biomarker analogous to total lesion glycolysis in FDG PET. Reductions in PSMA-TV and TLP have been shown to correlate with declines in prostate-specific antigen (PSA) levels and improved survival outcomes in mCRPC patients treated with Lu-177-PSMA or systemic therapies. For example, a study by *Calderoni et al.* has compared PET/CT to PSA response in 160 patients and correlated the results with PFS and OS¹⁷⁵. Twenty-five out of seventy PET/CT scans were evaluated as responders (stable disease, partial or complete response), and 45/70 as non-responders (progressive disease). Based on PET/CT response, median SUV_{max} on first PET/CT was numerically lower in non-responders than in responders (17.5 vs. 20.4; $P = 0.127$). Similarly, patients with a PSA increase had significantly lower median SUV_{max} on first PET/CT (15.8) than did those with a PSA decrease (30.4; $P = 0.018$). PSA change was, on average, 146% in non-responders and -57% in responders between first and second PET/CT. Agreement between PET/CT and PSA response was 79% ($k = 0.553$, $P < 0.001$). PET/CT response, independent of PSA variation, was a significant prognostic factor for PFS. OS was not significantly different between PET/CT responders and non-responders.

The first effort to standardise the measure of tumour response was published in 2020 by *Fanti et al.*¹⁷⁶. They have proposed the PSMA PET progression (PPP), which defines PSMA treatment response using three different criteria.

- The first criterion is the appearance of two or more new PSMA-positive distant lesions. This approach, in line with PCWG2, was chosen to reduce the risk of false positives, including the flare phenomenon. The presence of only one new lesion was insufficient to meet progression criteria under PCWG2, given ^{99m}Tc-BS poor specificity. Conversely, PSMA PET/CT has a high specificity.
- The second criterion is the appearance of one new PSMA-positive lesion, accompanied by consistent clinical or laboratory data, with confirmation by biopsy or correlative imaging within 3 months of PSMA PET.
- The third criterion is an increase in size or PSMA uptake of one or more existing lesions by at least 30%, together with consistent clinical or laboratory data or confirmation by biopsy or correlative imaging within three months of PSMA PET. They recommended an interval of four to eight weeks for response assessment, especially after ARPI, which can result in PSMA overexpression.

In 2021, the European Association of Nuclear Medicine (EANM) finally released the E-PSMA guidelines, providing a structured framework for consistent reporting of PSMA PET findings¹⁷⁷. These guidelines primarily address acquisition protocols, lesion characterisation, and qualitative assessment of response, but stop short of defining formal response thresholds. More recently, the Response Evaluation Criteria in PSMA Imaging (RECIP 1.0) were proposed in 2023 as the first attempt to establish objective PSMA PET-based response criteria¹⁷⁸. RECIP integrates morphologic and molecular parameters, defining progression as a $\geq 30\%$ increase in PSMA-TV or the appearance of two or more new PSMA-avid lesions. Preliminary validation studies demonstrate that RECIP-based progression correlates strongly with biochemical and clinical outcomes, suggesting its potential as a surrogate endpoint in trials.

Despite these advances, challenges remain before PSMA PET can be universally adopted for response evaluation. The dynamic regulation of PSMA expression by therapy, the lack of cross-platform harmonisation of quantitative metrics, and the need for prospective validation all limit immediate clinical implementation. Nonetheless, PSMA PET represents a robust biomarker for early treatment assessment, with the promise of complementing, if not replacing, traditional imaging soon. Ongoing multicentre studies incorporating PSMA-TV and RECIP endpoints will be key to establishing its definitive role in clinical practice. *Emmet et al.* have evaluated baseline PSMA-PET quantitative parameters as predictive and prognostic biomarkers in the Enza-p phase II trial, which randomised first-line mCRPC patients between Enzalutamide and Enzalutamide + ^{177}Lu -PSMA-617¹⁷⁹. Baseline PSMA-TTV was prognostic for OS and predictive for a beneficial effect on overall survival with the addition of ^{177}Lu -PSMA-617 to enzalutamide. By contrast, PSMA SUV_{mean} was not prognostic for PSA-PFS or OS when ^{177}Lu -PSMA-617 was administered with enzalutamide.

3.2.2.2. PSMA-PET/CT to guide PSMA-based radioligand therapies

PSMA PET imaging plays an indispensable role in the selection, planning, and monitoring of PSMA-targeted radioligand therapies (RLT). As PSMA expression is highly variable among tumour sites and patients, PET imaging with ^{68}Ga -PSMA-11 or ^{18}F -labelled ligands enables the identification of lesions with sufficient target expression to ensure therapeutic efficacy while minimising off-target toxicity. Baseline PSMA PET is now considered mandatory before ^{177}Lu -PSMA or ^{225}Ac -PSMA therapy, as only patients with high and homogeneous tracer uptake—typically exceeding hepatic background activity—derive clinical benefit. Moreover, integrating PSMA PET with FDG PET can reveal discordant, dedifferentiated lesions lacking PSMA expression, which predict poor response and guide exclusion or alternative treatment strategies. Quantitative metrics such as total PSMA-

positive tumour volume (PSMA-TV) and total lesion PSMA uptake (TLP) have emerged as potential biomarkers for treatment stratification and dosimetry optimisation. Early reductions in PSMA-TV or TLP after one or two treatment cycles correlate with PSA decline and improved survival, underscoring the potential of PSMA PET as an early surrogate of efficacy. Beyond patient selection, serial PSMA PET can detect heterogeneous response patterns, identify emerging resistant clones, and inform personalised adaptations in dosing or combination strategies. Thus, PSMA PET is evolving from a purely diagnostic tool into a comprehensive theranostics platform that enables precision-guided delivery, response assessment, and longitudinal management of radioligand therapy in advanced PCa.

- The **TheraP trial** was a randomised phase II study conducted by ANZUP in collaboration with the Australasian Radiopharmaceutical Trials Network ¹⁸⁰. It compared ¹⁷⁷Lu-PSMA-617 with cabazitaxel chemotherapy in patients with mCRPC who had progressed after docetaxel. The study has demonstrated a superior PSA response rate with ¹⁷⁷Lu-PSMA-617 compared with cabazitaxel (66% vs. 37%; $p < 0.0001$) and a longer rPFS. Although OS was similar between arms at early follow-up (median ~19 months), likely reflecting post-progression crossover and subsequent therapies, subsequent long-term analyses confirmed that ¹⁷⁷Lu-PSMA-617 achieved durable biochemical control with fewer grade ≥ 3 toxicities (33% vs 53%)¹⁸¹. In TheraP, ⁶⁸Ga-PSMA and ¹⁸F-FDG PET/CT parameters were analysed as predictive and prognostic factors. PSMA-PET $SUV_{mean} \geq 10$ was predictive of a higher likelihood of favourable response to ¹⁷⁷Lu-PSMA-617 than cabazitaxel, guiding optimal ¹⁷⁷Lu-PSMA-617 use. Among men with baseline PSMA-PET $SUV_{mean} \geq 10$, 32 (91%) of 35 men treated with ¹⁷⁷Lu-PSMA-617 had a PSA response (defined as a $\geq 50\%$ decline in PSA) compared with 14 (47%) of 30 men treated with cabazitaxel. In men with a PSMA-PET

SUV_{mean} ≥ 10 , the hazard ratio (HR) rPFS for ¹⁷⁷Lu-PSMA-617 vs. cabazitaxel was 0.46 (95% CI 0.25–0.84). High FDG-PET metabolic tumour volume (MTV) of 200 mL or higher was associated with lower responses regardless of randomly assigned treatment¹⁸².

- The **LuPIN trial** assessed 56 patients with mCRPC who received up to six cycles of PSMA-RLT combined with a radiation sensitizer (NOX66)¹⁸³. Univariable and multivariable analyses were performed to explore the relationships between changes in TTV (continuous and >30%) and SUV_{max}, PSA, and radiographic progression, and PSA PFS and OS. Among them, 37 patients had both baseline and post-treatment ⁶⁸Ga-PSMA and ¹⁸F-FDG PET/CT scans for analysis. Seventy per cent exhibited a PSA response of more than 50%. In responders, reductions in PSMA SUV_{max} and PSMA total tumour volume (TTV) were observed in 95% and 68% of cases, respectively. Change in PSMA SUV_{max} was not linked to PSA PFS or OS. ¹⁸F-FDG SUV_{max} decreased in 51%, and ¹⁸F-FDG TTV in 67%. An increase in ¹⁸F-FDG SUV_{max} was associated with poorer OS (median, 20.7 vs. 25.7 months; $P < 0.01$). An increase in ¹⁸F-FDG TTV by more than 30% correlated with shorter PSA PFS (median, 3.5 vs. 8.6 months; $P < 0.001$), but not OS. In multivariable analysis, only increased PSMA TTV and PSA progression remained independently prognostic of OS (HR 5.1 [95% CI, 1.5–17.1]; $P = 0.008$ and 3.5 [95% CI, 1.1–10.9]; $P = 0.03$, respectively). The study demonstrated that changes in quantitative PSMA-TTV serve as a reliable prognostic biomarker for RLT outcomes, independent of ¹⁸F-FDG PET/CT parameters, PSA levels, or radiographic progression.
- In a retrospective study by **Grubmüller et al.**, SUV_{mean} and total tumour volumes (TTV) were retrospectively assessed on PSMA PET in 38 of 55 mCRPC patients before and after RLT¹⁸⁴. The changes in both TTV and PSA levels were associated with OS (HR 1.001, 95% CI 1–1.003, $p =$

0.04, and HR 1.004, 95% CI 1.001-1.008, $p = 0.01$, respectively), while the changes in SUV_{mean} and the RECIST evaluation were not.

- **Kind et al.** have conducted a retrospective study on 70 patients¹⁸⁵. They underwent ^{68}Ga -PSMA PET/CT and ^{18}F -PSMA PET/CT, both at baseline and after completion of 2-4 of PSMA-RLT. The analysis demonstrated that higher baseline $PSMA_{TV50}$ values and greater $\Delta PSMA_{TV50}$ were associated with shorter OS for both ^{18}Ga -PSMA-11 and ^{18}F -PSMA-1007.

Quantitative ^{177}Lu SPECT/CT imaging after each ^{177}Lu -PSMA dose may also be valuable in response monitoring in addition to providing dosimetric information. Increased tumour volume on ^{177}Lu SPECT/CT at dose 3 (week 12) has been shown to predict early disease progression with ^{177}Lu -PSMA therapy¹⁸³. A prospective study investigated the role of quantitative ^{177}Lu -SPECT/CT parameters in monitoring treatment response to ^{177}Lu -PSMA-I&T in 127 men with progressive mCRPC who had previously received ARPI and chemotherapy. Patients received a median of three treatment cycles, with imaging performed at baseline and week 6. A $\geq 50\%$ PSA decline was achieved in 58% of patients, with median PSA PFS of 6.1 months and OS of 16.8 months. Quantitative analysis of serial ^{177}Lu -SPECT/CT showed a reduction in total tumour volume (TTV) in 74% of patients. At the same time, any increase in TTV between baseline and week 6 was significantly associated with shorter PSA PFS but not OS. Notably, patients with concurrent increases in PSA and SPECT TTV had markedly poorer outcomes compared with those showing reductions in both parameters (median PFS 2.8 vs. 9.0 months). These findings suggest that changes in SPECT-derived TTV represent a promising imaging biomarker for predicting early progression and may help guide decisions on continuing or adapting ^{177}Lu -PSMA therapy.

Kashyap et al. have shown that new metastases on posttherapy SPECT/CT after cycle 2 of ^{177}Lu -PSMA-617 are an independent prognostic biomarker

for OS in 85 mCRPC men¹⁸⁶. Patients had to receive at least 2 cycles of ¹⁷⁷Lu-PSMA-617 and have a follow-up of at least 12 months. Among these patients, 18 (21.2%) had new metastases visible on cycle 2 SPECT/CT, and this was prognostic for OS in univariate (HR 2.38; 95% CI, 1.36-4.18; $P = 0.002$) and multivariate (HR 2.85; 95% CI, 1.36-5.98; $P = 0.01$) analyses. Seven (8.2%) patients with PSA reductions had new lesions on posttherapy SPECT/CT. Reductions in total lesion activity (TLA) (HR 0.98; 95% CI, 0.97-1.00; $P = 0.016$) and metabolic tumour volume (MTV) (HR 0.98; 95% CI, 0.96-1.00; $P = 0.009$) (per 10% increase for both) were associated with OS on univariate analysis but not on multivariate analysis. Changes in SUV_{max} and SUV_{mean} were not associated with OS. There was moderate correlation among changes in PSA from cycle 1 to cycle 2 and MTV (correlation coefficient = 0.55; 95% CI, 0.39-0.69; $P < 0.001$) and TLA (correlation coefficient = 0.56; 95% CI, 0.40-0.69; $P < 0.001$).

During APCC24, panellists did not reach consensus on how to monitor ¹⁷⁷Lu-PSMA responses, although 92% voted in favour of recommending imaging for response monitoring, at least in selected patients⁹³. The question of monitoring remains open, possibly due to regional disparities in nuclear medicine practices and imaging reimbursement standards. However, they were confident that ¹⁷⁷Lu-PSMA could be discontinued after 4 cycles if imaging showed no residual uptake. Still, that treatment should continue for a total of six cycles if relevant tumour activity is detected on PSMA-based imaging.

4. Objective of the thesis

Imaging plays a pivotal role in oncology by detecting metastases and assessing treatment response. For decades, the imaging evaluation of prostate cancer has relied on thoraco-abdomino-pelvic CT scans and technetium bone scintigraphy. Recently, this “conventional imaging” has been replaced by more effective modern imaging techniques, including whole-body MRI and PSMA-PET/CT, which have fundamentally redefined PCa staging and disease monitoring.

The primary objective of this thesis is to define the impact of modern imaging on the management of high-risk PCa, specifically focusing on enhancing disease detection and improving treatment monitoring.

This research is structured into three successive steps:

1. To evaluate the present status of modern imaging.

The first step will evaluate the current status, limitations, clinical needs, and future directions of modern imaging in PCa through a narrative review. This research will systematically investigate the diagnostic performance and clinical impact of WB-MRI and PSMA PET/CT relative to conventional methods across primary staging, biochemical recurrence, and metastatic scenarios. More specifically, we aim to review the design and evolution of WB-MRI protocols, discuss the clinical roles of WB-MRI in the staging and therapeutic pathways of PCa patients, and assess the limitations of WB-MRI compared with other modern imaging methods. Finally, we will address challenges and future directions in modern imaging.

2. To compare the diagnostic accuracy of PSMA-PET/CT and WB-MRI for the detection of metastasis in advanced PCa.

While both PSMA-PET/CT and WB-MRI outperform standard technology for detecting metastases, direct comparisons between the two modalities remain scarce. We will compare the diagnostic performance of WB-MRI and PSMA-PET/CT for detecting distant metastasis in a high-risk PCa population.

3. Evaluate the added value and the prognostic implications of treatment response evaluation by modern imaging using WB-MRI

Standard assessment of metastatic response in advanced PCa relies on conventional imaging and PSA evaluation. We will assess the agreement between PSA and imaging responses using WB-MRI. We aim to explore the prognostic and complementary roles of WB-MRI relative to PSA response in patients with metastatic PCa, focusing on treatment duration and overall survival.

5. Clinical implications of modern imaging in the management of high-risk prostate cancer

The emergence of PSMA PET/CT and WB-MRI has triggered a fundamental redefinition of prostate cancer staging and disease conceptualisation. For decades, prostate cancer classification relied almost exclusively on anatomical imaging modalities—contrast-enhanced CT and technetium-99m bone scintigraphy (BS) to determine the extent of disease. Modern imaging breaks this paradigm by allowing direct visualisation of biological and molecular activities within both primary local tumour and metastatic sites, leading to a higher diagnostic accuracy. In a nutshell, we see better and earlier. Patients with localised disease are now re-adjudicated into low-burden oligo-metastatic disease.

5.1. Beware of the biases

While these innovations improve individual patient care, they also introduce important epidemiological biases, namely migration bias, length bias, and lead-time bias, which interfere with the interpretation of survival outcomes and treatment effectiveness.

- **Stage migration bias** arises when improved diagnostic accuracy reclassifies patients into different disease stages without altering the natural history of the disease. In prostate cancer, modern imaging detects metastatic or locally advanced disease that would previously have been missed by conventional modalities such as CT and bone scintigraphy. Consequently, patients once considered to have localised or biochemically recurrent disease are reclassified as oligometastatic or metastatic. This reallocation makes outcomes in lower stages appear better, while inclusion of patients with favourable biology in higher stages can artificially improve survival in advanced disease cohorts. This so-called **Will Rogers effect** creates the illusion of improved survival across stages without true prognostic change¹⁸⁷. As a result, outcomes from older trials using conventional imaging may not

be directly comparable with modern, highly staged cohorts, potentially leading to overestimation of treatment benefit^{5,93,111}.

- **Length-time bias** refers to the preferential detection of slow-growing, indolent tumours due to more aggressive screening or more sensitive diagnostic techniques¹⁸⁸. Prostate cancer is particularly susceptible to this bias because of its wide spectrum of biological behaviour, ranging from indolent disease to aggressive, rapidly progressive cancer. Modern imaging enhances the detection of clinically significant tumours while also identifying many slow-growing lesions that may never become symptomatic. Patients with indolent disease inherently have longer survival, regardless of intervention. Their overrepresentation in screened or intensively imaged populations can lead to inflated survival rates and an apparent benefit of early detection or treatment¹⁸⁹.
- **Lead-time bias** occurs when earlier detection increases the interval from diagnosis to death without extending actual survival. In prostate cancer, PSA testing or high-sensitivity imaging may make survival appear longer simply because disease is identified earlier in its natural history. Patients whose metastatic disease is detected earlier may therefore seem to survive longer than those diagnosed later using conventional methods, even if death occurs at the same biological time point. This artefactual survival gain can be misinterpreted as improved outcomes or treatment efficacy, particularly when survival is measured from diagnosis rather than from biologically meaningful endpoints such as symptom onset or cancer-specific mortality.

The combined effects of stage migration, length bias, and lead-time bias mean that apparent survival improvements with modern imaging may reflect diagnostic reclassification rather than true therapeutic benefit, highlighting the need for cautious interpretation of outcomes, robust trial endpoints, and thoughtful integration of advanced imaging to avoid overtreatment.

5.2. Diagnostic accuracy versus clinical utility, the Guideline paradox

The integration of modern imaging into international guidelines is ongoing but uneven. The European Association of Urology (EAU) guidelines now recommend PSMA PET/CT as the preferred staging modality in high-risk localised and locally advanced disease when available, and as an alternative to cross-sectional imaging plus bone scintigraphy in the unfavourable intermediate-risk group⁵. Similarly, the National Comprehensive Cancer Network (NCCN) guidelines acknowledge PSMA PET/CT and WB-MRI as valid alternatives for staging, particularly in unfavourable intermediate-, high-, and very high-risk disease⁶⁶. However, almost all therapeutic algorithms within these guidelines still derive from studies based on conventional imaging cohorts. This leads to a “guideline asymmetry”: imaging recommendations for staging have been updated, but treatment recommendations have not been re-evaluated in light of new imaging modalities.

While it is intuitively appealing to assume that earlier and more accurate detection of metastatic lesions will improve patient outcomes, this has not yet been demonstrated in prospective randomised trials for unselected populations. Identifying biologically indolent micro metastases risks overtreatment, potentially leading to earlier initiation and prolonged exposure to systemic therapies without a proven survival benefit. Conversely, failing to detect aggressive small-volume disease may delay intensification and result in undertreatment.

5.3. The risk of disrupting validated treatment because of new imaging technologies

The challenge for clinicians is integrating stage migration into everyday clinical decision-making. When modern imaging identifies additional nodal or distant lesions, should this automatically trigger a change in treatment plan?

Here is a perfect example. Let's assume a patient with a high-risk localised disease, because of a PSA at 17 ng/dl, a stage T1C and 2 biopsies positive for an ISUP 4. Conventional imaging shows no metastases. After discussion with the physicians, the patient opted for prostate radiotherapy and 18 months of androgen deprivation. He asked for a second opinion and has ordered a PET-PSMA. The PET PSMA shows 2 positive iliac lymph nodes. Based on this, the second opinion physician offered to add two years of abiraterone acetate, invoking the STAMPEDE trials ¹⁹⁰. The STAMPEDE has shown, unanimously, that in patients with pelvic lymph nodes detected by conventional CT, adding 2 years of abiraterone on top of 3 years of ADT significantly increases overall survival ¹⁹⁰. During the latest APCCC, 71% of the panellists recommended adding abiraterone to patients with cN0 on conventional imaging, positive pelvic lymph nodes on PSMA PET, and no distant lesions (M0), and who otherwise do NOT meet the STAMPEDE (high-risk, locally advanced M0) definition.

Earlier this year, another seminal trial, ENZARAD, evaluating the addition of 2 years of enzalutamide, showed no benefit in these patients ¹⁹¹.

This case study raises concerns regarding overtreatment, increased toxicity exposure, and quality of life impact in patients whose micro metastatic disease may have been indolent. Conversely, more precise identification of disease extent can lead to de-intensification of local therapies in patients whose disease burden is reclassified as advanced

5.4. How do we address the diagnostic accuracy vs. clinical utility gap

Future trials should randomise patients before staging, assigning them to either conventional imaging (CT and bone scan) or modern imaging (e.g. WB-MRI and/or PSMA PET), with all treatment decisions confined to the allocated imaging pathway. This preserves independent imaging strategies, avoids cross-contamination, and allows differences in overall and cancer-specific survival

to be attributed to imaging-guided management rather than stage reclassification or lead-time bias.

- **Example 1: Newly diagnosed disease** Men with newly diagnosed prostate cancer would be randomised at first staging to conventional versus modern imaging. Management in each arm (including active surveillance, local therapy, or upfront systemic treatment) would follow only that arm's imaging results, and long-term overall and prostate cancer-specific survival would be compared to determine whether intensified staging truly reduces mortality or simply upstages patients without improving outcomes.
- **Example 2: Biochemical recurrence:** After biochemical recurrence, patients would be randomised to conventional imaging versus PSMA PET-based imaging. Standard salvage strategies would be used in the conventional arm, while PET-guided management could include metastasis-directed therapy, broader radiotherapy fields, or earlier systemic treatment; overall survival and time to castration resistance would indicate whether treating PET-detected subclinical disease improves prognosis or merely delays diagnosis.
- **Example 3: mHSPC:** Patients with suspected metastatic hormone-sensitive prostate cancer would be randomised to conventional versus PSMA PET-based staging at first metastatic work-up. Treatment intensification (chemotherapy, prostate-directed radiotherapy, metastasis-directed therapy) would be tailored to disease burden within each imaging arm, and comparisons of overall and progression-free survival would clarify whether imaging-driven intensification improves outcomes or simply reclassifies biologically favourable patients as low-volume metastatic

5.5. The conundrum of clinical availability

One problem with new imaging technologies is their availability. Access to modern imaging modalities remains highly heterogeneous across healthcare systems and geographic regions¹⁹². PSMA PET/CT depends on the availability of specialised radiotracers, PET-capable infrastructure, and local regulatory approval for radiopharmaceutical use. However, these requirements limit its availability to a relatively small number of high-volume or academic centres, particularly in high-income countries. Even within these countries, access is often centralised to tertiary referral hospitals, leading to geographic disparities and long waiting times. In low- and middle-income settings, these barriers are magnified by limited radiopharmaceutical production capacity, regulatory delays, cost constraints, and insufficient nuclear medicine expertise.

While technically less widely available than PET, WB-MRI faces significant implementation barriers. It requires high-quality MRI platforms, optimised acquisition protocols, and experienced radiologists trained in WB-MRI interpretation. Many radiology departments lack the personnel, time, or standardised protocols to implement whole-body protocols efficiently. Scan duration is typically longer than PSMA PET/CT, making scheduling more complex, and inter-reader variability remains an issue without structured reporting. These factors can slow adoption even in well-resourced systems and can be prohibitive in smaller hospitals or regions with limited imaging capacity.

The result is a two-speed staging system, in which some centres have easy access to modern imaging, while others remain reliant on conventional cross-sectional imaging and bone scintigraphy. This geographic and institutional variability directly affects diagnostic accuracy and, consequently, therapeutic decision-making. A patient's disease classification may depend as much on where they are imaged as on the biology of their disease. This variability also introduces heterogeneity in clinical trial enrolment and accessibility.

6. First publication

Whole-body magnetic resonance imaging for PCa assessment: Current status and future directions.

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Summary

PCa (PCa) is the second most common malignancy in men and remains a significant cause of cancer-related death. Advances in systemic and local therapies have shifted the clinical need toward more accurate staging, disease quantification, and response monitoring. Conventional imaging with bone scintigraphy and computed tomography lacks sensitivity for small-volume or early metastatic disease. New-generation imaging, particularly whole-body magnetic resonance imaging (WB-MRI) and prostate-specific membrane antigen positron emission tomography (PSMA-PET/CT), provides superior detection and functional evaluation across the disease continuum.

Technological Advances

Modern WB-MRI combines anatomical and functional imaging to visualise bone, nodal, and visceral metastases within a single, radiation-free examination. Technological improvements in multichannel surface coils, faster gradient systems, and rolling-bed platforms have reduced scan times to under one hour.

Anatomical imaging employs T1- and T2-weighted sequences optimised by fat suppression (STIR, CHESS, or Dixon methods) to differentiate metastatic lesions from normal marrow. Three-dimensional fast spin-echo (FSE) and gradient-echo Dixon sequences enable isotropic voxel imaging and multiplanar reconstruction. The Dixon technique simultaneously produces fat-only and water-only images, improving lesion conspicuity while enabling quantitative fat-fraction (FF) mapping.

Low FF and low apparent diffusion coefficient (ADC) values are characteristic of active lesions and can serve as biomarkers of treatment response.

Functional imaging with diffusion-weighted imaging (DWI) exploits differences in water diffusivity between tumour and normal tissues. Whole-body DWI with background suppression (DWIBS) detects skeletal and soft-tissue lesions with high sensitivity. ADC maps derived from at least two b-values (50–100 and 800–1000 s/mm²) quantify tissue cellularity. While DWI excels in detecting bone metastases, distinguishing benign from malignant lymph nodes remains challenging due to overlapping signal characteristics.

Multiparametric WB-MRI and Standardization

The integration of anatomical and functional sequences defines multiparametric WB-MRI (mpWB-MRI), analogous to mpMRI of the prostate. To standardise imaging, the METastasis Reporting and Data System for PCa (MET-RADS-P) provides guidance on acquisition, quality control, and response assessment. The core protocol includes sagittal T1 and T2/STIR spine images, coronal or axial T1 GRE Dixon sequences, and axial DWI. Contrast-enhanced imaging is optional but not routinely required for metastasis detection.

Clinical Applications

- At **initial diagnosis**, WB-MRI outperforms BS and CT for detecting bone and nodal metastases, particularly in high-risk patients. Although guidelines (EAU, NCCN, AUA) still recommend conventional imaging for staging, evidence supports WB-MRI as a more accurate, radiation-free alternative, especially when PSMA-PET/CT is unavailable.
- In **biochemical recurrence** and **metastatic disease**, WB-MRI detects skeletal and visceral relapse earlier than BS and provides quantitative ADC and FF metrics for objective treatment monitoring. Standardised response criteria (MET-RADS-P) enable reproducible longitudinal assessments.

Comparison with PSMA-PET/CT and Future Directions

PSMA-PET/CT generally achieves the highest sensitivity for small nodal and bone metastases but is limited by cost and availability. WB-MRI offers complementary strengths—broader access, no ionising radiation, and superior assessment of diffuse marrow involvement and treatment response. Future developments, including artificial intelligence reconstruction, automated lesion segmentation, and hybrid PET/MRI systems, promise faster acquisition, better harmonisation, and improved clinical utility.

Conclusion

WB-MRI has become a reliable, multiparametric, whole-body imaging technique that surpasses conventional methods for detecting and monitoring metastatic PCa. With standardised protocols and quantitative biomarkers, it allows consistent evaluation of disease burden and response to therapy. Although PSMA-PET/CT remains the most sensitive modality, WB-MRI is a valuable, radiation-free, and widely accessible alternative and complementary tool in the precise management of PCa.

Whole-body magnetic resonance imaging for prostate cancer assessment: Current status and future directions

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Abstract

Over the past decade, updated definitions for the different stages of prostate cancer and risk for distant disease, along with the advent of new therapies, have remarkably changed the management of patients. The two expectations from imaging are accurate staging and appropriate assessment of disease response to therapies. Modern, next-generation imaging (NGI) modalities, including whole-body magnetic resonance imaging (WB-MRI) and nuclear medicine (most often prostate-specific membrane antigen [PSMA] positron emission tomography [PET]/computed tomography [CT]) bring added value to these imaging tasks. WB-MRI has proven its superiority over bone scintigraphy (BS) and CT for the detection of distant metastasis, also providing reliable evaluations of disease response to treatment. Comparison of the effectiveness of WB-MRI and molecular nuclear imaging techniques with regard to indications and the definition of their respective/complementary roles in clinical practice is ongoing. This paper illustrates the evolution of WB-MRI imaging protocols, defines the current state-of-the-art, and highlights the latest developments and future challenges. The paper presents and discusses WB-MRI indications in the care pathway of men with prostate cancer in specific key situations: response assessment of metastatic disease, “all in one” cancer staging, and oligometastatic disease.

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INTRODUCTION

Prostate cancer (PCa)¹ is the second most common cancer in men, with an estimated 1,276,106 new cases worldwide in 2018.² Despite improvement in therapy, PCa remains the fifth leading cause of cancer-related death and is responsible for 3.8% of total cancer deaths.²

Patients with newly diagnosed (ND) PCa are stratified into different risk groups based on their clinical state, International Society of Urological Pathology (ISUP) grading, and prostate-specific antigen (PSA) levels in order to define their prognosis and further care.³ Early detection of high-risk

recurrent cancer after definitive initial therapy is critical because salvage treatments can be successful. Later on, reliable quantification of metastatic burden and monitoring response to therapy are key expectations for imaging.

Next-generation imaging (NGI) techniques such as whole-body magnetic resonance imaging (WB-MRI) and prostate-specific membrane antigen (PSMA) positron emission tomography (PET)/computed tomography (CT) address the clinical need for better stratification of PCa states.^{4–6} These techniques are being evaluated for the assessment of local and distant metastasis at the time of initial staging, when

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biochemical recurrence (BCR) occurs, and in the follow up of men with metastatic disease.

Although there is compelling evidence that WB-MRI and PSMA PET/CT are superior to conventional imaging with bone scintigraphy (BS) and CT for determining disease volume and extent, NGI techniques are still not routinely recommended by international guidelines at the time of first diagnosis even in men with locally advanced PCa.⁷⁻⁹ Still, NGI techniques are increasingly recognized to have the potential to play an important role in select patients, and PSMA-PET/CT, due to the strength of the evidence, is already recommended in guidelines for BCR patients.^{10,11} Even so, the availability of PSMA-PET/CT remains limited, and while awaiting its wider availability, WB-MRI has been proposed as a viable alternative because it does not require a separate, extensive supportive radionuclide production infrastructure, and it provides reliable information for decision-making.

WB-MRI protocols are constantly evolving in order to reliably detect every single lesion, with more time-efficient acquisitions and workflows, so that the necessary information is obtained for clinical decision-making. Anatomical and diffusion sequences have been improved, and several quantitative parameters, for example, apparent diffusion coefficient (ADC; unit mm²/s) values and fat fraction (FF; %), bring objectivity to the measurements. Recommendations regarding the choice of sequences and technique, as well as the reading and reporting of images, have emerged.^{12,13}

In this paper, we review the design of WB-MRI protocols and their evolution, discuss their clinical roles in the staging and therapeutic pathway of PCa patients, assess their place and limitations compared to other NGI methods, and address future and challenging directions.

WB-MRI TECHNIQUE: EVOLUTION OF HARDWARE AND SOFTWARE

WB-MRI consists of the acquisition of consecutive stacks of high spatial resolution images of consecutive parts of the body that are then fused using reconstruction software. Initially, WB-MRIs were limited by the need to reposition the patient between each station along with long acquisition times per station, but the introduction of rolling bed platforms and the acceleration of sequences eliminated the need for repositioning and made it possible to scan patients in less than 1 h.¹⁴⁻¹⁶ Advances in radiofrequency coils led to changes from built-in body coils, first used to increase z-axis coverage, to whole-body surface coils that combine numerous integrated coil elements, which improved contrast-to-noise-ratio (CNR) and spatial image resolution.^{17,18} Today, a continuous increase in the number of receiving channels and improvements in the design and weight of surface coils are increasing the overall performance, resolution, and rapidity of WB-MRI examinations.¹⁸

Advances in software and acceleration techniques such as parallel imaging technique have enabled faster acquisition of images and have contributed to the emergence of functional techniques such as diffusion-weighted imaging (DWI) using single-shot spin echo planar imaging (ssEPI)^{19,20} and quantitative fat imaging using gradient echo-based Dixon approaches. In addition, the growing use of 3T magnets in clinical practice has led to increases in signal-to-noise ratios (SNR) and faster acquisition times and has made acquisition of three-dimensional (3D) isotropic T1 sequences possible.^{21,22} Nevertheless, performing 3T WB-MRI is more prone to artifacts and is more challenging.²³

TARGET ORGANS: FROM BONE TO ALL-ORGAN IMAGING

In general, the setup of MRI protocols depends on the likely distribution of metastases, which in turn depends on the primary cancer location, stage, and histotype. In PCa, metastatic disease is initially observed in the skeleton and the lymph nodes; visceral locations are less common.²⁴⁻²⁶ However, increasingly effective therapies have resulted in an increased incidence of multiorgan metastases during later stages of disease,²⁷ and an autopsy study of 1589 patients revealed that hematogenous metastases were present in 35% of the patients, and these metastases were located in the skeleton in 90%, the lung in 46% (pleura 21%), the liver in 25%, and the adrenals in 13%.²⁸ This requires imaging protocols that are able to depict metastases at a variety of anatomic sites during a single examination.

WB-MRI ANATOMICAL IMAGES

From Axial Skeleton to Whole-Body and All-Organ Screening

Axial skeleton (spine and pelvis) MRI (AS-MRI) combining T1- and short inversion time inversion recovery (STIR)-weighted images of the spine in the sagittal plane, often complemented with coronal images of the bony pelvis, were initially used to study skeletal red bone marrow areas most likely to harbor bone metastases.^{29,30} The presence of lesions, epidural extension, and spinal cord compression is assessable.³¹ The AS-MRI technique alone was very competitive with BS, although this technique could not detect appendicular, sternal, or rib lesions, but involvement of these sites alone is exceptional.^{32,33} The assessment of the spine still remains necessary to complement other WB-MRI sequences in modern practice.

The availability of WB-MRI anatomic sequences made coverage of the whole skeleton in the coronal or axial plane possible, although in practice, this is limited to the region from the eyes to the mid-thighs; more distal limb metastases are exceptional.³³⁻³⁵ Compared to AS-MRI for the detection of bone lesion, coronal WB-MRI did not detect significantly

more bone metastases (134 with WB-MRI vs. 124 with AS-MRI) in 60 patients.³³ With the introduction of dedicated sequences, for example, breath-hold 3D T1 gradient echo (GRE), WB-MRI protocols evolved to encompass all organs and now enable more complete staging evaluations, which include assessments of lymph nodes, lung and liver parenchyma, and the prostatic bed.^{12,36,37}

Initially, WB-MRI protocols relied exclusively on anatomical sequences such as T1 and T2 with fat suppression or STIR-weighted images, sequences that enable the detection of bone metastases. Compared to the normal bone marrow, bone metastases exhibit low signal intensity (SI) on T1-weighted images, and an intermediate to high SI lesion is observed on T2-weighted images, depending on the mineralization status and water content of lesions, and sometimes with a peripheral “cellular” high SI T2 halo thought to reflect more active or aggressive disease surrounding a more mineralized central portion of the lesion.³⁸

T2-weighted sequences have been optimized to improve lesion detection by increasing contrast between lesions and the surrounding normal marrow using different methods to suppress the fat signal, that is, chemical shift selective saturation (CHESS), STIR, or the Dixon method (see below).^{29,39} These anatomical MRI sequences are sufficient to distinguish bone metastasis from the normal fatty bone marrow background in the majority of patients. Difficulties may be encountered in patients with more cellular marrow, such as in younger individuals and patients being administered bone marrow-stimulating factors, due to the reduced contrast between lesions and the background hyperplastic marrow.⁴⁰

As with CT scans, anatomical WB-MRI sequences also have limited diagnostic value for detecting pathological lymph nodes because the main criterion of metastatic lymph node involvement is based on its size. Anatomic images have low sensitivity and specificity in detecting the microscopic infiltration of normal-sized nodes, a common phenomenon in PCa.⁴¹

As already noted, visceral metastases mainly affect the liver and lungs and occur at later stages of the disease.⁴² WB-MRI anatomical images are progressively being optimized for detecting lung metastases, but there is little objective information concerning their use in the literature.¹² Liver metastases can be efficiently detected using DWI, and characterization of lesions can be carried out using anatomic signal characteristics using DWI (see below) and contrast-enhancement (if necessary).^{36,43}

From 2D to 3D Imaging: Multiplanar Capability and Speed

Anatomic images acquired using two-dimensional (2D) sequences are obtained in the coronal or axial plane for skeletal and node screening but also in the sagittal plane for optimal study of the spine. Advances in both hardware and

software have made it possible to obtain 3D images, which allow multiplanar reformatting after acquisition of a single-volume sequence. Initial approaches involved acquiring coronal 3D-T1 fast spin echo (FSE); Sampling Perfection with Application optimized Contrasts using different flip angle Evolution (SPACE); or cube sequences using very thin, nearly isotropic voxels (section thickness of 1.2 mm). These approaches facilitated the detection of bone and node metastases, especially in difficult-to-evaluate anatomic areas (e.g., posterior vertebral elements, pelvic nodes, etc.), and avoided the need for acquiring additional dedicated images of the spine and retroperitoneal lymph nodes²² (Figure 1), hence saving time. However, a remaining drawback of 3D FSE sequences was an acquisition time of more than 4 min for each station and more than 12 min for whole-body coverage, and the Dixon approach can address this limitation.

Contribution of the Dixon Technique to WB-MRI

The Dixon technique obtains images using two (two-point Dixon) or more (multipoint Dixon, mDixon) echoes.⁴⁴ Fat suppression takes advantage of the fact that the nuclei in water and fat molecules precess at different frequencies, alternating over time to being in-phase (IP) and out-of-phase/opposed-phase (OP) with each other. The Dixon technique enables the reconstruction of four types of images: IP and OP images but also fat-only (FO) and water-only images (WO, which correspond to fat-saturated images).

Breath-hold 3D-T1 GRE images acquired using the Dixon technique can decrease the acquisition time for anatomical images. The value of one pelvic 3D T1-weighted GRE sequence with a 2-point Dixon fat–water separation was compared to T1W FSE in 39 PCa patients. The sequence provided better image quality, equivalent performance for node and bone detection, and a reduced acquisition time (2 min 37 s vs. 5 min 16 s).⁴⁵ The Dixon technique was first introduced in WB-MRI for bone lesion screening in metastatic breast cancer^{46–48} and in myeloma⁴⁹ in association with DWI sequences. The FO images improved contrast between tumoral lesions and the normal marrow, which is sometimes limited on T1 IP images.⁵⁰ A WB-MRI study compared the performance of the 3D T1 GRE breath-hold mDixon sequence to 3D T1-FSE for the detection of node and bone metastases in 30 patients with high-risk PCa and demonstrated that the accuracy of 3D mDixon T1 GRE was comparable to 3D T1 FSE, while acquisition times were shortened significantly from 14 min to 1 min 20 s.⁵¹ The T1 GRE mDixon technique has also been assessed for node and bone metastases screening in PCa and was found to perform better than BS for detecting bone metastases and similar to ¹⁸F choline-PET/CT for detecting malignant node involvement.⁵² The Dixon acquisition also showed promise for detecting lung metastases and exhibited a similar performance to low-dose CT on a per-patient basis. Of note, ultra-short



Figure 1: Comprehensive whole-body magnetic resonance imaging (WB-MRI) used for staging of newly diagnosed prostate cancer in a 74-year-old man at high risk of metastasis. (a) Coronal 3D T1-weighted (W) turbo-spin echo (TSE) sequence shows a unique left femoral neck metastasis (arrow). (b) Coronal reformatted DWIBS image at b 1000 s/mm² diffusion DWI (multiplanar reconstruction, inverted grayscale) confirms left femoral neck lesion (arrow). Note that the dark signal of the brain, spleen, and spinal cord and small lymph nodes in the neck, axillae, and groin are a normal finding. (c) Sagittal reformatted 3D T1W FSE image of the spine show no vertebral metastasis. (d) Transverse reformatted 3D T1W TSE image confirms the presence of a left femoral neck metastasis. (e) Fat fraction (F%) map obtained using the Dixon technique shows complete disappearance of fat pixels within the metastatic deposits. (f) ADC map shows abnormal signal within the femoral lesion (1235 $\mu\text{m}^2/\text{s}$). F% and ADC values may be used for lesion monitoring

echo time (UTE) acquisitions can also be used to assess lung parenchyma as UTE can detect pulmonary nodules that are 5 mm or larger, but this adds significantly to scan time.⁵³ Conventional Dixon MR images are less able to detect nodules smaller than 10 mm.^{54–56} Recent advances include breath-hold lung sequences, which promise shorter acquisition times while maintaining lesion detection sensitivity of lesions sized 5 mm or more; these sequences require further evaluations.

Fat Fraction Measurements

Dixon acquisitions can be used to generate fat fraction maps.⁵⁷ The signal or relative fat fraction (sFF/rFF; unit %) is calculated using the formula: $(\text{SI FO}/[\text{SI FO} + \text{SI WO}]) \times 100$. The calculated sFF value is reproducible with a small standard deviation for repeated measurements ($\sigma R = 13\%–32\%$).^{58,59} sFF maps provide a quantitative assessment of bone marrow fat and can be used to assess treatment response.^{58,60–62} A retrospective comparison of sFF and ADC values of 43 bone lesions with histology showed that active bone lesions had a significantly lower sFF (11.5% vs. 62%) and median ADC (898×10^{-6}

vs. $1617 \times 10^{-6} \text{ mm}^2/\text{s}$) compared to responding lesions⁶³ (Figure 1).

T2-Dixon: Tomorrow's Single Anatomic Sequence?

According to guidelines, whole-spine sagittal fat-suppressed T2 or STIR images are recommended in WB-MRI protocols to study vertebral lesions and their complications.¹² The added value of the T2 Dixon method is notable because it provides a more uniform suppression of the fat signal and higher SNR and CNR, making bone lesions more conspicuous compared to other techniques, including CHES or STIR sequences.^{46–48} In one sequence, the T2 Dixon technique offers improved sensitivity emanating from WO images (equivalent to T2 fat-saturated or STIR images); the effectiveness of T2 IP images for the study of the spinal canal, discs, and marrow; the ability to evaluate lymph nodes; and the “T1-like” information of FO/FF images, which provide high contrast between bone metastases and normal marrow.

In the spine, a retrospective analysis compared whole-spine sagittal T2 mDixon FSE to T1 FSE in 121 patients with metastatic involvement and found an equivalent

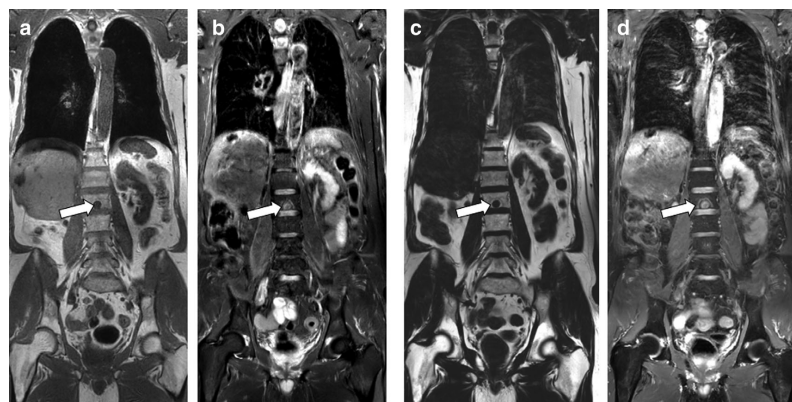


Figure 2: Value of a single T2 Dixon sequence as alternative to the combination of T1 and STIR sequences as anatomical sequences. Staging in 55-year-old man with ND prostate cancer (PCa) at high risk of metastasis. (a, b) Coronal T1 TSE and STIR images show a metastasis within the L2 vertebral body (arrow). (c, d) Fat only (c) and Water only (d) images obtained from one single T2 Dixon TSE acquisition show the same lesion (arrows)

performance between the FO images derived from the T2 Dixon acquisition and the T1 images.⁶⁴ Furthermore, T2 mDixon had better CNR (181 vs. 84.7) and good to very good interobserver agreement. Another retrospective study compared the performance of sagittal mDixon T2-TSE to the conventional T1-TSE images in 33 patients with 68 metastases and also found no differences between FO images from the T2 Dixon acquisition and T1 sequence.⁶⁵ The acquisition time of the T2 Dixon sequence is longer (6 min 15 s vs. 4 min 14 s for the T1 sequence), but, overall, the Dixon approach provides both FO (T1-like) and WO (STIR-like) images in shorter times than the guideline-recommended combination of T1 and STIR images. Using T2 Dixon sequences as an alternative to the sum of T1 and STIR for WB-MRI anatomical sequences images could drastically shorten the acquisition times, but this remains to be evaluated in comparative studies (Figure 2).

Both T2- and T1-weighted sequences acquired using the Dixon method can be affected by the fat–water swapping artifacts, especially in heterogeneous anatomic regions (neck, close to metallic implants), leading to the replacement of a part of the fat-only image by part of the water-only image and vice versa. This artifact is quite easy to identify, and the reading must then be made by side-by-side analysis of FO and WO images.^{66,67}

FUNCTIONAL MRI: DWI

Standard DWI

The introduction of whole-body DWI with background body signal suppression (DWIBS) using STIR–echo-planar imaging sequence (STIR EPI) during free breathing

allowed acquisition of whole-body DWI with reduced slice thickness and homogeneous fat suppression.^{29,30,33,34,68–72}

Fat-suppressed (most frequently using the inversion recovery technique) DWI sequences using high-diffusion sensitizing gradients (b-values; unit s/mm^2) are generally acquired in the axial plane from head to mid-thigh. For DWIBS, STIR is preferred over CHES for more uniform fat suppression because of its lower sensitivity to magnetic field inhomogeneities, and images are acquired using free breathing.⁷² Two or more b-values are acquired, and ADC maps are calculated with monoexponential fitting of the signal intensity data. A lower b-value in the range 50–100 s/mm^2 minimizes the contribution of microcirculation perfusion effects. A higher b-value set between 800 and 1000 s/mm^2 attenuates the SI of normal tissues without compromising SNR.⁷³ Intermediate b-values of 500–600 s/mm^2 may be considered to improve the accuracy of calculated ADC maps.¹²

DWI sequences are usually read on Picture Archiving and Communication System (PACS) workstations using multiplanar reformatting (MPR) and maximal intensity projection (MIP). Both lower and high b-value images should be evaluated synchronously with the anatomical images.¹² Reconstructed high b-values DWI images allow the visualization and measurement of focal lesions on native or inverted grayscale contrast, usually displayed as multiplanar reformatted views or MIPs.

Before interpreting WB-DWI images, the reader should be familiar with the normal appearance of the bone marrow and lymph nodes. Normal yellow bone marrow in adults has low perfusion and is mainly composed of large fat cells, which impede the movement of extracellular water molecules,

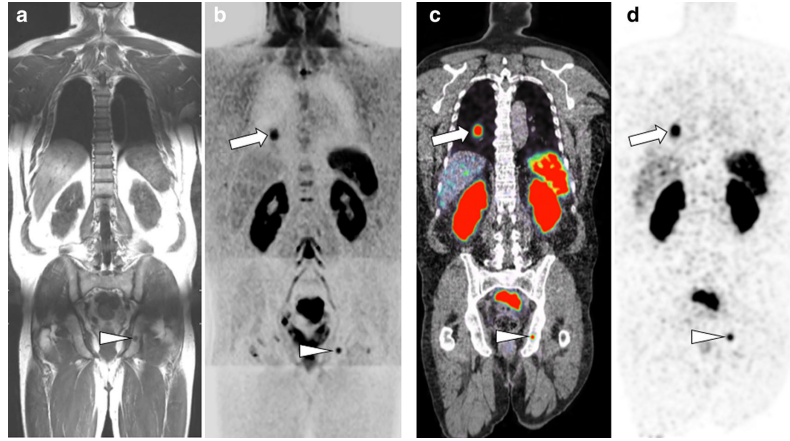


Figure 3: Whole-body magnetic resonance imaging (WB-MRI) and ^{64}Ga -PSMA PET/CT obtained in the same week in a 63-year-old man with advanced prostate cancer (PCa). (a, b) Coronal WB-MRI (a) T1 TSE and (b) coronal reformatted DWIBS (b 1000; inverted grayscale) images show right lung (arrow) and left ischiopubic bone (arrowhead) metastasis. (c, d) ^{64}Ga -PSMA-PET/CT: reformatted fused PET/CT (c) and metabolic PET (d) images show the same lung (arrow) and bone metastasis (arrowhead)

causing a low SI in high b-value images and low ADC values.⁷⁴ Normal red bone marrow has a higher perfusion, cellularity, and water content, which results in higher SI in high b-value images and higher ADC values. Of note, false-positive observations due to high SI on high-b-value images include the T2 shine-through effect from benign vertebral lesions (e.g., hemangioma, endplate degenerative changes), but these pitfalls can be easily overcome by correlating high b-values images to anatomical sequences and corresponding ADC values.⁷⁵

Normal ADC values of adult bone marrow range from $0.2 \times 10^{-3} \text{ mm}^2/\text{s}$ to $0.6 \times 10^{-3} \text{ mm}^2/\text{s}$.²⁰ ADC values of bone marrow decrease with aging in proportion to an increase in fat content accompanying osteoporosis and age-related marrow atrophy.^{76,77} Bone metastatic disease appears as focal or diffuse areas of increased SI on high b-value images and higher ADC compared to normal bone marrow. Tumor ADC values have an upper range value of $1.2\text{--}1.4 \times 10^{-3} \text{ mm}^2/\text{s}$. An ADC threshold of $0.655 \times 10^{-3} \text{ mm}^2/\text{s}$ was shown to separate normal bone marrow in healthy volunteers from abnormal bone marrow in 23 PCa, 9 breast cancer, and 11 myeloma patients.⁷⁸

The presence of bone edema, increased cellularity from bone marrow stimulation, or focal bone marrow hyperplasia may be responsible for increased marrow signal and should not be misinterpreted as a diffuse or progression disease.⁷³ False-negative DWI results may be encountered in hypercellular bone marrow due to reduced contrast between metastases and the marrow background,⁷³ in densely sclerotic bone lesions,⁷⁹ and in some difficult anatomical areas such as the lower neck and ribs.

The detection of abnormal lymph nodes remains difficult with DWI. Both normal and pathological nodes have high SI in high-b value images because of their high cellularity. Hence, similar to anatomic images, size remains the main diagnostic criterion for abnormal nodes. ADC measurements have been proposed to improve the value of DWI sequences to distinguish malignant from benign lymph nodes presenting a “normal” size. Malignant nodes have been shown to have significantly lower ADC values ($1.07 \pm 0.23 \times 10^{-3} \text{ mm}^2/\text{s}$) than benign nodes ($1.54 \pm 0.25 \times 10^{-3} \text{ mm}^2/\text{s}$) in several studies.^{80–82} Studies have also found lower but nonsignificant ADC values in metastatic lymph nodes (0.92 ± 0.22 and $0.94 \pm 0.18 \times 10^{-3} \text{ mm}^2/\text{s}$) than in benign nodes (1.04 ± 0.18 and $1.01 \pm 0.28 \times 10^{-3} \text{ mm}^2/\text{s}$).^{83,84}

As for visceral metastases, pulmonary nodules and liver lesions may be detected as focal high-signal lesions on high b-value images (Figure 3). A study including 22 patients (17 with PCa) demonstrated a high sensitivity (96%) of WB-MRI for the detection of visceral metastases compared to CT, ^{18}F fluorodeoxyglucose (FDG) PET/CT, and ^{11}C choline acetate PET/CT⁸⁵ (Figure 4).

Computed DWI and Semiautomatic Segmentation

Computed WB-DWI consists of generating postprocessed images at user-defined higher b-values based on voxel MR signal and ADC values.⁸⁶ The generated images can help reduce the T2 shine-through effect on MIP images; reduce near-field flare signal, especially on images acquired at 3T; and can facilitate semiautomatic segmentation on MIP WB-DWI with better delineation of the tumor volumetric burden (total

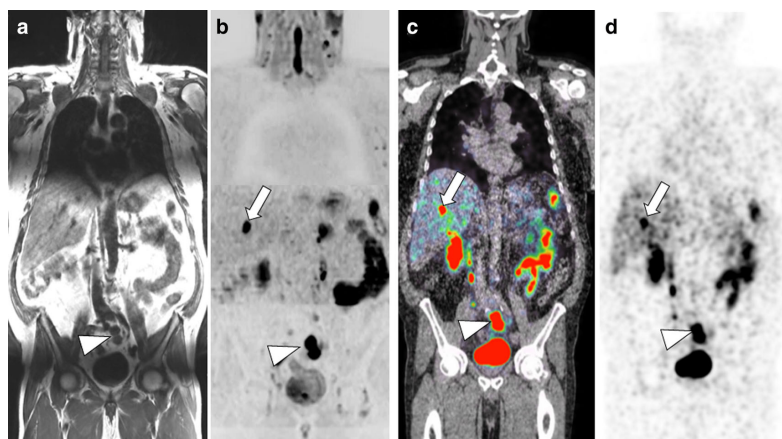


Figure 4: Whole-body magnetic resonance imaging (WB-MRI) and PSMA PET/CT obtained in the same week in a 68-year-old man with advanced prostate cancer (PCa). (a, b) Coronal WB-MRI (a) T1 TSE and (b) coronal reformatted DWIBS (b 1000; inverted grayscale) images show liver metastasis (arrow) and common iliac metastatic lymph nodes (arrowhead). (c, d) ^{68}Ga -PSMA-PET/CT: reformatted fused PET/CT (c) and metabolic PET (d) images show the same lung (arrow) and bone metastasis (arrowhead)

Diffusion Volume, tDV).⁸⁷ However, their routine use is not recommended.

Simultaneous MultiSlice-DWI

Simultaneous excitation and acquisition of multiple slices allows an acceleration of data acquisition with a limited impact on SNR.⁸⁸ Parallel imaging and the CAIPIRINHA technique (controlled aliasing in parallel imaging results in higher acceleration) permit the potential use of simultaneous multislice (SMS)-DWI in whole-body DWI.⁸⁹ Using PET/MRI, a study compared SMS-DWI to DWIBS in 10 volunteers and 20 patients at 3 T.⁹⁰ Acquisition time was reduced by 40% (84 s vs. 140 s) with a subjective cost in image quality and more artifacts observed in the thoracoabdominal area of the SMS-DWI images. Still, SMS-DWI provided reliable lesion conspicuity, and the ADC values were reliable and comparable to standard DWI. Whole-body SMS-DWI was recently used for bone metastases screening in PCa and showed similar image quality compared to standard DWI.⁹¹ Deep learning methods for image reconstruction are also emerging, which will further reduce DWI sequence acquisition times. These methods are still not widely available, and their impact on WB-MRI use cannot yet be evaluated.

MULTIPARAMETRIC WB-MRI AND CHOICE OF SEQUENCES

Multiparametric (mp) MRI, the association of anatomical and at least two functional sequences, represents the current standard for studies dealing with the local assessment of

prostate,⁹² breast,⁹³ bladder,⁹⁴ and brain⁹⁵ cancers. WB-MRI provides the same qualitative and quantitative mp approach, relying on anatomical T1 and STIR sequences and functional DWI sequences, along with ADC maps and FF maps for the quantitative evaluation of bone lesions.

In 2016, an international expert panel designed the METastasis Reporting and Data System for prostate cancer (MET-RADS-P) in an attempt to harmonize and standardize WB-MRI protocols in terms of content, quality, and reporting. The core protocol comprises anatomical sequences, including sagittal T1 and T2 fat-suppressed or STIR images of the spine and coronal or axial whole-body T1 GRE Dixon images along with FF mapping (Table 1). The 3D T1 FSE was proposed as the single alternative to the previous T1 sequences. Axial WB-DWI with two b-values (b 50–100 and b 800–1000 s/mm²) is also part of this protocol (Figure 1). MET-RADS-P also proposed a more comprehensive protocol with coronal and axial T1 GRE, axial FSE T2-weighted sequences for node and visceral screening, a higher number of b-values for the WB-MRI sequence, and optional contrast-enhanced sequences. MET-RADS-P also provided response evaluation criteria for bone, node, and visceral lesions.¹²

The United Kingdom Quantitative WB-DWI Technical Workgroup addressed the question of harmonization of quantitative DWI in order to optimize the response assessment of bone metastases, and they proposed that the calculation of ADC be based on two b-values, b = 50–100 s/mm² and b = 800–1000 s/mm².²⁹

A recent study compared the diagnostic accuracy of the individual T1, STIR, and DWI sequences and their various

Table 1. Proposed whole-body magnetic resonance imaging (WB-MRI) sequences and acquisition parameters at 3T (modified according to METastasis Reporting and Data System for prostate cancer (MET-RADS-P) ¹²)							
Sequence type	T1 GRE DIXON	Spine T1 TSE	3D T1 TSE ^a (alternative)	Spine T2 STIR	T2 TSE DIXON ^b (alternative)	T2 TSE ^c	DWI (DW/BS)
Imaging plane	Coronal and/or axial ^c	Sagittal	Coronal	Sagittal	Sagittal	Axial	Axial
Fat suppression	—	—	—	STIR	—	—	STIR
Respiratory control	Breath-hold	Free breathing	Free breathing	Free breathing	Free breathing	Breath-hold	Free breathing
TR, TE (ms)	3.8/1.46,2.6	555/10	285/21	4714/50	4340/88	562/80	6000/66
FOV (mm)	300 × 450	360 × 360	500 × 299	360 × 360	260 × 349	400 × 300	440 × 348
Slice thickness /Gap (mm)	3 mm/0	3.5/0.35	1.2/0	3.5/0.35	3.5/0.35	4/0	6/0.1
Matrix	300 × 200	260 × 285	320 × 320	320 × 256	260 × 285	308 × 186	128 × 96
Voxel size (mm ³)	1.5 × 1.5 × 3	0.8 × 1 × 3.5	1.14 × 1.13 × 1.2	0.8 × 1 × 3.5	0.8 × 1 × 3.5	1.3 × 1.6 × 4	4.5 × 4.5 × 6
Diffusion b-value (s/mm ²)	—	—	—	—	—	—	50/800
Functional map	Fat fraction	—	—	—	—	—	50/500/800 ^d
TA per station (min, s)	0 min 19 s	4 min 20 s	4 min 36 s	3 min 32 s	4 min 24 s	0 min 20 s	ADC 3 min 06 s
Abbreviations: 3D, three-dimensional; ADC, apparent diffusion coefficient; DWI, diffusion-weighted imaging; DW/BS, diffusion-weighted whole-body imaging with background body signal suppression; GRE, gradient echo; MET-RADS-P, METastasis Reporting and Data System for Prostate Cancer; STIR, short tau inversion recovery; TA, time acquisition; TSE, turbo spin echo.							
^a 3D T1 FSE may replace T1 Dixon and T1 TSE of the spine.							
^b Sagittal T2 Dixon may replace T1 and T2 FSE STIR of the spine.							
^c MET-RADS-P: comprehensive protocol includes both axial and coronal T1 GRE Dixon, axial T2 on the abdomen to detect nodes, and 3b-values in the DWI sequence (additional b 500 s/mm ²).							

combinations (T1-DWI, T1-STIR, STIR-DWI, and T1-STIR-DWI) to detect bone metastases in WB-MRI in 50 patients with PCa and showed that the combination of sequences T1-DWI and T1-STIR was sufficient with no difference in performance using the combination of all three, T1-STIR-DWI, sequences ($p > 0.07$).⁹⁶ In practice, however, the combination of T1 and DWI may be preferred as DWI outperforms SNR in detecting node and visceral metastasis (Figures 3 and 4). Moreover, another study found that STIR images did not lend incremental value to WB-MRI coronal T1-weighted images in metastatic screening.⁹⁷

The need for sequences to be used following contrast injection is often questioned. Bone lesions can be differentiated from normal bone marrow (where perfusion is low) with quantitative and semiquantitative parameters on dynamic contrast-enhanced (DCE) images. For example, PCa lesions have been shown to have a significantly higher transfer constant (K^{trans} , the permeability surface area product) and high increases in SI and the gradient of the upslope using DCE-MRI sequences.⁹⁸ Some investigators have suggested including regional DCE for the detection and characterization of bone metastases, as well as performing a delayed whole-body contrast-enhanced phase in the equilibrium phase at approximately 3 min after contrast medium injection as the contrast medium concentration levels last for about 5.5 min.^{99,100} Although recent work suggests that contrast-enhanced 3D T1 GRE sequences represent the most effective sequence along with DWI to detect metastases,¹⁰¹ contrast-enhanced sequences have limited value for the detection of bone and node lesions and are not included in routine WB-MRI protocols for metastasis⁵² or myeloma lesion detection.¹⁰²

TECHNICAL CHALLENGES

Registration and Postprocessing Strategies

Reconstruction of multistation anatomical and DWI sequences requires postprocessing software that combines the different stacks of images in one volume dataset. WB-MRI is a sum of three to six stacks of high-resolution images that have variations in SI and contain artifacts that are sequence-specific or related to patient motion. In order to overcome these inconsistencies, images acquired for each section are overlapped. Consequently, interscan inhomogeneities at the edge of each section and intrascan inhomogeneities within each stack may be seen,¹⁰³ and a variety of methods has been proposed to overcome these inhomogeneities and allow optimal reconstruction.¹⁰⁴ Even so, postprocessing software may fail to provide perfect image alignment and can result in artifacts such as “broken/dancing spine,” with DWI sequences being particularly sensitive to misalignments. Geometrical artifacts can lead to inaccurate assessments of ADC values or lesion sizes. A recently proposed postprocessing, noise-corrected, exponentially weighted DWI (niceDWI) approach

was developed to standardize SI and generate quantitative contrast in WB-MRI studies on PCa.⁴ An alternative method consists of using integrated slice-by-slice shimming, which significantly improves the SNR of WB-DWI in the neck region.¹⁰⁵

Artificial Intelligence

In the future, we can expect the routine use of deep-learning, artificial intelligence (AI) reconstruction techniques to further optimize data acquisition and image reconstructions free of artifacts. Deep learning can reduce the computational time for the reconstruction of parallel imaging and compressed sensing techniques. Indeed, trained deep-learning models optimize the reconstruction process or reduce artifacts in a better assessment of sparsity and sampling of k-space.¹⁰⁶ The diagnostic performance with regard to the reading time of WB-MRI by the radiologist alone or with the assistance of AI is under study.¹⁰⁷

CLINICAL INDICATIONS AND POSITIONING OF WB-MRI AMONG OTHER TECHNIQUES

Newly Diagnosed Prostate Cancer

The imaging workup at initial diagnosis must distinguish localized/locally advanced from metastatic PCa and evaluate the metastatic load (Tables 2 and 3). Indeed, patients with localized disease will be treated with local treatment, while those with metastatic disease may benefit from combined systemic and local treatment if they present with fewer than five bone metastases.^{1,121} European guidelines recommend at least cross-sectional abdominopelvic imaging (CT or MRI) and a BS for metastatic screening in patients with unfavorable intermediate- and high-risk localized or locally advanced disease, that is, those with a Gleason score of 7 (4 + 3) or a PSA level between 10 and 20 ng/mL (Table 2).^{8,9} National Comprehensive Cancer Network (NCCN) guidelines recommend performing abdominopelvic imaging only if nomograms based on clinical features predict >10% probability of pelvic lymph node involvement and performing bone imaging in unfavorable intermediate- and high-risk localized PCa^{7,122} (Table 2).

Currently, WB-MRI and PET/CT are not recommended by guidelines for routine use at initial staging, except for equivocal bone lesions on conventional imaging.¹¹ This is because the clinical benefit of an earlier detection of metastases remains unclear for the whole population.¹²³ However, it has been abundantly demonstrated that WB-MRI and PET/CT can more accurately define the extent of the disease, locally and remotely, and help tailor a more personalized treatment plan for patients. According to the recent American Society of Clinical Oncology guidelines, however, WB-MRI may be proposed as a second line in high-risk patients with negative/equivocal conventional imaging or in

Table 2. Current recommendations for imaging workup in localized newly diagnosed prostate cancer (PCa)

Any risk group staging
Use prebiopsy mpMRI for staging information
Low risk (PSA $\leq$ 10 ng/mL and ISUP1 and cT1-2a)
No additional imaging is indicated for staging purposes
Intermediate Risk (PSA 10-20 ng/mL or ISUP2-3 or cT2b)
EAU
In ISUP grade $\geq$ 3, include at least a cross-sectional abdominopelvic imaging and bone scan for metastatic screening.
NCCN
Bone imaging: only recommended if PSA > 10 ng/mL or T2
Abdominopelvic imaging: recommended if nomogram predicts >10% probability of pelvic lymph node involvement.
AUA
Clinicians should consider staging unfavorable intermediate-risk localized PCa with cross-sectional imaging (CT or MRI) and BS.
High risk (PSA $\geq$ 20 ng/mL or ISUP 4–5 or $\geq$ cT2c) or locally advanced (any PSA, any ISUP, cT3–4 or cN+)
EAU
Perform metastatic screening including at least cross-sectional abdominopelvic imaging and bone scan.
NCCN
Bone imaging: recommended.
Abdominopelvic imaging: recommended if nomogram predicts >10% probability of pelvic lymph node involvement.
AUA
Clinicians should stage high-risk localized PCa with cross-sectional imaging (CT or MRI) and BS.

Note: Recommendations based on European Association of Urology, European Society for Radiotherapy and Oncology, and International Society of Geriatric Oncology (EAU-ESTRO-SIOG) guidelines 2020 and National Comprehensive Cancer Network (NCCN) guidelines, version 2.2020.

Abbreviations: c, clinical; CT, computed tomography; EAU, European Association of Urology; ISUP, International Society of Urological Pathology; mpMRI, multiparametric magnetic resonance imaging; MRI, magnetic resonance imaging; N, node; NCCN, National Comprehensive Cancer Network; T, tumor.

patients with a few deposits on BS/CT scans that may benefit from additional metastasis-directed therapies (MDT).^{124–126} Thus, current guidelines still do not recommend first-line NGI use outside clinical trials.^{127,128}

In bones, standard imaging modalities have poor diagnostic accuracy for metastatic staging. CT has a modest pooled sensitivity, 72.9%, and specificity, 94.8%, for detecting bone metastases.¹²⁹ Technetium 99 m (⁹⁹Tc) diphosphonate demonstrates up to 40% false-positive results as it detects osteoblastic activity that can be seen in either metastasis but also in benign conditions like inflammation or fractures.¹³⁰ Single Photon Emission Computed Tomography (SPECT)–CT can improve the specificity and the positive predictive value of BS, improving

the accuracy of metastatic staging and allow downstaging of metastatic disease in 29.5% of PCa patients.¹³¹ Numerous studies have shown that AS-MRI and WB-MRI outperform BS for bone metastatic screening,¹¹³ and a comparison of WB-MRI with other modalities for newly diagnosed (ND) and BCR of PCa is presented in Table 3 (Panels A and B).

Few studies have investigated the diagnostic performance of ⁶⁸Ga-PSMA PET/CT in the assessment of bone metastasis at initial staging,¹³² but a recent systematic analysis did conclude that ⁶⁸Ga-PSMA PET/CT detects more bone metastases than BS and improves the diagnostic performance for staging ND PCa.¹³³ In the prospective, multicenter ProPSMA study, the sensitivity and specificity of ⁶⁸Ga-PSMA

Table 3. Comparisons of whole-body magnetic resonance imaging (WB-MRI) to other modalities

Imaging modality	Study design	Magnetic field strength	Sequences	Reference standard	Patients (n), status (ND, BCR), M (n)	Sensitivity (patient basis)	Specificity (patient basis)
Panel A: Comparisons of WB-MRI to other modalities in ND PCa							
AS-MRI vs. BS +/- TXR ¹⁰⁸	Prospective consecutive enrollment	1.5T	T1/T2W	BVC	66, 26 High risk ND PCa, 28 progression under ADT, 12 BCR, 41 BM	46% BS, 63% BS/TXR, 83% BS/TXR/MRI, 100% MRI	32% BS, 64% BS/TXR, 100% BS/TXR/MRI, 88% MRI
WB-MRI vs. ¹¹ C-Choline PET/CT ¹⁰⁹	Prospective consecutive enrollment	1.5T	T1/STIR/DWI	BVC	11, NR, 11 BM	Not reported, DWI = ¹¹ C-choline PET/CT	Not reported
AS-MRI vs. BS +/- TXR ³⁰	Retrospective	1.5 T	T1/T2W	BVC	39 High risk ND PCa, 7 BM	70% BS, 100% MRI	70% BS, 100% MRI
AS-MRI vs. BS ¹¹⁰	Retrospective	1.5T	T1/STIR	BVC	99, High risk ND PCa, 14 BM	71.4% BS, 85.7% MRI	96.5% BS, 97.7% MRI
WB-MRI vs. BS ¹¹¹	Prospective consecutive enrollment	1.5T	DWI	BVC	36 (11 PCa - 3 exclusion/25 BCa), High risk ND PCa, 7 BM (1 PCa/6 BCa)	Patient <5 BM: 58% - 67% BS, 33% - 58% DWI; Patient >10 BM: 42% - 48% BS, 91% - 97% DWI	Patient <5 BM: 97% BS, 99% DWI; Patient >10 BM: 97% BS, 99% DWI
WB-MRI vs. ¹⁸ F-NaF PET/CT ¹¹²	Prospective Consecutive enrollment	1.5T	T1/STIR/DWI	BVC	49, High risk ND PCa, 5 BM	Not reported, MRI = PET/CT	Not reported, 1 FP MRI, 4 FP PET/CT
WB-MRI vs. BS +/- TXR CT (node) ¹¹³	Prospective Consecutive enrollment	1.5T	T1/STIR/DWI	BVC	100, 44 ND High risk PCa, 35 progression under ADT, 21 BCR, 51 BM, 44 NM, 68 B + NM, 13 VM	BM: 86% BS/TXR, 98% - 100% MRI, NM: 77% - 82% CT, 77% - 82% MRI, BM + NM: 84% BS/TXR + CT, 91% - 94% MRI	BM: 98% BS/TXR, 98% - 100% MRI, NM: 95% - 96% CT, 96% - 98% MRI, BM + NM: 94% - 97% BS/TXR + CT, 91% - 96% MRI
BS, SPECT, SPECT/CT, ¹⁸ F-	Prospective Consecutive enrollment	1.5T	T1/STIR/DWI	BVC	53 (27 PCa/ 26 BCa), High risk ND PCa, 8 BM	79% BS, 89% SPECT, 89% SPECT/CT	91% BS, 80% SPECT, 94% SPECT/CT

Table 3. Continued

Imaging modality	Study design	Magnetic field strength	Sequences	Reference standard	Patients (n), status (ND, BCR), M (n)	Sensitivity (patient basis)	Specificity (patient basis)
NaF, PET/CT, WB-MRI ¹¹⁴						95% PET/CT, 100% MRI	97% PET/CT, 97% MRI
WB-MRI vs. BS ¹⁸ F-choline PET/CT ⁵²	Prospective Consecutive enrollment	3T	mDIXON pre- and post-contrast/T2W/DWI	BVC	56, 6 Intermediate/50 high ND risk PCa, 10 BM, 8 NM	NM: 100% MRI, 100% PET/CT, BM: 88% MRI, 80% PET/CT, 60% BS	NM: 96% MRI, 82% PET/CT, BM: 88% MRI, 92% PET/CT, 100% BS
BS, CT, SPECT-CT, ¹⁸ F-PSMA-1007 PET/CT, WB-MRI ¹¹⁵	Prospective Consecutive enrollment	1.5T	Axial T2 FS HASTE, BVC STIR DWI, coronal T1 3D VIBE Dixon, sagittal T1, T2 STIR TSE of spine	BVC	80 High risk ND PCa (1 exclusion)	33%–57% CT, 33%–67% SPECT-CT, 43%–67% WB-MRI, 86%–95% PSMA PET/CT	33%–98% CT, 74%–98% SPECT-CT, 80%–96% WB-MRI, 76%–90% PSMA PET/CT
Panel B: Comparisons of WB-MRI to other modalities at BCR in PCa							
¹⁸ F-choline PET/CT vs. AS-MRI ¹¹⁶	Prospective Consecutive enrollment	Not reported	T1/STIR/T2FS	BVC	64, BCR postlocal treatment, 15 BCR (BM)	BR: 87% PET/CT, 100% MRI	BR: 96% PET/CT, 100% MRI
¹¹ C-choline PET/CT vs. WB PET/MRI ¹¹⁷	Prospective Consecutive enrollment	3T	3D-T1 VIBE/T1W/T2 HASTE + Axial T2/DWI/DCE pelvis	BVC Histology (n = 19)	75, BCR post-RP (57), RT (14), ADT (4), 37 BCR (37 LR, 37NR, 14BR)	Not reported, Detection rate 84.7% PET/MRI, 77.3% PET/CT (p > 0.05)	Not reported
¹¹ C-choline PET/CT vs. WB-MRI ¹¹⁸	Prospective Consecutive enrollment	1.5 T	T1/STIR/DWI	BVC Histology (n = 14)	57, BCR post-RP, 24 BCR (24LR, 27NR, 22BR)	LR: 83.3% PET/CT, 54.2% MRI, NR: 81.4% PET/CT, 77.9% MRI, BR: 92.9% PET/CT, 78.6% MRI	LR: 93.9% PET/CT, 81.8% MRI, NR: 99.7% PET/CT, 87.5% MRI, BR: 98.4% PET/CT, 87.5% MRI
⁶⁸ Ga-PSMA PET/CT vs. ¹⁸ NaF PET/CT versus WB-DWI ¹¹⁹	Prospective Consecutive enrollment	3T	T1/T2/STIR/DWI	BVC	68, BCR post-RP (46), RP + RT (17), RT (5), BCR 10, (10 BR)	80% ⁶⁸ Ga-PSMA PET/CT, 90% ¹⁸ NaF PET/CT, 25%–38% DWI	98%–100% ⁶⁸ Ga-PSMA, 90%–98% ¹⁸ NaF PET/CT, 87%–92% DWI

Table 3. Continued

Imaging modality	Study design	Magnetic field strength	Sequences	Reference standard	Patients (n), status (ND, BCR), M (n)	Sensitivity (patient basis)	Specificity (patient basis)
WB-MRI vs. ⁶⁸ Ga-PSMA PET/CT ¹²⁰	Prospective Consecutive enrollment	1.5T	T2FS/T2TIRM/ T1 VIBE post contrast/ ax T2TSE prostatic fossa	BVC Histology (n = 7)	28, post-RP, 20 BCR (7 LR, 5 NR, 5 BR, 2 NR + BR, 1 VR)	100% PSMA PET/CT, 55% WB-MRI, PSMA PET/CT > WB-MRI in NR	Not reported

Abbreviations: AS-MRI, axial skeleton MRI; BCR, breast cancer; BCR, biochemical relapse; BM, bone metastasis; BR, bone recurrence; BS, bone scintigraphy; BVC, best valuable comparator; DCE, dynamic contrast-enhanced imaging; DWI, diffusion-weighted imaging; FO, fat only; GRE, gradient echo pulse sequence; HASTE, half Fourier acquisition single shot turbo spin echo; LR, local recurrence; NM, not metastasis; NR, Node recurrence; PCa, prostate cancer; RP, radical prostatectomy; RT, radical radiotherapy; STIR, short tau inversion recovery; T1, T1-weighted imaging; T2, T2-weighted imaging; T1 LAVA, liver acquisition with volume acquisition; T1 VIBE, Volumetric Interpolated Breath-hold Examination; TIRM, turbo inversion recovery measurement; TXR, targeted X-rays; VM, visceral metastasis; VR, visceral recurrence (lung or liver); WB-MRI, whole-body MRI.

PET/CT compared to BS for distant metastasis were 92% versus 54% and 99% versus 93%, respectively. It should be noted that first-line PSMA detected abdominal nodal metastasis in 9% of the cohort, bone metastasis in 10%, and visceral metastasis in 1%.¹³⁴

Although WB-MRI and PSMA-PET/CT appear to outperform BS for detecting bone metastases, few studies have directly compared the two methods. One study prospectively determined the diagnostic accuracy of ⁶⁸Ga-PSMA-PET/CT in comparison to ¹⁸F-fluoride-PET/CT and WB-MRI for detecting bone metastases in patients with PCa.¹³⁵ More than two-thirds of the 55-patient cohort were under androgen deprivation therapy (ADT) or had castration-resistant PCa (CRPC). The patient-based diagnostic sensitivity, specificity, and overall accuracy were, respectively, 100%, 100%, and 100% for PSMA-PET/CT; 95%, 97%, and 96% for NaF-PET/CT; and 80%, 83%, and 82% for WB-MRI; the overall diagnostic accuracy of PSMA-PET/CT was significantly superior to that of WB-MRI ($p = 0.004$) but not to NaF-PET/CT ($p = 0.48$). Another study found higher sensitivity, 90%–96%, but lower specificity, 70%–90%, for ¹⁸F PSMA-PET/CT compared to WB-MRI (sensitivity 43%–80%; specificity, 80%–96%).¹¹⁵ As PSMA-PET/CT showed a relatively high number of false-positive bone lesions in this study (15%), WB-MRI may be proposed as a direct solving tool, and it may also be proposed as an alternative tool when the diagnosis of polymetastatic disease is expected on the basis of clinical and biological findings at presentation (Table 4).

Lymph node staging has always been a challenge in PCa, and despite NGL, no technique has shown an optimal performance for detecting metastatic lymph nodes. Surgical lymph node dissection (LND) is used as a gold standard and is still routinely performed and recommended during radical surgery.^{7,8,137} However, LND has failed to improve oncologic outcomes, including survival, and lymph node invasion status only provides prognostic information.¹³⁸ Therefore, functional imaging, for example, DWI MRI and PET/CT, is of interest for lymph node staging. ⁶⁸Ga-PSMA PET/CT, because of its rapid development and promising detection rates in other stages of the disease, has been proposed for primary lymph node staging.¹³⁹ A recent meta-analysis found both a higher sensitivity (65% vs. 41%) and specificity (94% vs. 92%) for ⁶⁸Ga-PSMA PET over mpMRI in detecting pathological nodes in the pelvis,¹⁴⁰ and an analysis of 20 ND intermediate- and high-risk patients with PCa who underwent ⁶⁸Ga-PSMA-11 PET/CT, anatomical MRI or contrast-enhanced CT, and DWI-MRI prior to laparoscopic, template-based, extended LND showed that the sensitivity and specificity for detecting lymph node metastases were, respectively, 39% and 100% with ⁶⁸Ga-PSMA PET/CT, 8% and 100% with MRI/CT, and 36% and 83% with DWI-MRI.¹³⁹

Table 4. Current clinical positioning of whole-body magnetic resonance imaging (WB-MRI) in prostate cancer (PCa)

Newly diagnosed PCa
Consider WB-MRI:
After equivocal conventional imaging (unconfirmed BS findings, CT, or MRI)
After negative conventional imaging (BS, CT, or MRI) in unfavorable intermediate or high/very high risk PCa
As a problem-solving tool in patients with ambiguous findings at PET/CT screening (numerous false positives of PSMA-PET/CT) ¹¹⁵
As a first line “all in one” screening approach (local, regional, global) for locally advanced or high-risk disease
In de novo OMD by conventional imaging being considered for ablative therapy: validation–invalidation tool = accurate diagnosis > > > role for metastasis directed therapy
Along with PET/CT for confident and comprehensive diagnosis of OMD: combinatorial approach ¹³⁶
Alternative to conventional imaging if PMD is expected, as baseline before the start of systemic treatment, for future therapy response assessments
Biochemical recurrence
Consider WB-MRI:
After conventional imaging (BS, CT, or MRI) or PSMA-PET/CT if they are negative or equivocal in high-risk patients suitable for salvage pelvic or distant therapy
If no access to PSMA-PET/CT ¹²⁶
Castration-resistant prostate cancer
Consider WB-MRI:
Before initiating a new treatment: evaluate disease presence, extent, distribution, and as baseline for future response assessments
At follow-up: therapy response assessment using MET-RADS-P criteria
To select bone and soft-tissue biopsy sites for approved genomic directed therapies
Abbreviations: OMD, oligometastatic disease; PMD, polymetastatic disease.

Biochemical Recurrence (Table 5)

The American Urological Association (AUA) defines BCR after radical prostatectomy (RP) as a detection of increasing PSA > 0.2 ng/mL on two consecutive tests and defines BCR after radiotherapy as an increase in PSA level 2 ng/mL above PSA nadir.¹⁴¹

Salvage local treatment is often applied in selected patients. Because most patients do not show metastases on standard imaging assessment, the decision to start systemic treatment was mostly based on PSA kinetics. Recent developments in NGI revealed that a fair proportion of these patients was actually harboring limited metastatic spread using WB-MRI, often occurring outside the pelvic region, and this result challenged the concept of salvage pelvic treatment. For example, an assessment of metastatic spread showed that more than two-thirds of 96 patients with metastatic disease had lesions located outside the usually recommended targets of extended pelvic LND (eLND) and external beam radiation therapy (EBRT).¹⁴²

NGI has profoundly modified the approach to BCR. An earlier and more precise assessment of metastatic deposit allows a better selection of patients for salvage local treatment or further surveillance. As for those with limited metastatic deposit, intervention with MDT, mostly by stereotactic ablative radiation (SABR), delays progression.¹²⁸ In the ORIOLE Phase 2 Randomized Clinical Trial, 54 men with recurrent hormone-sensitive PCa and one to three metastases detectable by conventional imaging were randomized to receive systemic treatment alone or in combination with SABR. Treatment with SABR improved median progression-free survival (not reached vs. 5.8 months; hazard ratio, 0.30; 95% confidence interval, 0.11–0.81; $p = 0.002$).¹⁴³ The most interesting observation was that total consolidation of PSMA radiotracer decreased the risk of new lesions at 6 months (16% vs. 63%; $p = 0.006$), thus confirming the importance of accurate imaging staging by PSMA PET/CT.

At BCR, PSMA PET/CT has become the technique of choice. European Association of Urology (EAU) guidelines

Table 5. Indications for imaging workup at biochemical recurrence (BCR)

Post-RP (two consecutives rising prostate-specific antigen [PSA] >0.2 ng/mL)	
EAU	
If PSA level >0.2 ng/mL and results influence treatment decisions: PSMA PET/CT	
If PSA level >1 ng/mL, PSMA PET/CT is not available, and results influence treatment decisions case: ¹⁸ F-Fluciclovine or ¹¹ C-choline PET/CT.	
NCCN	
Bone imaging, chest CT, abdominopelvic CT or MRI.	
¹⁸ F-NaF or ¹¹ C-choline or ¹⁸ F-Fluciclovine PET/CT or PET/MRI can be considered after BS if high clinical suspicion of metastasis.	
Post-RT (any PSA increase ≥2 ng/mL higher than PSA nadir value)	
EAU	
In patients who are candidates for local salvage therapy: prostate mpMRI	
In patients who are candidates for curative salvage treatment: PSMA PET/CT (if available) or ¹⁸ F-Fluciclovine PET/CT or ¹¹ C-choline PET/CT.	
NCCN	
In patients who are candidates for local therapy: prostate mpMRI, BS, chest CT, abdominopelvic CT/MRI.	
¹⁸ F-NaF or ¹¹ C-choline or ¹⁸ F-fluciclovine PET/CT or PET/MRI can be considered after BS when clinical suspicion of metastasis is high.	
In patients who are not candidates for local therapy: BS.	
¹⁸ F-NaF or ¹¹ C-choline or ¹⁸ F-fluciclovine PET/CT or PET/MRI can be considered after bone scan when clinical suspicion of metastasis is high.	
<i>Note:</i> Recommendations are based on European Association of Urology, European Society for Radiotherapy and Oncology, and International Society of Geriatric Oncology (EAU-ESTRO-SIOG) guidelines 2019, and National Comprehensive Cancer Network (NCCN) guidelines, version 2.2020. Abbreviations: ¹¹ C-choline, carbon-11-choline; ¹⁸ F-Fluciclovine, ¹⁸ F-FACBC; ¹⁸ F-NaF, fluorine 18–sodium fluoride; mpMRI, multiparametric MRI; RP, radical prostatectomy; RT, radical radiotherapy.	

recommend performing PSMA PET/CT in patients with relapse PSA >0.2 ng/mL after RP or, in case of unavailability of PSMA PET/CT and a PSA level ≥ 1 ng/mL, fluciclovine choline PET-CT is used. After radiotherapy, guidelines recommend performing prostate gland mpMRI to localize abnormal areas and guide further biopsies (Table 5) (Figure 5). WB-MRI has not been widely evaluated in BCR because of its limited value for the detection of early metastatic involvement in normal-sized lymph nodes. The vast majority of experts at the St. Gallen Advanced Prostate Cancer Consensus Conference (APCCC) 2019 recommended performing ⁶⁸Ga PSMA PET-CT +/- mpMRI rather than WB-MRI in patients with BCR after RP or RT.

One retrospective report described the potential use of WB-MRI combined with mpMRI in BCR after RP in 76 patients with low PSA level (median, 0.36 ng/mL).¹⁴⁴ WB-MRI with mpMRI identified recurrence in 21% and

local recurrence in 9% of the patients. MRI was found to be a feasible modality for clinical practice and provided incremental information compared to conventional imaging (Figure 5). Due to the high lesion to background contrast of DWI, compared to anatomical sequences, the detection of distant metastasis, except sclerotic bone metastasis, should be facilitated by DWI.¹⁴⁵ The LOCATE trial is comparing WB-MRI to conventional imaging (BS and CT) in a cohort of 213 patients for detecting nodes and bone metastasis in BCR after radiotherapy.¹⁴⁶

The diagnostic accuracies of ⁶⁸Ga-PSMA PET/CT, ¹⁸F-NaF PET/CT, and DWI-MRI for the detection of BM were prospectively compared in 68 patients with BCR.¹¹⁹ On a patient level, sensitivity and specificity were, respectively, 0.80 and 0.98–1.00 for ⁶⁸Ga-PSMA PET/CT, 0.90 and 0.90–0.98 for ¹⁸NaF PET/CT, and 0.25–0.38 and 0.87–0.92 for DW₆₀₀-MRI. The diagnostic performance of

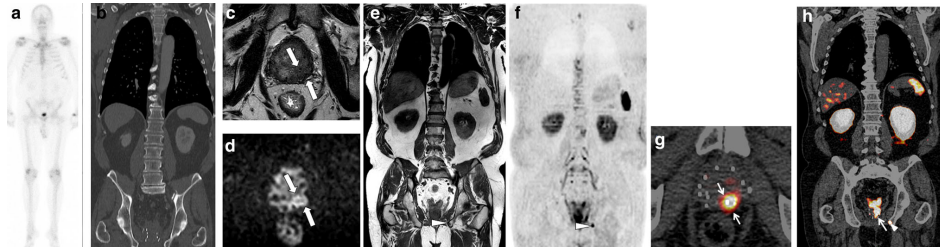


Figure 5: “All in one” whole-body magnetic resonance imaging (WB-MRI) and ^{68}Ga PSMA PET/CT workup at BCR in a 65-year-old man with rapid rising prostate-specific antigen (PSA) 2 years after brachytherapy (5.84 ng/mL) shows intraprostatic and oligometastatic bone recurrence. (a, b) Normal AP bone scintigraphy (a) and coronal MPR thoracoabdominal CT image (b) show no abnormality. (c–f) All-in-one WB-MRI at 3T: (c, d) mpMRI, transverse T2 TSE (c) and DWI (b 1500 s/mm²) (d) images show intraprostatic recurrence (arrows) with low SI on T2 and restricted diffusion on DWI; coronal 3D T1 FSE (e) and DWI (b 1000 s/mm², inverted grayscale) (f) images show a single bone metastasis in the left ischiatic bone (arrowhead) of low SI on T1 (e) and high signal on DWI (f). (g, h) Fused ^{68}Ga PSMA PET/CT images: transverse section at the level of the prostate (g) and coronal MPR image (h) show intraprostatic recurrence (arrows in g and h) with focal high uptake (SUV max 6.92) and focal left ischiatic bone metastasis (arrowhead in H) (SUV max 13.88). Patient was treated with stereotactic radiotherapy on both bone and prostate lesions and 6 months of ADT with subsequent drop in PSA level at <0.2 ng/mL.

DWI-MRI was significantly lower than that of ^{68}Ga -PSMA PET/CT and ^{18}F -NaF PET/CT for diagnosing bone metastases. ^{68}Ga -PSMA PET/CT showed a higher detection rate (100%) than WB-MRI (23%) for lesions in 28 patients with BCR following RP.¹²⁰

Advanced Disease and Response Assessment

Imaging plays an intrinsic role in defining the metastatic state (M1) when PSA increases in patients with normal testosterone levels (hormone sensitive state) or when a patient has suppressed testosterone levels (castration-resistant state). Imaging also has important roles to play when men with metastatic disease undergo treatment to assess response to therapy and also to detect the emergence of primary or secondary therapy resistance. In both hormonal states, the volume and distribution of metastases are highly prognostic and can affect therapy options.

Therapy options for the treatment of advanced metastatic disease continue to evolve, and a layered approach is often employed (Figure 6). Treatments include drugs targeting the androgen axis (enzalutamide, abiraterone, darolutamide, apalutamide), chemotherapy (docetaxel, cabazitaxel), and bone-seeking agents including bisphosphonates and ^{223}Ra . More recently, drugs targeting poly(ADP)-ribose polymerase (PARP) and immunotherapy have been introduced. In the short term, we can expect to see the successful deployment of anti-PSMA directed therapies. When faced with these different therapeutic options, the evaluation of therapy response in metastatic patients is crucial for deciding whether to continue, adapt, or change treatment strategies.¹⁴⁷

Quantitative measurements tools have been validated for assessing the effectiveness of cancer therapy in soft-tissue lesions using CT¹⁴⁸; however, CT is ineffective for assessing

response to therapy in bones because it relies on bone reaction rather than assessing the tumor itself.⁶

BS is still recommended to assess bone disease response in patients with metastatic CRPC (mCRPC),⁷ but it suffers from major limitations. The “flare phenomenon” (pseudoprogression), defined by the development of new uptake foci on an early follow-up BS and due to osteoblastic reaction, can occur within 8–12 weeks of treatment initiation.¹⁴⁹ Hence, Prostate Cancer Working Group 3 defines imaging progression in mCRPC based on BS as the appearance of ≥ 2 lesions during treatment continuation and confirmed 6 weeks later by a second BS. This considerably lengthens decision times and can cause the continuation of ineffective and potentially toxic treatment.¹⁵⁰ Furthermore, BS progression only relies on the emergence of new lesions and does not account for an increase in the size of preexisting lesions.¹⁵¹ Finally, patients with diffuse metastatic bone disease on BS (so-called superscans) cannot be monitored because new lesions cannot be identified in the background of diffusely elevated tracer uptake.⁶

Nodes and visceral metastasis detected by abdominopelvic CT or MRI must be recorded and quantified and followed per RECIST.¹⁵² For PCWG3, nodes are considered pathological when they are between 10 mm and 15 mm on the short axis and are subject to clinical discretion, but they are only considered measurable when they are over 15 mm in size.¹⁵⁰

MRI provides the opportunity to assess the response to therapy in bone lesions, the most frequent metastatic site in mCRPC and one that cannot be correctly evaluated with standard imaging tests.¹⁵³ The feasibility and the value of size criteria determined using axial skeleton MRI to quantify bone metastasis and measure tumor response have been demonstrated.¹⁵⁴

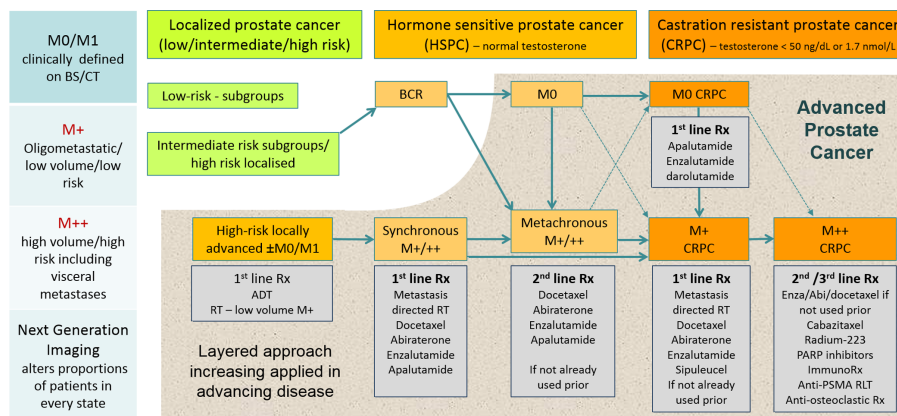


Figure 6: Substantial progress is being made in the management of bone metastatic disease in prostate cancers. Optimal management of metastatic bone disease utilizes a layered approach as more potential treatments are added to the armamentarium. Choosing the right treatment, for the right patient, for the right duration and the correct sequence and combination remain challenges that next-generation imaging (NGI) may help to inform

Response assessment with WB-MRI relies on an mp approach combining anatomical and functional sequences (Table 6). Response to therapy can be characterized quantitatively by a decrease in the number and size of detectable lesions and can be characterized qualitatively by a replacement of the peripheral zone of lesion by fat cells, creating a “fatty halo sign,” followed by a return of normal-appearing bone marrow.³⁸ Potential limitations of anatomical sequences in the evaluation of treatment response are the difficult interpretation of residual low-signal tissue on T1-weighted images, which may represent inactive lesions due to fibrosis or necrosis, and also a rare “flare phenomenon” corresponding to an increase in diameter of the lesion on T1 images due to edema posttherapy.¹⁶⁰ Another potential limitation is the reconversion of yellow bone marrow to red bone marrow during the treatment, leading to diffuse “pseudoprogression.”¹⁶⁰

Thus, bone lesions must also be assessed qualitatively or quantitatively using functional DWI-MRI sequences or total DWI (tDV) measurements.⁷³ A decrease in the SI of lesions on high b-value images and an increase in ADC measured on ADC maps may be indicative of response (Figure 7). Lesions responding to systemic or radiation therapy may, however, present an increased SI on high b-value DWI with a corresponding increase in ADC values, known as the “T2 shine-through effect,” resulting from increase in water content due to necrosis or edema.¹⁶¹ Quantitative assessment relies on ADC measurement (ADC_{mean} , ADC_{low} without the perfusion effect of lower b-values) and global ADC (gADC) in case of total DWI.

MET-RADS-P defines criteria for the assessment of response in metastatic PCa, using mpMRI to reliably evaluate

the likelihood of the effectiveness of a treatment using a Likert-like category scale from 1 to 5, where category 1 indicates very high likelihood of response and 5 indicates high likelihood of progression. Category 3 indicates stable disease. Bone disease response is divided into progression, stable disease, response, and discordant categories. Soft-tissue disease is recorded using RECIST 1.1 criteria. MET-RADS-P is still being evaluated in clinical practice, as well as clinical trials, to assess its impact on the care pathway for advanced PCa.¹⁶² One study assessed the value of MET-RADS-P criteria in 72 patients with mCRPC when disease progression was suspected at the start of a new line of treatment and found that a high number of bone (≥ 10) and visceral metastases, as determined by MET-RADS-P, was significantly associated with shorter cancer-specific survival.¹⁶³ This suggests the potential value of MET-RADS-P volume score as a prognostic biomarker.

A retrospective study found that some lesions in responder (13%) and nonresponder patients (13%) presented a decrease in ADC values, while other lesions had increased ADC.¹⁵⁶ MET-RADS-P offers the possibility to record these heterogeneous observations in their response evaluation and categorizes the response as discordant if some soft-tissue or bone lesions are progressing without meeting the criteria of progression of disease, while others are stable or are responding¹⁶² (Figure 7).

WB-MRI does not rely on the affinity of tumor cells for a tracer or on the presence of receptors, and this makes it a consistent and universal tool for response assessment. PSMA PET/CT, which has been shown to be very efficient at BCR and in newly diagnosed disease for detection, should be

Table 6. Value of whole-body magnetic resonance imaging (WB-MRI) for response assessment in metastatic prostate cancer (PCa) at 1.5T

Sequences	Study design	Coverage	Approach	Reference standard	Patient characteristics	Results
T1/T2W FSE ¹⁵⁴	Prospective consecutive enrollment	Axial skeleton	RECIST-like	BVC	20 eligible mCRPC patients, 13 NM, 22BM, 1 VM, imaging before and after therapy (6 m)	Number of measurable lesions compared to CT (30%–66%), CR = 2, PR = 2, SD = 5, PD = 11
DWI SPIR/T2 FSE ¹⁵⁵	Prospective consecutive enrollment	Axial skeleton	Quantitative mean ADC correlated with PSA levels, DM/ADC voxel	NR	9 patients, 20 BM, imaging before and after therapy (1, 2, 3 m)	Response of BM to ADT: ↑ mean ADC (15%–27%) correlated with ↓ PSA level ($r = -0.439$). Spatial heterogeneity within lesion, DM analysis: 47.3% voxels ↑ ADC
DWI T1/T2 FSE ¹⁵⁶	Prospective consecutive enrollment	Axial skeleton	Quantitative ADC- _{slow}	PSA RECIST	26 patients, 6 BM + ST, 20 BM, imaging before and after therapy (12 weeks)	Responders: ↑ mean ADC (52.5%), ADC _{slow} (35.8%); Nonresponders: ↑ mean ADC (19%) and ADC _{slow} (16.7%), mean ADC = not appropriate measurement tool of bone response
DWI T1 GRE ¹⁵⁷	Prospective consecutive enrollment	WB-MRI	Quantitative tDV/gADC	BVC	4 BCa– 7 PCa, 7 BM, imaging before and after therapy (12–38 weeks)	Responders: ↓ tDV (–85% to +27%), ↑ gADC (–0.07 to +0.78); Nonresponders: ↑ tDV (3%–284%), stable gADC (–0.10 to +0.05)
DWI T1 GRE ¹⁵⁸	Retrospective	WB-MRI	Correlation tDV with OS and PF (Hb, PSA, LD, ALP level)	OS	43 eligible mCRPC patients, 20 BM, 17 BM + NM, 6 BM + VM, imaging before and after therapy (1 y)	↑ TDV = poor OS (HR: 1.74). Correlation between tDV and PF; Hb level: $r = -0.521$, PSA level: $r = 0.556$, LD level: $r = 0.534$, ALP: $r = 0.572$
DWI T1 GRE ¹⁵⁹	Prospective consecutive enrollment	WB-MRI	RECIST 1.1, Quantitative tDV, mean ADC	RECIST 1.1	21 mCRPC patients, 21BM, 12BM + NM, 11 BM + VM, Imaging	Responders: ↓ tDV (5.6%–58.8%) Nonresponders: ↑ tDV (0%–76.9%), volume of 5 target lesions associated with

Table 6. Continued

Sequences	Study design	Coverage	Approach	Reference standard	Patient characteristics	Results
					before and after therapy (12 weeks)	response (OR = 0.89; 95% CI: 0.80, 0.99)
Abbreviations: ADC _{slow} , ADC without the effect of perfusion; ADT, androgen deprivation therapy; ALP, alkaline phosphatase; BCa, breast cancer; BM, bone metastasis; CR, complete response; CT, computed tomography; DM, functional diffusion map; gADC, global ADC; Hb, hemoglobin; HR, hazard ratio; LD, lactate dehydrogenase; mCRPC, metastatic castration-resistant prostate cancer; NR, not reported; OR, odds ratio; OS, overall survival; PD, progressive disease; PI, prognosis factors; PR, partial response; r, Pearson correlation coefficient; SD, stable disease; ST, soft tissue metastasis; T, Tesla; tDV, total diffusion volume; VM, visceral metastasis.						

considered with caution for response evaluation at the CRPC stage not only because it shows variable affinity but because this affinity may vary with the line and type of treatment. The interaction between androgen signaling and PSMA expression is quite complex and still under evaluation. Prolonged androgen blockade (AB) leads to the downregulation of PSMA expression, reducing the visibility and the possibility of following metastatic PCa lesions on PSMA-PET/CT.¹⁶⁴ Conversely, short-term AB rapidly upregulates PSMA expression in CRPC, leading to a flare effect. This flare phenomenon does not seem to be as transient compared to BS, and it could plateau and lead to the misinterpretation of false progressive lesions.^{165,166} Experts recommend performing PSMA-PET/CT before the start of treatment and not earlier than 3 months after initiating systemic therapy and, most importantly, agree to not routinely follow PCa patients with PSMA PET/CT.¹⁰ Precise and reproducible criteria (akin to MET-RADS-P) for evaluating therapy response with PSMA PET/CT are needed to standardize interpretations, and reporting of PET/CT is required to decrease inter- and intraobserver variability.¹⁶⁷

Current Developments and Future Perspectives

“All in One” PCa Staging: Combining mpMRI and WB-MRI

An “all in one” MRI approach of PCa consists of a single MRI examination combining diagnostic mpMRI of the prostate for locoregional staging with WB-MRI for node and general metastatic staging. Both mpMRI and WB-MRI acquisitions have been accelerated to make such an “all in one” imaging approach possible. PI-RADS v.2 guidelines have reduced the importance of the DCE sequence for the characterization of PCa, with others showing low value of the full mpMRI approach for men with clinically obvious locally advanced disease at presentation.¹⁶⁸ This has led to the development of a biparametric approach relying on T2 and DWI sequences for local disease detection, biopsy planning, and staging.¹⁶⁹ A recent meta-analysis of 31 studies for the detection of PCa in naïve patients demonstrated no statistical differences between biparametric MRI and mpMRI in terms of sensitivity and specificity.¹⁷⁰

We have already noted that the use of 3D or Dixon imaging decreases the number of necessary anatomical sequences for WB-MRI examinations. This reduces the acquisition time of the “all in one” protocol combining bpMRI of the prostate and WB-MRI (WB 3D T1GREmDixon and DWI sequence) to less than 40 min. This protocol enables a one-step tumor node metastasis (TNM) staging and is mostly relevant in men with newly diagnosed, high-risk locally advanced and high-risk BCR

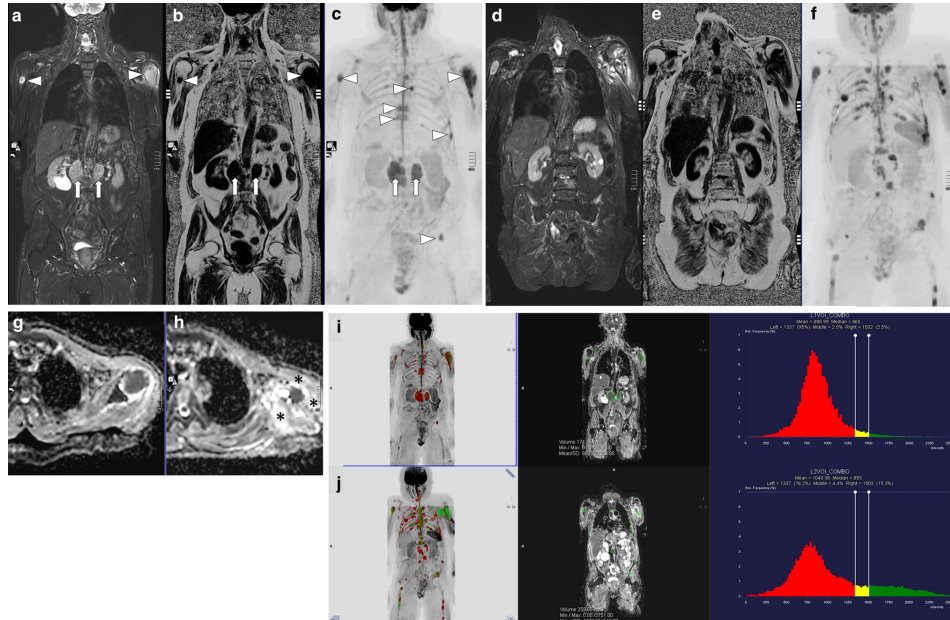


Figure 7: A 74-year-old man with metastatic castration-resistant prostate cancer (PCa). Prior androgen deprivation therapy (ADT) and pelvic radiotherapy for node-positive Gleason 3 + 3 prostate cancer. Previous docetaxel chemotherapy for metastatic castration-resistant PCa (mCRPC). Baseline whole-body magnetic resonance imaging (WB-MRI) and 3-m follow up on androgen receptor directed therapy (enzalutamide). (a–c) Baseline (BL) WB-MRI. Coronal water-only T2 Dixon (a), F% (b), and b 900 s/mm² diffusion-weighted imaging (DWI) (c) (maximal intensity projection [MIP]; inverted grayscale) images show retroperitoneal nodal enlargement (vertical up arrows) and multiple bone deposits (horizontal arrowheads). A left humeral expansive metastasis with extraosseous soft tissue disease is seen, suggesting significant fracture risk. (d–f) Follow-up (FU) WB-MRI shows corresponding images after enzalutamide therapy. A “mixed” response is observed with significant reduction in the size of the retroperitoneal lymphadenopathy but marked skeletal progression with increase in number and size of bone lesions. Fracture of the left humerus is seen with edema of the surrounding soft tissues. Note that there was no intervening shoulder radiotherapy. (g, h) Comparison of BL (g) and FU (h) axial ADC maps shows preserved malignant signal within the fractured humerus but marked edema of the surrounding soft-tissue following the fracture (*). (i, j) Comparison of BL (i) and FU (j) examinations by quantitative MRI. WB tumor load segmentation undertaken on syngo via onco-trend software (Siemens Healthineers, Erlangen, Germany). The MIP images on the high b-value (900 s/mm²) are overlaid with ADC value color classes using the thresholds indicated on the histograms. The green voxels are values $\geq 1500 \mu\text{m}^2/\text{s}$ (voxels that are “highly likely” to be responding). The yellow voxels are set to lie between the 95th centile ADC value of the pretreatment histogram ($1337 \mu\text{m}^2/\text{s}$) and $1500 \mu\text{m}^2/\text{s}$ (voxels “likely” to be responding). Red voxels represent mostly untreated and still active disease. An increase in the volume of the active (red voxels) disease is measured (166 mL [95% of 174 mL before therapy] and 198 mL [76.2% of 259.7 mL after therapy]). The increase in mean ADC due to increasing numbers of green voxels located mostly in the left shoulder region is due to the fracture-related edema, but there is also some response of the bone disease in the right femur and left iliac bone. Mixed responses between tissues (in this case, between nodes versus bone) and within tissues (bones) strongly indicates that secondary resistance is due to Darwinian selection pressures. This phenomenon is commonly seen in men with castration-resistant prostate cancer being treated with targeted therapies. WB-MRI can enable the identification of skeletal sites at high risk of developing adverse events such as fractures even if they are asymptomatic

PCa to guide the choice between local or systemic treatment (Figure 6, Table 7).

Oligometastatic Disease

NGI allow the recognition of some patients with a low volume of metastases to be defined as patients with oligometastatic disease (OMD) either at diagnosis, BCR, or

after treatment. First described using BS,¹⁷¹ the current definition of oligometastases consists of three to five lesions (usually node or bone) detected with NGI, including PET/CT and WB-MRI.¹⁷² In patients with ND PCa or BCR, the role of imaging is to truly discriminate patients with OMD who can potentially benefit from extended radical treatment or salvage with MDT from polymetastatic patients who require

Table 7. Research indications for whole-body magnetic resonance imaging (WB-MRI) in prostate cancer (PCa)

Newly diagnosed PCa
De Novo OMD detected by conventional imaging: use WB-MRI as a validation–invalidation tool, adjunct to PSMA-PET/CT, to validate the use of local treatment with MDT + ADT.
In case of de novo polymetastatic PCa detected by conventional imaging: use DWI WB-MRI to optimize therapy response assessment in the follow-up.
Fast “all in one” screening approach: first line, quick, effective, nonirradiating “triage tool” for unfavorable intermediate/high to very high risk PCa.
Integrate hybrid PET/MRI modalities in primary staging.
Biochemical recurrence
Integrate hybrid PET/MRI modalities in BCR restaging.
As a prognostic marker to distinguish candidate lower-risk patients for PSA-directed surveillance versus high risk for ADT + MDT.
Castrate-Resistant Prostate Cancer: use WB-MRI
As a prognostic marker to distinguish candidate patients for surveillance or ARPI + MDT after negative conventional imaging (nmCRPC).
To confirm OMD CRPC to validate the use of MDT in addition of ARPI.
To evaluate homogeneity or heterogeneity of disease response/progression before initiating any subsequent treatment.
As a biomarker to assess therapy response regarding concordance or discordance with biology or clinical features.
To assess total tumor load when selecting patients for anti-PSMA directed therapies (theragnostic role)
Abbreviations: ADT, androgen deprivation therapy; ARPI, androgen receptor pathway inhibitor; BCR, biochemical recurrence; MDT, metastasis-directed therapy; MET-RADS-P, metastasis reporting and data system for prostate cancer; nmCRPC, nonmetastatic castration resistant prostate cancer; OMD, oligometastatic disease; PMD, polymetastatic disease.

systemic therapy. In a cohort of 96 patients with metastatic ND PCa, WB-MRI identified patients with OMD in 28% of the metastatic hormone-naïve PCa and in 52% of the mCRPC.¹⁴²

The scientific community has recently used PET/CT (¹⁸F-Na or PSMA) or WB-MRI to stage ND disease in case of negative or equivocal results with conventional imaging tests and in BCR in case of salvage local therapy to ensure that there is no distant metastasis.¹²⁶ The potential impact of NGI in the selection of these patients and in long-term outcomes is not yet clearly understood and deserves further study, although patients benefiting from MDT have better ADT-free survival rates.^{142,173–177} There is no evidence that the primary treatment influences the metachronous metastatic status (oligo vs. polymetastatic).¹⁷⁸

As previously mentioned, functional PET imaging and high-contrast MRI are complementary, and hybrid PET/MRI outperforms PET/CT or MRI alone in staging and in BCR patients.^{179–183} A combination of both techniques may allow better identification of patients with OMD at the ND or BCR, which is fundamental for the effective treatment of men with OMD.

HYBRID PET/MRI: THE BEST OF BOTH WORLDS

PSMA PET/CT and WB-MRI appear to be the techniques of choice for staging and evaluating recurrence in PCa. Therefore, PSMA PET/MRI could be of clinical interest as it combines the best abilities of both techniques, provided that PET/MRI scanners can perform the most effective MRI sequences with quality similar to that of standalone MRI systems.

Hybrid PET/MRI combines functional assessment with the sensitivity of DWI and specificity of PET tracers and with the high-contrast resolution and anatomical detail of MRI (Figure 8). It is performed at 3T and obtains T2- (T2SSFE/HASTE) and T1 Dixon images and DWI sequences.^{184,185} After intravenous injection of the PET tracer, emitted 511-keV photons from the radiotracers undergo attenuation through the body before being detected. A key step in obtaining high-quality images and the accurate calculation of standardized uptake values (SUV) is to correct the attenuation effect of the photons via attenuation correction maps. In PET/CT, this correction is done with CT attenuation values. In PET/MRI, MR-based attenuation correction (MRAC)

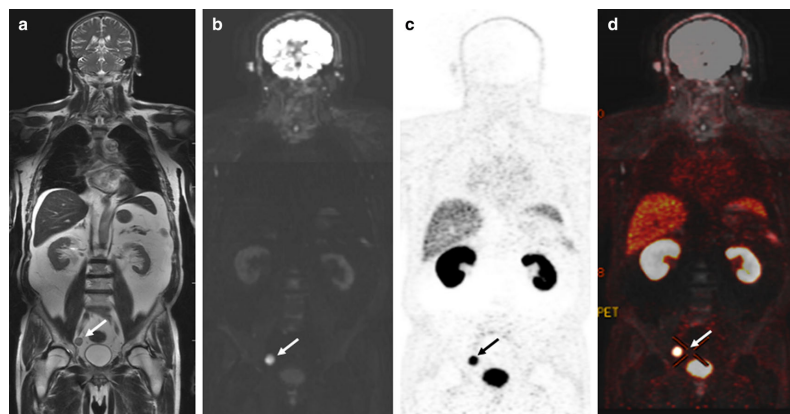


Figure 8: Prostate-specific membrane antigen (PSMA)-positron emission tomography (PET)/magnetic resonance imaging (MRI) at biochemical recurrence in a 56-year-old man with rising prostate-specific antigen (PSA) (2.2 ng/mL) after prostatectomy. (a) Coronal T2W image shows enlarged right iliac lymphadenopathy (arrow). (b) Coronal diffusion-weighted imaging (DWI) (b 1000) confirms nodal recurrence. (c) Simultaneous PET image shows increased PSMA uptake. (d) Image fusion of DWI and PSMA-PET shows the coherence of both techniques

maps are based on a breath-hold two-point Dixon Volumetric Interpolated Breath-hold Examination (VIBE) sequence that generates water and FF signal with different frequencies.¹⁸⁶

Recent works demonstrated better results using PET/MRI compared to mpMRI of the prostate for local staging.^{179–181} In studies comparing PET/MRI to PET/CT, either using Ga-PSMA-11 (81% of studies) or 11C-choline (19% of studies), PET/MRI appeared more accurate for detecting local recurrences and slightly better for detecting nodal metastases.¹⁸⁷ MRI was crucial for the better detection of local recurrences, and the longer tracer accumulation at PET/MRI was likely responsible for the better lymph node staging. As for detecting bone metastases, there is no advantage to either imaging technique.

A current important limitation is the duration of PET/MRI examinations compared to PET/CT (60 min vs. 20 min). This depends on the inclusion of dedicated pelvic and mp sequences and can make its integration in clinical practice difficult. Going forward, it will be important to determine the specific indications where PET/MRI would deliver information critical for treatment selections or prognostication in order to justify the higher costs for PET/MRI. Nevertheless, hybrid PET/MRI provides a unique research opportunity to compare differences and complementary values of PSMA PET and WB-MRI techniques at different stages of PCa and for the development of new tracers such as ¹⁸F-labeled PSMA radiopharmaceuticals with longer half-lives, which enable higher spatial resolution images with different biodistributions; ¹⁸F 16-βfluoro-5-α-dihydrotestosterone (FDHT), which binds to the intracellular androgen receptor; and ¹⁸F fluciclovine, which takes advantage of upregulated glutamate transporters in PCa.³

The use of PET/MRI appears promising at BCR, and the superiority of ⁶⁸Ga PET-CT/mpMRI compared to ⁶⁸Ga PSMA-PET/CT alone for local recurrence assessment was demonstrated in two studies.^{183,188}

CONCLUSION

Accurate staging and assessment of disease response to therapies are the two main expectations for imaging in the era of high-precision oncology. NGI modalities now stand beside conventional imaging techniques in guidelines recommending imaging use at the various stages of PCa. Currently, NGI modalities mostly include WB-MRI and PSMA PET/CT. In the future, we can expect the increasing use of NGI methods in clinical practice because of improved disease detection sensitivity and more accurate response assessments compared to BS and CT. The impacts on patients' outcomes resulting from the reclassification of patients using NGI methods, combined with improved therapeutics, are yet to be determined.

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7. Second publication

Comparison of ^{68}Ga -Prostate Specific Membrane Antigen (PSMA) Positron Emission Tomography Computed Tomography (PET-CT) and Whole-Body Magnetic Resonance Imaging (WB-MRI) with Diffusion Sequences (DWI) in the Staging of Advanced PCa.

Van Damme J, Tombal B, Collette L, Van Nieuwenhove S, Pasoglou V, Gérard T, Jamar F, Lhommel R, Lecouvet FE. *Cancers (Basel)*. 2021 Oct 21;13(21):5286.

Summary

Our first paper sought to directly compare the diagnostic accuracy of these two advanced imaging modalities in PCa patients with high-risk features.

The study was a retrospective analysis of prospectively collected data from a single institution between December 2016 and December 2019. The cohort included 134 consecutive patients: 81 with newly diagnosed (ND) PCa at high risk for metastases (defined by PSA > 20 ng/mL, Gleason score ≥ 8 , or $\geq \text{cT3}$), and 53 presenting with biochemical recurrence (BCR) after local treatment (PSA > 0.2 ng/mL after radical prostatectomy or > 2 ng/mL after radiation therapy with PSA doubling time < 12 months). Patients underwent both PSMA-PET/CT and WB-MRI, including DWI sequences, within one month.

Due to the lack of a systematic histologic gold standard, the diagnostic accuracy of both modalities was measured against a Best Valuable Comparator (BVC). The BVC was defined by a multidisciplinary panel using consensus adjudication based on all available baseline and follow-up imaging (modern and standard), clinical follow-up data (PSA kinetics, skeletal events), and histopathological proofs when available.

Imaging interpretation protocols differed for lymph node assessment: PSMA PET-CT considered moderate-to-intense focal nodal uptake as positive, regardless of node size. In contrast, WB-MRI defined lymph nodes as abnormal primarily based

on size, typically a short-axis diameter greater than 10 mm (or >8 mm for perivisceral nodes).

The primary endpoint compared the diagnostic performance of the two modalities for detecting metastases at the patient level.

Based on the BVC, 66 of 134 patients (49%) were adjudicated as having metastatic disease. Overall, the study found no significant difference between PSMA-PET/CT and WB-MRI in identifying metastatic patients when considering lymph nodes, skeletal, and visceral metastases combined ($p = 0.09$). The Area Under the Curve (AUC) for PSMA-PET/CT was 0.96 (95% CI, 0.92–0.99). The AUC for WB-MRI was 0.90 (95% CI, 0.85–0.95).

PSMA PET-CT demonstrated a sensitivity of 0.98 and a specificity of 0.93 for detecting metastatic patients, while WB-MRI had a sensitivity of 0.85 and a specificity of 0.96. PSMA PET-CT correctly identified 65 of the 66 metastatic patients (1 false negative), and WB-MRI detected 56 (10 false negatives). The inter-technique agreement for overall metastatic status was relatively good (adjusted kappa = 0.72).

The secondary endpoints compared performance for lymph node, bone, and visceral metastases separately.

- PSMA-PET/CT clearly outperformed WB-MRI for **lymph node detection**, with statistical significance across the entire cohort (AUC 0.96 vs. 0.86; $p = 0.0096$). This superiority is attributed to PSMA-PET/CT's higher sensitivity in detecting small metastatic lymph nodes. WB-MRI had 14 false-negative cases, 12 of which were due to the small size (<10 mm) of the metastatic nodes. In contrast, PSMA PET-CT showed only 3 false-negative lymph nodes.
- PSMA-PET/CT and WB-MRI performed equally well for detecting **bone metastases**. WB-MRI showed 100% sensitivity, detecting all bone metastases, whereas PSMA PET-CT missed one bone lesion. The AUC for WB-MRI was 0.98, and for PSMA PET-CT it was 0.95 ($p = 0.32$). Both modalities face challenges

with false positive findings due to degenerative changes, benign fractures, or benign bone lesions. Both techniques directly identify tumoral cell deposits: PSMA PET-CT targets membrane antigens, and WB-MRI detects replacement of normal bone marrow and altered water diffusivity (DWI).

- PSMA-PET/CT detected 9 **visceral metastases**, while WB-MRI detected 6. The AUC comparison showed no statistically significant difference ($p = 0.14$).

Subgroup Analysis

The comparison was analyzed separately for the ND PCa and BCR subgroups.

- **Newly Diagnosed (ND) PCa Patients (n=81):** PSMA PET-CT significantly outperformed WB-MRI at the patient level (AUC 0.96 vs. 0.87; $p = 0.045$). This superiority was driven by the detection of lymph node metastases, with an AUC of 0.98 for PSMA-PET/CT compared to 0.83 for WB-MRI ($p = 0.002$). In this subgroup, WB-MRI detected all bone metastases (100% sensitivity), and the modalities performed equally (AUC $p = 0.24$).
- **Biochemical Recurrence (BCR) Patients (n=53):** PSMA-PET/CT and WB-MRI performed equally well at the patient level, not reaching statistical significance (AUC 0.96 vs. 0.89; $p = 0.25$). Both modalities also performed equally well for bone lesions (AUC 0.96; $p = 1$). For lymph node detection, the difference was not statistically significant ($p = 0.34$), although the results suggested that WB-MRI may underestimate the global metastatic load in cases of small lymph node involvement.

Conclusion

In conclusion, PSMA-PET/CT surpassed WB-MRI in overall metastasis detection, mainly due to its higher accuracy in detecting metastatic lymph nodes during the initial staging of newly diagnosed patients. The dependence of WB-MRI on anatomical size thresholds (e.g., >10 mm) led to lower sensitivity for small metastatic lymph nodes compared to PSMA-PET/CT, which relies on functional criteria.

While PSMA-PET/CT is becoming the most widely accepted imaging technique, WB-MRI is recognised as a high-performing alternative, particularly as it avoids ionising radiation. Physicians must weigh diagnostic effectiveness against factors like local accessibility, costs, and lack of ionising radiation when choosing between these two advanced staging modalities.

Article

Comparison of ⁶⁸Ga-Prostate Specific Membrane Antigen (PSMA) Positron Emission Tomography Computed Tomography (PET-CT) and Whole-Body Magnetic Resonance Imaging (WB-MRI) with Diffusion Sequences (DWI) in the Staging of Advanced Prostate Cancer

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Simple Summary: Precise staging is key for the optimal management of advanced prostate cancer. PSMA PET-CT and WB-MRI outperform standard imaging technology for staging high-risk prostate cancer, but direct comparison between both modalities is lacking. The primary endpoint of our study was to compare the diagnostic accuracy of both techniques in the detection of lymph node, bone and visceral metastases against a best valuable comparator (BVC), defined as a consensus adjudication of all lesions on the basis of baseline and follow-up imaging, biological and clinical data and histopathologic confirmation when available. Knowing the diagnostic accuracy of both next generation imaging modalities might influence the diagnostic and therapeutic strategy in prostate cancer by tailoring therapy. However, the impact on treatment and patient outcome of an improved detection of metastases has not been determined yet.

Abstract: Background: Prostate specific membrane antigen (PSMA) positron emission tomography computed tomography (PET-CT) and whole-body magnetic resonance imaging (WB-MRI) outperform standard imaging technology for the detection of metastasis in prostate cancer (PCa). There are few direct comparisons between both modalities. This paper compares the diagnostic accuracy of PSMA PET-CT and WB-MRI for the detection of metastasis in PCa. One hundred thirty-four patients with newly diagnosed PCa ($n = 81$) or biochemical recurrence after curative treatment ($n = 53$) with high-risk features prospectively underwent PSMA PET-CT and WB-MRI. The diagnostic accuracy of both techniques for lymph node, skeletal and visceral metastases was compared against a best valuable comparator (BVC). Overall, no significant difference was detected between PSMA PET-CT and WB-MRI to identify metastatic patients when considering lymph nodes, skeletal and visceral metastases together (AUC = 0.96 (0.92–0.99) vs. 0.90 (0.85–0.95); $p = 0.09$). PSMA PET-CT, however, outperformed WB-MRI in the subgroup of patients with newly diagnosed PCa for the detection of lymph node metastases (AUC = 0.96 (0.92–0.99) vs. 0.86 (0.79–0.92); $p = 0.0096$). In conclusion, PSMA PET-CT outperforms WB-MRI for the detection of nodal metastases in primary staging of PCa.

Keywords: PSMA; PET-CT; WB-MRI; prostate cancer; staging

1. Introduction

Precise staging is key for the optimal management of advanced prostate cancer (PCa). It supports local treatment, and, increasingly, emerging therapies such as metastasis targeted therapies (MDT) [1]. Current treatment guidelines recognize thoraco-abdominal computed tomography (CT), abdominal magnetic resonance imaging and ^{99m}Tc -bone scintigraphy (BS) as the cornerstone imaging techniques for metastatic assessment in PCa. There is compelling evidence that emerging imaging technologies such as ^{68}Ga -PSMA-11 positron emission tomography CT (PSMA PET-CT) and whole-body magnetic resonance imaging (WB-MRI) with diffusion weighted imaging (DWI) outperform bone scintigraphy and thoraco-abdomino-pelvic CT for the detection of PCa metastases [2–6].

Despite this evidence, international guidelines still do not recommend the use of these new imaging techniques, apart for PSMA PET-CT which is now acknowledged as a standard of care in patients presenting with a PSA recurrence (BCR) after local treatment [7–9]. One of the main reasons, is the limited evidence that this increased diagnostic accuracy positively impacts the PCa care pathway and results in improved oncological outcome. Hence, detection of metastases may reclassify patients with newly diagnosed (ND) PCa from high-risk localized to metastatic with the consequence of omitting local treatment or consolidating systemic treatment with a last generation androgen receptor targeted agent (ARTA). In patients with biochemical recurrence after local treatment, more rapid detection of low volume metastatic deposit has boosted the emergence of metastatic directed ablative strategies in absence of clinical equipoise, since this approach is only supported by small phase II trials [10].

Several whole-body imaging techniques compete to replace BS and CT as standard of care imaging, but, unfortunately, there is limited data available to compare their diagnostic accuracy. Hence, this study compares PSMA PET-CT and WB-MRI for the detection of lymph node, bone and visceral metastases in PCa patients.

2. Materials and Methods

2.1. Study Design

This retrospective study of data prospectively collected in a single institution was conducted between 12/2016 and 12/2019 in 155 consecutive patients with newly diagnosed PCa at high risk for metastases (patients were included only if 2 or the 3 high-risk criteria were present: PSA > 20 ng/mL, Gleason score ≥ 8 or $\geq cT3$) or PSA recurrence after local treatment (defined as a PSA level >0.2 ng/mL after radical prostatectomy or >2 ng/mL after radiation therapy with a PSA doubling time <12 months). The trial was approved by the local ethical committee. After consenting, patients underwent both ^{68}Ga -PSMA PET-CT and WB-MRI including DWI sequences within 1 month.

“Standard” imaging modalities (CT and BS) were not systematically performed, as both PSMA PET-CT and WB-MRI are available in our center and as the diagnostic superiority of these two techniques has been repeatedly established [2–6]. Patients were treated at the referring physician’s discretion based on international recommendations and were followed up for at least 12 months.

2.2. Imaging Methods

Imaging protocols were predefined, both for PSMA PET-CT including PET-CT acquisition parameters, quality control and specifications for the radiopharmaceutical production, and for WB-MRI examinations that were designed after the METastasis Reporting and Data System (METRADS) guidelines for PCa [11].

2.2.1. PSMA-PET/CT Acquisition and Readings

⁶⁸Ga-PSMA-11 radio-pharmaceutical was synthesized onsite as previously described in good medical practice environment using a Scintomics GRP4V synthesizer (PSMA-HBED-11 labelling kits provided by ABX, Germany; ⁶⁸Ge/⁶⁸Ga Galli Ad generator, IRE Elite, Fleurus, Belgium). All ⁶⁸Ga-PSMA PET/CT examinations were performed in clinical routine conditions after intravenous injection of a target activity of 110 MBq (mean, 123 ± 33 MBq, range 73–207 MBq) [12]. PET/CT images were acquired at least 60 min post injection (mean 79 ± 17 min, ranging from 59 to 137 min p.i.), either on Gemini-TF 64 slices or Vereos digital PET/CT (Philips Healthcare, Best, The Netherlands). Low dose CT was acquired first for attenuation correction, then followed, when no contraindication was present, by a diagnostic thoraco-abdomino-pelvic CT with iodinated contrast injection in portal phase (Iobitridol, Xenetix 350 mg/mL, Guerbet, Roissy, France) and dose-reduction protocol (iterative reconstruction/dose modulation). PET/CT were acquired from the vertex to mid-thighs with arms above the head in 3D mode and reconstructed following standard manufacturer parameters (isometrics voxels of 4 mm for the Gemini-TF and 4–2 mm for the Vereos) after usual attenuation, scatter and time-of-flight corrections. Furosemide was not applied routinely. Perfusion of 500 mL 0.9% saline before injection was used to correctly hydrate the patient during the incorporation time. No dedicated fasting instructions were required for the PSMA PET/CT.

Two board certified nuclear medicine physicians performed all readings in consensus in a randomized order, blinded to clinical data and other imaging results. All examinations were reviewed using Osirix MD software (Pixmeo SARL, Bernex, Switzerland).

Eight anatomical regions for bones (skull, thoracic cage, cervical spine, thoracic spine, lumbar spine, pelvis, humeri, femurs) and seven regions for nodes (inguinal, internal and external iliac together, common iliac, lumbo-aortic, thoracic, axillary, cervical regions) were considered for the metastatic assessment.

Regarding bones, in each region, the bone marrow was considered as being either normal or presenting focal or diffuse tumoral involvement. Regarding lymph nodes, moderate (at least superior to the blood pool) to intense focal nodal uptake was considered for positivity without any consideration of the node size, especially within the pelvic and retroperitoneum area which are at higher risk of lymph node involvement in both ND and BCR stages. Visceral metastases were recorded by organ (mainly lung, liver and peritoneal cavity/carcinomatosis). The number and the presence of metastases were recorded in each region and the metastatic status was summarized in a per-organ approach (bones, nodes, visceral lesions present or not) and in a per-patient approach (metastatic or not).

2.2.2. WB-MRI Acquisition and Readings

WB-MRI examinations were performed on a 3.0-T MRI magnet (Ingenia, Philips Medical Systems, Best, The Netherlands). Five stacks of coronal 3D fast spin echo (FSE) T1, STIR, and axial DWI (three b-values: 0, 150 and 1000 s/mm²) images were obtained, covering the body from the vertex to mid-thighs, as recommended in the METRADS guidelines, and using previously published imaging parameters [11,13,14]. Total image acquisition time was less than 45 min.

Two board-certified musculoskeletal radiologists with more than 10 years' experience in WB-MRI reading performed all readings in consensus in a randomized order, blinded to clinical data and other imaging results. All images were read on PACS workstations (Carestream Vue; Carestream Health, Rochester, NY, USA), using the multiplanar reformation, link, scroll and zoom tools for side-by-side reading of anatomical and DWI sequences.

In each region, the bone marrow was considered as being either normal or presenting either focal or diffuse metastatic involvement based on widely accepted categorization criteria [15,16].

Lymph nodes were considered abnormal on WB-MRI when their short-axis diameter was larger than 10 mm. Perivisceral (perivesical, perirectal, etc.) nodes were defined as abnormal when their short-axis diameter was larger than 8 mm. Lymph nodes were also

considered abnormal when their contour was irregular or when there was loss of either the normal kidney shape, of the fatty hilum, or both. This widely accepted categorization has been repeatedly described [13,17–20].

The same per-organ and per-patient summary was used as for PSMA-PET/CT. For both PSMA PET/CT and WB-MRI, additional relevant information provided by the whole-body examinations about the local PCa status or incidental findings (e.g., kidney, lung, brain tumors, etc.) were not considered in this study, being beyond its scope.

2.3. Reference Standard or “Best Valuable Comparator”

In the absence of a systematic histologic gold standard, a “best valuable comparator” (BVC) was used to adjudicate the presence of metastases at the region, organ and patient levels, in line with previous diagnostic trials [21–23]. The BVC included results from all available baseline and follow-up imaging modalities (modern, i.e., PSMA PET-CT and WB-MRI, and standard, i.e., BS and CT when available), clinical follow-up data (PSA kinetics, skeletal events), histopathological proofs when available after biopsy of lesions (bone, lymph nodes or visceral) or surgical treatment (salvage lymph node dissection). A multidisciplinary panel including one nuclear medicine physician and one radiologist distinct from those who had performed the prospective readings, one urologist, one medical oncologist and one pathologist determined the benign or malignant nature of each lesion reported from each modality based on this BVC.

2.4. Endpoints

The primary endpoint was to compare the diagnostic performance of WB-MRI and PSMA PET-CT for detecting metastases at the patient level using BVC as reference standard. The secondary endpoints were to compare the diagnostic performance of WB-MRI and PSMA PET-CT for detecting lymph nodes, bone and visceral metastases separately, and to measure the inter-reader agreement of WB-MRI and of PSMA PET-CT at the lymph node/bone/visceral and patient levels. The analyses were also performed in the ND and BCR subpopulations separately.

2.5. Statistical Analysis

The diagnostic accuracy of each modality is described by its sensitivity, specificity, positive predictive value, negative predictive value, with their 95% exact confidence interval and summarized by the area under the receiver operating characteristic (ROC) curves ($AUC = (sensitivity + specificity)/2$). These values of imaging modalities to detect metastases are expressed at the patient level and by organ (bones, lymph nodes, visceral metastases). The AUCs were compared by the Wald test from a logistic regression model.

False positive and negative rates were also reported for each modality at each level.

Analyses were performed for the whole population and separately for the ND PCa population and for the BCR population. All tests and confidence intervals (CI) are 2-sided with $\alpha = 0.05$. The statistical analysis software, version 9.4 (SAS, Bethesda, MD, USA) was used for these analyses.

Inter-rater agreement was measured using prevalence-adjusted bias-adjusted kappa coefficients [24]. The study is exploratory and the sample size was not prospectively planned. No multiplicity adjustment was applied.

3. Results

Of the 155 clinically eligible patients, 2 were excluded because of contraindication to MRI (pacemaker) and 19 for an interval between the imaging procedures exceeding 1 month. The median time interval between examinations was 8 days (IQR: 15 days; SD: 20.05 days). The study flowchart is presented in Figure 1. The baseline clinical characteristics of the 134 patients included in the final analysis are detailed in Table 1. Eighty-one patients were newly diagnosed high-risk PCa and 53 were presenting with a biochemical recurrence after surgery or radiotherapy.

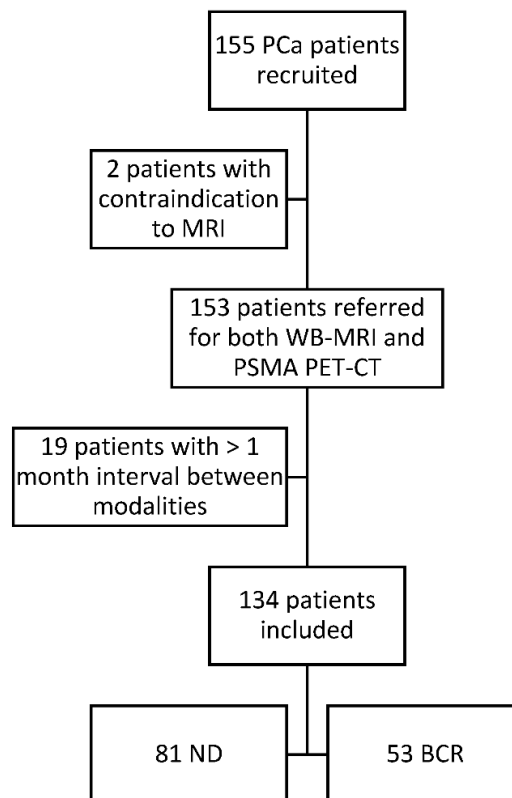


Figure 1. Study flow chart. All patients were diagnosed with biopsy-proven prostate cancer and all patients underwent a WB-MRI and a PSMA PET-CT at the University Clinic Saint-Luc Brussels from August 2016 to November 2019. PCa: prostate cancer; WB-MRI: whole body magnetic resonance imaging; PSMA PET-CT: prostate specific membrane antigen positron emission tomography; ND: newly diagnosed; BCR: biochemical recurrence.

Table 1. Patient demographics, disease characteristics and primary treatment.

Variable	Newly Diagnosed (n = 81)	Biochemical Recurrence (n = 53)
Age, year		
Median (IQR)	67 (62–72)	67 (62–73)
PSA, ng/mL		
Median (IQR)	12.29 (7.93–29)	6.85 (1.44–13.67)

Table 1. Cont.

Variable	Newly Diagnosed (<i>n</i> = 81)	Biochemical Recurrence (<i>n</i> = 53)
Clinical Stage, cT		
cT1	40	27
cT2	25	17
cT3	11	7
cT4	5	2
ISUP grade group		
1	1	7
2	5	15
3	7	13
4	30	11
5	38	7
D'AMICO risk group classification		
Low	1	8
Intermediate	5	27
High	75	18
Primary treatment		
WAWA	1	0
RP	16	17
EBRT	51	31
Brachy	1	5
ADT + ARTA	7	0
ADT + chemo	5	0

PSA: prostate specific antigen; ISUP: International Society of Urological Pathology; WAWA: watchful waiting; RP: radical prostatectomy; EBRT: external beam radiotherapy; Brachy: brachytherapy; ADT: androgen deprivation therapy; ARTA: antiandrogen receptor targeted agent; Chemo: chemotherapy.

3.1. Primary Endpoint

Based on the BVC, 66/134 patients (49%) were adjudicated metastatic and 68/134 (51%) non-metastatic (Table 2). Thirty-three patients (25%) had at least one bone metastasis, 51 (38%) had pathologic lymph nodes and 8 (5%) had visceral metastases. PSMA PET-CT detected metastases in 65 of the 66 metastatic patients considered metastatic by the BVC (true positive) and in 5 of the 68 non-metastatic patients (false positive). WB-MRI detected metastases in 56 of the 66 considered metastatic patients by BVC (true positive), and in 3 of the 68 the non-metastatic patients (false positive). Table 3 details the discordant cases. The AUC for identifying metastatic patients was 0.96 (95% CI, 0.92–0.99) and 0.90 (0.85–0.95) for PSMA PET-CT and WB-MRI, respectively ($p = 0.09$). The inter-technique agreement was relatively good but far from perfect (adjusted kappa = 0.72; 0.60–0.83).

Table 2. Comparison of the diagnostic effectiveness of PSMA PET-CT and WB-MRI in 134 patients with prostate cancer (at the organ and patient levels).

Variable	Patient Level		Bone Level		Lymph Node Level		Visceral Level	
Imaging Modality	PSMA PET-CT	WB-MRI	PSMA PET-CT	WB-MRI	PSMA PET-CT	WB-MRI	PSMA PET-CT	WB-MRI
Sensitivity	0.98 (0.96–1.00)	0.85 (0.76–0.94)	0.97 (0.91–1.00)	1.00 (1.00–1.00)	0.94 (0.88–1.00)	0.73 (0.60–0.85)	1.00 (1.00–1.00)	0.75 (0.45–1.00)
Specificity	0.93 (0.86–0.99)	0.96 (0.90–1.00)	0.94 (0.89–0.99)	0.95 (0.91–0.99)	0.98 (0.94–1.00)	0.99 (0.96–1.00)	0.99 (0.98–1.00)	1.00 (1.00–1.00)
Positive Predictive Value	0.92 (0.87–0.99)	0.95 (0.89–1.00)	0.84 (0.73–0.96)	0.87 (0.76–0.98)	0.96 (0.91–1.00)	0.97 (0.92–1.00)	0.89 (0.68–1.00)	1.00 (1.00–1.00)
Negative Predictive Value	0.98 (0.95–1.00)	0.87 (0.79–0.94)	0.99 (0.97–1.00)	1.00 (1.00–1.00)	0.96 (0.92–1.00)	0.85 (0.78–0.92)	1.00 (1.00–1.00)	0.98 (0.96–1.00)

Table 2. Cont.

Variable	Patient Level		Bone Level		Lymph Node Level		Visceral Level	
Imaging Modality	PSMA PET-CT	WB-MRI	PSMA PET-CT	WB-MRI	PSMA PET-CT	WB-MRI	PSMA PET-CT	WB-MRI
False Positive	5	3	6	5	2	1	1	0
False Negative	1	10	1	0	3	14	0	2
Diagnostic Accuracy	0.96 (0.92–0.99)	0.90 (0.85–0.95)	0.95 (0.92–0.99)	0.98 (0.95–1.00)	0.96 (0.92–0.99)	0.86 (0.79–0.92)	1.00 (0.99–1.00)	0.88 (0.71–1.00)
<i>p</i> value comparing AUC *	0.09		0.32		0.0096		0.14	
Cohen's Kappa PET-CT vs. WB-MRI **	0.72 (0.60–0.83)		0.88 (0.80–0.96)		0.70 (0.58–0.82)		0.96 (0.90–1.00)	

WB-MRI: whole body magnetic resonance imaging; PSMA PET-CT: prostate specific membrane antigen positron emission tomography; AUC: area under the curve; * all *p* values of <0.05 were considered statistically significant; ** The inter-technique agreement was defined using adjusted Cohen's kappa; all values between parentheses are the 95% confidence interval.

Table 3. Causes of false positive and negative observations in the patient-based analysis of the whole patient population, as adjudicated after the analysis of the files by the time of BVC.

Variable	PSMA PET-CT	WB-MRI
Bone		
False Positive	<i>N</i> = 6	<i>N</i> = 5
	Degenerative changes (<i>n</i> = 2) Benign fractures (<i>n</i> = 2) Benign bone lesion (<i>n</i> = 1)	Benign fractures (<i>n</i> = 2) Degenerative changes (<i>n</i> = 2) Hemangioma (<i>n</i> = 1)
False Negative	<i>N</i> = 1	<i>N</i> = 0
	Lack of PSMA expression	
Lymph Node		
False Positive	<i>N</i> = 2	<i>N</i> = 1
	Subtle uptake in benign LN (<i>n</i> = 2)	Inflammatory adenopathy
False Negative	<i>N</i> = 3	<i>N</i> = 14
	Small nodes without uptake shown metastatic at follow-up (<i>n</i> = 2) Subtle uptake without CT abnormality (<i>n</i> = 1)	Small size of metastatic nodes (<10 mm) (<i>n</i> = 12) Missed mediastinal LN (<i>n</i> = 1) Missed inguinal LN (<i>n</i> = 1)
Viscera		
False Positive	<i>N</i> = 1	<i>N</i> = 0
	Benign liver lesion	
False Negative	<i>N</i> = 0	<i>N</i> = 2
		Lung metastases (<i>n</i> = 2)

PSMA: prostate specific membrane antigen; LN: lymph node.

3.2. Secondary Endpoints

At the organ level, PSMA PET-CT and WB-MRI detected 180 and 177 bone metastases, 217 and 141 pathologic lymph nodes and 9 and 6 visceral metastases, respectively. The AUC for identifying bone metastases was 0.95 (0.92–0.99) and 0.98 (0.95–1.00) for PSMA PET-CT and WB-MRI, respectively (*p* = 0.32). WB-MRI detected all bone metastases resulting in 100% sensitivity, whereas PSMA PET-CT missed one bone lesion. The AUC for identifying lymph node metastases was 0.96 (0.92–0.99) and 0.86 (0.79–0.92) for PSMA PET-CT and WB-MRI, respectively (*p* = 0.0096).

3.3. In the Subgroup of Patients with Newly Diagnosed PCa

PSMA PET-CT significantly outperformed WB-MRI (Table 4). At the patient level, the AUC was 0.96 (0.92–1.00) and 0.87 (0.79–0.95) for PSMA PET-CT and for WB-MRI, respectively (*p* = 0.045). The inter-technique agreement was good (adjusted kappa = 0.70;

0.55–0.86). The AUC for pathological lymph node detection was 0.98 (0.96–1.00) and 0.83 (0.74–0.92) for PSMA PET-CT and WB-MRI, respectively ($p = 0.002$). The AUC for bone metastases detection was 0.94 (0.87–1.00) and 0.99 (0.96–1.00) for PSMA-PET and WB-MRI, respectively ($p = 0.24$) (Figure 2). At the bone level, WB-MRI detected all lesions, whereas PSMA PET-CT missed one.

Table 4. Comparison of the diagnostic effectiveness of WB-MRI and PSMA PET-CT in 81 newly diagnosed prostate cancer patients.

Variable	Patient Level		Bone Level		Lymph Node Level		Visceral Level	
Imaging Modality	PSMA PET-CT	WB-MRI	PSMA PET-CT	WB-MRI	PSMA PET-CT	WB-MRI	PSMA PET-CT	WB-MRI
Sensitivity	1.00 (1.00–1.00)	0.74 (0.59–0.90)	0.93 (0.79–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)	0.67 (0.49–0.84)	1.00 (1.00–1.00)	1.00 (1.00–1.00)
Specificity	0.92 (0.84–0.99)	1.00 (1.00–1.00)	0.95 (0.90–1.00)	0.97 (0.93–1.00)	0.96 (0.91–1.00)	1.00 (1.00–1.00)	0.99 (0.96–1.00)	1.00 (1.00–1.00)
Positive Predictive Value	0.88 (0.78–0.99)	1.00 (1.00–1.00)	0.81 (0.62–1.00)	0.87 (0.71–1.00)	0.93 (0.84–1.00)	1.00 (1.00–1.00)	0.75 (0.33–1.00)	1.00 (1.00–1.00)
Negative Predictive Value	1.00 (1.00–1.00)	0.86 (0.77–0.95)	0.98 (0.95–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)	0.86 (0.77–0.94)	1.00 (1.00–1.00)	1.00 (1.00–1.00)
False Positive	4	0	3	2	2	0	1	0
False Negative	0	8	1	0	0	9	0	0
Diagnostic Accuracy	0.96 (0.92–1.00)	0.87 (0.79–0.95)	0.94 (0.87–1.00)	0.99 (0.96–1.00)	0.98 (0.96–1.00)	0.83 (0.74–0.92)	0.99 (0.99–1.00)	1.00 (1.00–1.00)
p value comparing AUC *	0.045		0.24		0.002		0.32	
Cohen's Kappa PET-CT vs. WB-MRI **	0.70 (0.55–0.86)		0.95 (0.88–1.00)		0.73 (0.58–0.88)		0.98 (0.93–1.00)	

WB-MRI: whole body magnetic resonance imaging; PSMA PET-CT: prostate specific membrane antigen positron emission tomography; AUC: area under the curve; * all p values of <0.05 were considered statistically significant; ** The inter-technique agreement was defined using adjusted Cohen's kappa; all values between parentheses are the 95% confidence interval.

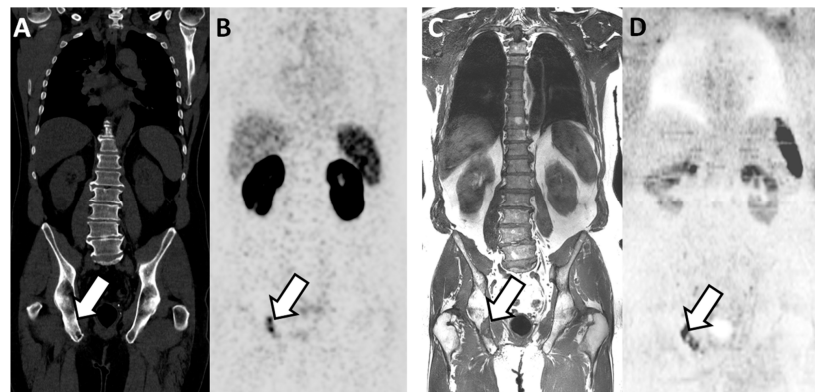


Figure 2. Concordant findings between PSMA PET/CT and WB-MRI/DWI: true positive observation of bone metastasis by WB-MRI/DWI in 65-year-old patient with ND prostate cancer at high risk for metastasis. (A,B) PSMA PET/CT: reformatted coronal CT (A) and PET (B) images show sclerotic lesion within the right ilio-ischiatic ramus with evident tracer uptake (arrows in (A,B)). (C,D) WB-MRI/DWI images: corresponding reformatted high resolution T1 (C) and diffusion-weighted (D) MRI images show bone lesion of low signal intensity on T1 and high signal intensity on MR images (inverted grey scale in the figure) within the right ilio-ischiatic ramus. The best valuable comparator confirmed the metastatic nature of the lesion.

3.4. In the Subgroup of Patients with Biochemical Recurrence after Local Treatment

PSMA PET-CT had higher sensitivity and specificity without reaching statistical significance (Table 5). At the patient level, the AUC for identifying metastatic patients was 0.96 (0.90–1.00) and 0.89 (0.79–0.98) for PSMA PET-CT and WB-MRI, respectively ($p = 0.25$). WB-MRI missed one additional patient (false negative) compared to the PSMA PET-CT. The inter-technique agreement was good (adjusted kappa = 0.74; 0.55–0.92). At the lymph node level, the AUC was 0.94 (0.87–1.00) and 0.88 (0.79–0.97) for PSMA PET-CT and WB-MRI, respectively ($p = 0.34$) (Figure 3). At the bone level, both modalities performed equally well with an AUC of 0.96 (0.90–1.00).

Table 5. Comparison of the diagnostic effectiveness of WB-MRI and PSMA PET-CT in 53 PCa patients at biochemical recurrence.

Variable	Patient Level		Bone Level		Lymph Node Level		Visceral Level	
Imaging Modality	PSMA PET-CT	WB-MRI	PSMA PET-CT	WB-MRI	PSMA PET-CT	WB-MRI	PSMA PET-CT	WB-MRI
Sensitivity	0.97 (0.92–1.00)	0.94 (0.87–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)	0.87 (0.74–1.00)	0.79 (0.63–0.95)	1.00 (1.00–1.00)	0.60 (0.17–1.00)
Specificity	0.94 (0.84–1.00)	0.83 (0.66–1.00)	0.91 (0.82–1.00)	0.91 (0.82–1.00)	1.00 (1.00–1.00)	0.97 (0.90–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)
Positive Predictive Value	0.97 (0.92–1.00)	0.92 (0.83–1.00)	0.86 (0.72–1.00)	0.86 (0.72–1.00)	1.00 (1.00–1.00)	0.95 (0.85–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)
Negative Predictive Value	0.94 (0.84–1.00)	0.88 (0.73–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)	0.90 (0.80–1.00)	0.85 (0.73–0.97)	1.00 (1.00–1.00)	0.96 (0.91–1.00)
False Positive	1	3	3	3	0	1	0	0
False Negative	1	2	0	0	3	5	0	2
Diagnostic Accuracy	0.96 (0.90–1.00)	0.89 (0.79–0.98)	0.96 (0.90–1.00)	0.96 (0.90–1.00)	0.94 (0.87–1.00)	0.88 (0.79–0.97)	1.00 (1.00–1.00)	0.80 (0.56–1.00)
p value comparing AUC *	0.25		1		0.34		0.10	
Cohen's Kappa PET-CT vs. WB-MRI **	0.74 (0.55–0.92)		0.77 (0.60–0.94)		0.66 (0.46–0.86)		0.92 (0.82–1.00)	

WB-MRI: whole body magnetic resonance imaging; PSMA PET-CT: prostate specific membrane antigen positron emission tomography; AUC: area under the curve; * all p values of <0.05 were considered statistically significant; ** The inter-technique agreement was defined using adjusted Cohen's kappa; all values between parentheses are the 95% confidence interval.



Figure 3. Cont.

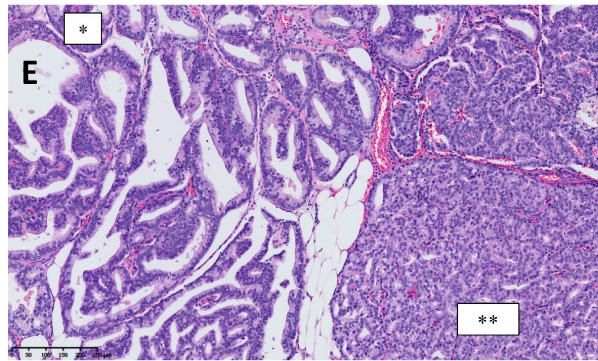


Figure 3. Discordant findings between PSMA PET/CT and WB-MRI/DWI: false negative observation of metastatic lymph node by WB-MRI/DWI in 62-year-old patient with prostate cancer at BCR (rapidly rising PSA up to 3.5 ng/mL after radical prostatectomy and pelvic irradiation). (A,B) PSMA PET/CT: reformatted coronal CT (A) and PET (B) images show unique 10 mm radiotracer-positive (SUVmax 12) left iliac lymph node considered as metastatic on the PET image (arrows in (A,B)). (C,D) WB-MRI/DWI images: corresponding reformatted high resolution T1 (C) and diffusion-weighted (D) MRI images show single left lymph node (arrows in (C,D)) that was not considered as metastatic based on its size (small diameter < 10 mm). (E) Hematoxylin and eosin stained section of resected node after robotic-assisted salvage lymphadenectomy shows the presence of a PCa metastasis with a mixed intra-ductal (*) and cribriform (**) morphology (original magnification $\times 300$; scale bar in lower left corner).

4. Discussion

New imaging techniques providing high resolution whole-body anatomical coverage and functional information on tissues are clearly reshaping the PCa treatment landscape. It is only a matter of time before they replace BS and CT, depending on local accessibility and development of expertise to address the different clinical needs and referring physician expectations. Besides local availability and costs, physicians will have to choose amongst different techniques based on their diagnostic effectiveness, which requires objective comparison studies.

The primary endpoint of our study was to compare the diagnostic accuracy of PSMA PET-CT and WB-MRI to detect bone, lymph node and visceral metastases in a broad group of patients with newly diagnosed and recurrent PCa, thus reflecting current indications. After adjudication with a best valuable comparator, metastases were found in 38% of the ND patients and 66% of the BCR patients, in line with previous reports [5,21,22,25].

In the present study, BVC adjudicated 5 false positive and 1 false negative results with PSMA PET-CT and 3 false positive and 10 false negative results with WB-MRI. There was no significant difference in AUCs.

For the detection of lymph node metastases, PSMA PET-CT clearly outperformed WB-MRI, resulting from a higher sensitivity of PSMA PET-CT to detect small metastatic lymph nodes. These findings are in line with the results from the systematic review and meta-analysis of Perera et al., highlighting the high sensitivity and specificity of PSMA PET-CT to detect small lymph nodes at low PSA levels [5]. WB-MRI has a lower sensitivity and specificity for lymph node detection because of its inability to detect tumoral infiltration in normal size lymph nodes [18]. Noteworthy, in absence of systematic pathological verification, the BVC used in this study cannot rule-out all false positive findings of imaging. In a study by Montorsi et al., 16 patients with BCR after local treatment underwent salvage lymph dissection based on a positive PSMA PET-CT, and positive lymph nodes were identified at pathologic analysis in only 68% of the patients, thus 32% being false positive [26]. A study by Herlemann et al. comparing PSMA PET-CT and histologic

findings after lymph node dissection found lower false positive rates for lymph nodes detected by PSMA-PET (less than 8% in the region-based analysis, 12% in the patient-based analysis) [27]. Another report, comparing PSMA PET/CT to pathological findings after template pelvic lymph node dissection in 130 patients, underlined the excellent specificity (98.9%) and accuracy (88.5%) of PSMA PET/CT for metastatic lymph node detection, but also pointed out its lower effectiveness to detect small truly positive lymph nodes (sensitivity of 65.9%, compared to pathological findings) [28].

In contrast to lymph nodes, PSMA PET/CT and WB-MRI performed equally for the detection of bone metastases, with PSMA PET-CT missing only one bone metastasis. Our study thus confirms the high diagnostic performance of WB-MRI for bone lesions detection that was primarily demonstrated in comparison with conventional techniques [22,29–31]. This study, however, suggests that PSMA PET-CT reaches similar diagnostic accuracy for bone metastasis detection, in line with published comparisons between MRI and PET/CT using either choline or PSMA ligands [32,33].

In contrast to conventional imaging, that indirectly identifies the presence of bone metastasis by highlighting the bone sclerosis or osteolysis induced by metastatic cells, ⁶⁸Ga-PSMA-PET-CT and WB-MRI directly identify tumoral cell deposits within the skeleton. PSMA PET-CT targets membrane antigens on the surface of metastatic cells. Although the uptake of ⁶⁸Ga-PSMA-PET is higher in osteolytic metastases compared to osteoblastic lesions due to a lower tumor cell content, abundant literature shows that both lytic and sclerotic bone lesions can be accurately imaged by PSMA PET/CT, at least as long as the PSMA expression is preserved [34,35]. MRI detects the replacement of the normal bone marrow content by neoplastic cells which leads to alteration of the signal intensity on the morphologic sequences and alteration of water diffusivity on molecular DWI sequences.

Interestingly, a high rate of false positive bone lesions (12/79) has been reported in the PROSTAGE PSMA PET-CT study [21]. In the current study, PSMA PET-CT and WB-MRI only had 5 and 6 false positive bone lesions, respectively. The false positive PSMA PET-CT and WB-MRI were both due to degenerative changes, benign fractures or benign bone lesions (observed in different patients for PSMA PET-CT and WB-MRI). This is in agreement with the literature, which reports that fractures, degenerative joint disease, hemangiomas, Paget's disease or fibrous dysplasia may be challenging for both PSMA PET-CT and WB-MRI [36]. Regarding this point, training of the different readers is crucial to identify the frequent pitfalls of both techniques.

PSMA PET-CT mainly outperformed WB-MRI in the subgroup of ND PCa for the detection of nodal metastases, confirming the results of previous randomized controlled trials. In the PROSTAGE study, 80 ND patients with high-risk features were assigned to bone scintigraphy, computed tomography, SPECT-CT, WB-MRI and ¹⁸F-PSMA PET-CT for primary staging. PSMA PET-CT outperformed all other imaging modalities for the detection of primary distant metastases. At patient level, the AUC (optimistic analysis) was 0.89 (0.80–0.97), 0.88 (0.80–0.97), 0.85 (0.76–0.94) and 0.81 (0.71–0.91) for PSMA PET-CT, WB-MRI, SPECT-CT and CT, respectively [21]. In the ProPSMA study (*n* = 302), ⁶⁸Ga-PSMA PET-CT had a significantly higher accuracy than conventional imaging (92% (88–95) vs. 65% (60–69); *p* < 0.0001) [25]. A recent prospective trial by Malaspina compared the performance of ¹⁸F-PSMA-1007 PET/CT, WB-MRI with DWI and CT for the primary pelvic nodal staging of PCa using robot-assisted laparoscopic prostatectomy and pelvic lymph node dissection as gold standard. Thirty-nine percent of patients had pelvic lymph node metastases. PSMA PET/CT, WB-MRI and CT detected 87%, 45% and 26% of the lesions, respectively. At the patient level, the inter-reader agreement and concordance with histopathology findings were higher for PSMA PET-CT compared to those of WB-MRI and CT (kappa values of respectively 0.89 vs. 0.47 and 0.69, respectively [37]. Noteworthy, these authors also demonstrated that 74% of the metastatic lymph nodes were smaller than the anatomical cut-off size of 8 mm, confirming our previous report that 70% of PSMA PET-CT positive lymph nodes were presenting a size below 8 mm, with a smallest positive lesion size of 1.7 mm [38].

In contrast, our results show that PET-PSMA and WB-MRI performed equally well at the patient level in the subgroup of patients with BCR after local therapy. Although it did not reach statistical significance, our study suggests that WB-MRI may lead to an underestimation of the global metastatic load, in case of small lymph node involvement.

Our study does not include a cost-effectiveness analysis. The high cost of new generation imaging is increasingly recognized as an important issue in the healthcare system, although it fluctuates between countries and continents. The costs of WB-MRI or PSMA PET-CT, offering a one-step and accurate diagnostic approach, should be put in balance against the use of multiple techniques and against the cost of futile or harmful therapeutic strategies based on inaccurate information about the real metastatic status. An additional advantage of WB-MRI over PET/CT is that MRI does not use ionizing radiation.

5. Conclusions

In this study, PSMA PET-CT outperformed WB-MRI to detect metastases, mainly due to a higher accuracy for metastatic lymph node detection in the primary staging of newly diagnosed patients. Although PSMA PET-CT has become the most widely accepted imaging technique, WB-MRI can be an alternative.

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Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Ethics Committee of the Cliniques Universitaires Saint Luc (protocol code 2019/24DEC/581 and date of approval 13 January 2020).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to ethical and privacy reasons.

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Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

ARTA	androgen receptor targeted agents
AUC	area under the curve
BCR	biochemical recurrence
BS	Bone scintigraphy
BVC	best valuable comparator
CT	computed tomography
TAP	thoraco-abdomino-pelvic
MDT	metastasis targeted therapies
ND	newly diagnosed
NGI	next generation imaging
PCa	prostate cancer
PSMA PET-CT	prostate specific membrane antigen positron emission tomography computed tomography
PSA	prostate specific antigen
ISUP	international society of uropathological pathology
WB-MRI	whole body magnetic resonance imaging

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8. Third publication

Value of Whole-body Magnetic Resonance Imaging Using the MET-RADS-P Criteria for Assessing the Response to Intensified Androgen Deprivation Therapy in Metastatic Hormone-naïve and Castration-resistant PCa.

Van Damme J, Tombal B, Michoux N, Van Nieuwenhove S, Pasoglou V, Triqueneaux P, Padhani AR, Lecouvet FE. Eur Urol Oncol. 2025 Jun;8(3):689-699.

Summary

This study assessed concordance between PSA and WB-MRI responses, and their prognostic implications for treatment duration and overall survival (OS) in patients receiving intensified hormonal therapy.

Methods

We have conducted a prospective study and enrolled 88 patients treated at a single academic center (37 mHNPC, 51 mCRPC). All received ADT plus an AR pathway inhibitor (abiraterone, enzalutamide, or apalutamide) and underwent baseline and follow-up WBMRI, at 12 months for mHNPC and 6 months for mCRPC.

MET-RADS-P compliant sequences were performed on a 3T scanner, including T1-, T2-, and short-tau inversion recovery (STIR)-weighted anatomical imaging and diffusion-weighted imaging (DWI) (b-values 0–1000 s/mm²). Apparent diffusion coefficient (ADC) maps were reconstructed. Three experienced radiologists, blinded to clinical data, reviewed scans in consensus.

Response assessment was performed based on the MET-RADS-P Response Assessment Categories (RACs): RAC 1: Highly likely to be responding; RAC 2: Likely to be responding; RAC 3: Stable disease; RAC 4: Likely to be progressing; RAC 5: Highly likely to be progressing. A WBMRI responder was defined as RAC 1–2; a progressor as a RAC 4–5. PSA response was described as a PSA ≤ 0.2 ng/mL in mHNPC or $\geq 50\%$ decline from baseline in mCRPC. Statistical analyses included

Cohen's κ for agreement, Fisher's exact test for categorical associations, and Cox regression for associations with time to subsequent treatment and OS.

Results

Baseline characteristics

Median age was 69 years (mHNPC) and 63 years (mCRPC). Bone metastases were nearly universal (95–100%). Node involvement occurred in 49% of mHNPC and 26% of mCRPC patients.

Response rates

- PSA response: 43% in mHNPC; 57% in mCRPC.
- WBMRI response: 73% in mHNPC; 14% in mCRPC.
- Concordant PSA and WBMRI responses: 41% (mHNPC); 12% (mCRPC).
- Discordant cases were common: 79% of PSA responders in mCRPC showed wbMRI progression.

Agreement between PSA and WBMRI

- mHNPC: Fair agreement ($\kappa = 0.30$; 62% observed concordance).
- mCRPC: None to slight agreement ($\kappa = 0.15$; 55% observed concordance).

Prognostic impact

In patients with mHNPC, PSA responders were less likely to require additional treatment (HR 0.36, $p = 0.034$) while WBMRI responders had a markedly lower probability of treatment escalation (HR 0.13, $p < 0.001$). WBMRI progression predicted significantly shorter overall survival (HR 8.59, $p = 0.002$).

In patients with mCRPC, nearly all patients (96%) required further treatment. Neither PSA nor WB-MRI responses correlated with time to subsequent therapy or OS.

Discussion

This study highlights the poor concordance between biochemical (PSA) and imaging (WB-MRI) responses in metastatic PCa treated with intensified hormonal therapy—especially in the castration-resistant setting.

In patients with mHNPC, WB-MRI and PSA responses were often aligned, and imaging progression was strongly predictive of mortality, supporting WBMRI's prognostic value. Patients achieving both PSA and wbMRI responses had prolonged time to subsequent treatment and longer OS, indicating that combined biochemical–imaging assessment offers a more complete evaluation of therapeutic efficacy.

In patients with mCRPC, however, PSA decline often failed to reflect accurate disease control: two-thirds of PSA responders exhibited radiologic progression. This discordance aligns with evidence from the PREVAIL trial and PSMA PET studies showing radiographic progression in the absence of PSA rise. It reflects the biological heterogeneity of mCRPC, where androgen receptor (AR)–independent tumor clones emerge under selective pressure from AR-targeted therapies, leading to PSA-silent progression.

The findings suggest that WBMRI can identify early disease progression not captured by PSA, helping guide timely therapeutic escalation. Conversely, in mHNPC, the absence of WB-MRI progression among deep PSA responders (≤ 0.2 ng/mL) supports the potential for treatment de-intensification strategies in this subgroup.

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Value of Whole-body Magnetic Resonance Imaging Using the MET-RADS-P Criteria for Assessing the Response to Intensified Androgen Deprivation Therapy in Metastatic Hormone-naïve and Castration-resistant Prostate Cancer

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Abstract

Background and objectives: We assessed the agreement between prostate-specific antigen (PSA) and imaging responses using whole-body magnetic resonance imaging (wbMRI). Our aim was to explore the potential prognostic value of PSA and wbMRI responses in metastatic hormone-naïve prostate cancer (mHNPC) and castration-resistant PC (mCRPC).

Methods: wbMRI was prospectively performed in 37 patients with mHNPC and 51 with mCRPC before and after 6–12 mo of androgen deprivation therapy and an androgen receptor pathway inhibitor (ARPI). Imaging responses were defined according to the Metastasis Reporting and Data System for PC (MET-RADS-P) criteria. A PSA response was defined as PSA ≤ 0.2 ng/ml in mHNPC and a $\geq 50\%$ decrease from the pretreatment level in mCRPC. Agreement between PSA and wbMRI responses was assessed using Cohen's κ . The association between time to subsequent treatment and overall survival (OS) was analyzed using Cox regression analysis.

Key findings and limitations: Agreement between PSA and wbMRI responses was fair in mHNPC ($\kappa = 0.30$) but none to slight in mCRPC ($\kappa = 0.15$). In mHNPC, patients with a PSA or wbMRI response were less likely to receive subsequent treatments; wbMRI progression was associated with a significantly higher risk of death (hazard ratio 8.59; $p = 0.002$). In mCRPC, two-thirds of patients with a PSA response showed progression on wbMRI; neither PSA nor wbMRI progression changed the likelihood of starting a subsequent treatment or the risk of death.

Conclusions and clinical implications: In mHNPC, wbMRI progression was associated with a higher risk of needing subsequent treatment and shorter OS.

Patient summary: We evaluated the agreement between routine PSA (prostate-specific antigen) test results and whole-body MRI (magnetic resonance imaging) scans for assessing the response of metastatic prostate cancer to treatment. There was disagreement between the PSA and MRI results, mainly for patients with cancer that was

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resistant to hormone-based treatment. Combining PSA with whole-body MRI might provide a more accurate picture of the response of advanced prostate cancer to treatment.
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1. Introduction

Modern treatment for metastatic hormone-naïve prostate cancer (mHNPc) and castration-resistant prostate cancer (mCRPC) is based on intensification of androgen deprivation therapy (ADT) via addition of an androgen receptor pathway inhibitor (ARPI) [1,2]. Standard assessment of the metastatic response in advanced PC is based on contrast-enhanced computed tomography (CT) of the thorax, abdomen, and pelvis and ^{99m}Tc bone scintigraphy [3]. Unfortunately, the tumor response cannot be objectively assessed in bone metastases, the most common metastatic site in PC, via these modalities [4]. Consequently, investigators have relied on the prostate-specific antigen (PSA) response to distinguish good and poor responders, with many studies confirming that the magnitude of the PSA decline is strongly associated with better outcomes in both mCRPC and metastatic hormone-naïve PC (mHNPc) [5–7]. However, because of tumor heterogeneity, the Prostate Cancer Clinical Trials Working Group 3 criteria emphasize the strength of the association between early changes in individual outcome measures, whether clinical, biochemical, imaging, or other molecular parameters, to establish the value of continuing a therapy when there are signs that the disease is beginning to progress [3].

Whole-body magnetic resonance imaging (wbMRI), including diffusion-weighted imaging (DWI) sequences, allows objective measurement of nodal, visceral, and skeletal bone metastases and their response to therapy [8–14]. The Metastasis Reporting and Data System for Prostate Cancer (MET-RADS-P) was proposed in 2017 to standardize wbMRI acquisition, interpretation, and reporting and to optimize response assessment in men with advanced PC [9].

We analyzed the value of measuring tumor responses according to MET-RADS-P in patients with metastatic PC treated with ADT and an ARPI.

2. Patients and methods

2.1. Study design and participants

For this study we prospectively enrolled 37 patients with newly diagnosed with mHNPc and 51 patients with mCRPC who were treated with ADT and an ARPI from July 2012 to August 2022 at a single academic institution. All patients underwent wbMRI at baseline and after 12 mo (mHNPc) or 6 mo (mCRPC) of treatment. PSA was measured every 3 mo. The study was approved by the ethics committee of Cliniques Universitaires Saint Luc (Brussels, Belgium; protocol code 2019/24DEC/581). mHNPc and mCRPC data were analyzed separately and independently.

2.2. wbMRI image acquisition and readings

All MRI acquisitions were performed on a 3.0-T scanner (Ingenia, Philips Healthcare, Eindhoven, The Netherlands). The imaging protocol included MET-RADS-P-compliant sequences (anatomic T1-weighted, T2-weighted, and short tau inversion recovery-weighted images; and DWI obtained with b values of 0, 50, 150, and 1000) from which apparent diffusion coefficient (ADC) maps were reconstructed [9]. The detailed MRI protocol has been published elsewhere and can be found in [Supplementary Table 1](#) [14,15].

Three radiologists with at least 11 yr of experience in wbMRI reading who were blinded to patient demographics, disease stage, and treatments reviewed the imaging studies and agreed on consensus. Paired baseline and follow-up wbMRI studies for a given patient were read during the same session to determine the response assessment category (RAC) as defined in the MET-RADS-P guidelines: RAC 1 = highly likely to be responding; RAC 2 = likely to be responding; RAC 3 = stable disease; RAC 4 = likely to be progressing; and RAC 5 = highly likely to be progressing [9]. Intraosseous lesions >1.5 cm in diameter showing low signal intensity on T1-weighted images and abnormal signal intensity on both high- b -value DWI and the ADC map were considered active bone lesions [16]. Lymph nodes ≥ 1.5 cm on the short axis or soft tissue lesions ≥ 1 cm on the long axis were considered active metastases according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

Seven skeletal areas, three nodal areas, and visceral disease were assessed separately for the RACs. These regional patterns determined the primary (dominant) response pattern at the patient level. The second most frequent pattern was also recorded to account for potential response heterogeneity as anticipated in MET-RADS-P.

2.3. Endpoints and response evaluation

The primary endpoint was the agreement or disagreement between PSA and wbMRI MET-RADS-P response assessments. The secondary endpoint was an exploratory assessment of the association of wbMRI and PSA responses with time to subsequent active treatment and overall survival (OS).

For the PSA response, a PSA responder was defined as a patient achieving $\text{PSA} \leq 0.2$ ng/ml in mHNPc and a decrease of $\geq 50\%$ from the pretreatment level in mCRPC [5,7].

For the wbMRI response, a patient with progressive disease in any organ was categorized as RAC 4/5 (Fig. 1). A patient with a highly likely response in all organs was categorized as RAC 1 (Fig. 2). A patient with a response in the nodes but with stable bone disease was categorized as a

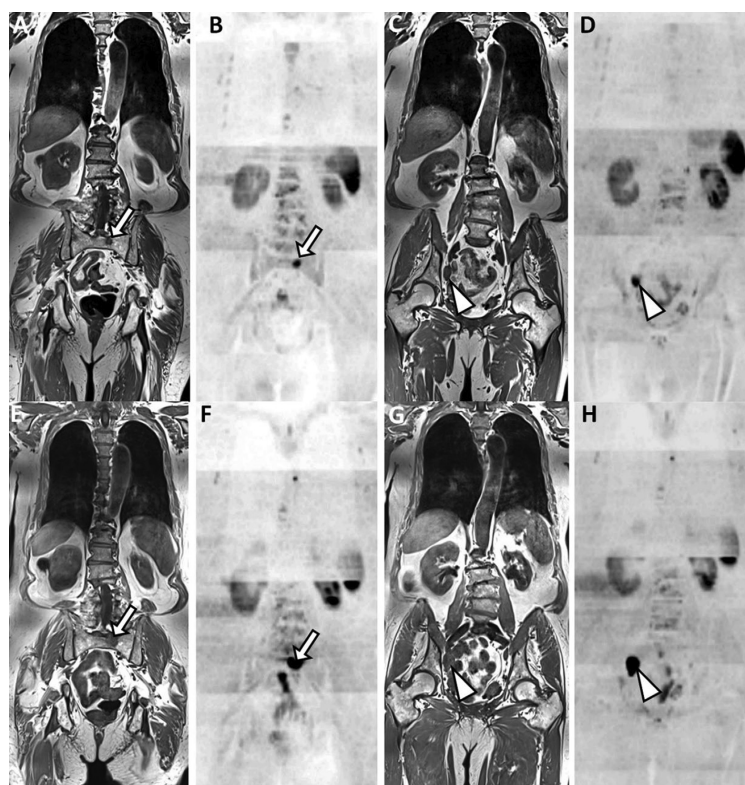


Fig. 1 – Progression of bone and node metastases in a 77-yr-old man with metastatic hormone-naïve prostate cancer (response assessment category 5). Comparison of whole-body magnetic resonance imaging before and after treatment. (A,C) Coronal T1-weighted images and (B,D) DWI scans ($b = 1000 \text{ s/mm}^2$, inverted gray scale) at baseline show bone metastasis in the sacrum (arrows in A, B), and right iliac node (arrowheads in C, D). Corresponding (E,G) T1-weighted images and (F,H) DWI scans at 6-mo follow-up show progression in the size of metastatic foci. DWI = diffusion-weighted imaging.

likely responder (RAC 2; Fig. 3). A patient with only stable disease was categorized as RAC 3. The heterogeneity of the imaging response (discordant responses identified via separate analyses of bone, nodes, and visceral organs) was included in the imaging response assessment to reflect its prognostic importance, as previously validated [13].

2.4. Statistical analysis

Summary characteristics of the study population are reported as the mean value for continuous variables, or the median value if the data followed a non-normal distribution according to the Shapiro-Wilk test, and as the proportion and associated 95% confidence interval (CI) for categorical variables.

The following analyses were performed separately for the mHNPc and mCRPC groups. A two-sided Fisher's exact

test was performed to evaluate the difference in the proportion of wbMRI progressors in PSA progressors compared to PSA responders. Agreement between the wbMRI response and the PSA response was assessed using Cohen's κ (weighted) statistic and the actual agreement observed. The strength of the agreement was interpreted as follows: $\kappa < 0.20$ = none to slight; $0.21 \leq \kappa < 0.40$ = fair; $0.41 \leq \kappa < 0.60$ = moderate; $0.61 \leq \kappa < 0.80$ = good; $\kappa \geq 0.80$ = very good agreement [17].

Cox regression models were constructed to examine the association between the absence of a wbMRI response, a PSA response, or both wbMRI and PSA responses and the risk of death and the likelihood of subsequent therapy. Hazard ratio (HR) estimates with 95% CIs were calculated and survival and cumulative probability plots were generated.

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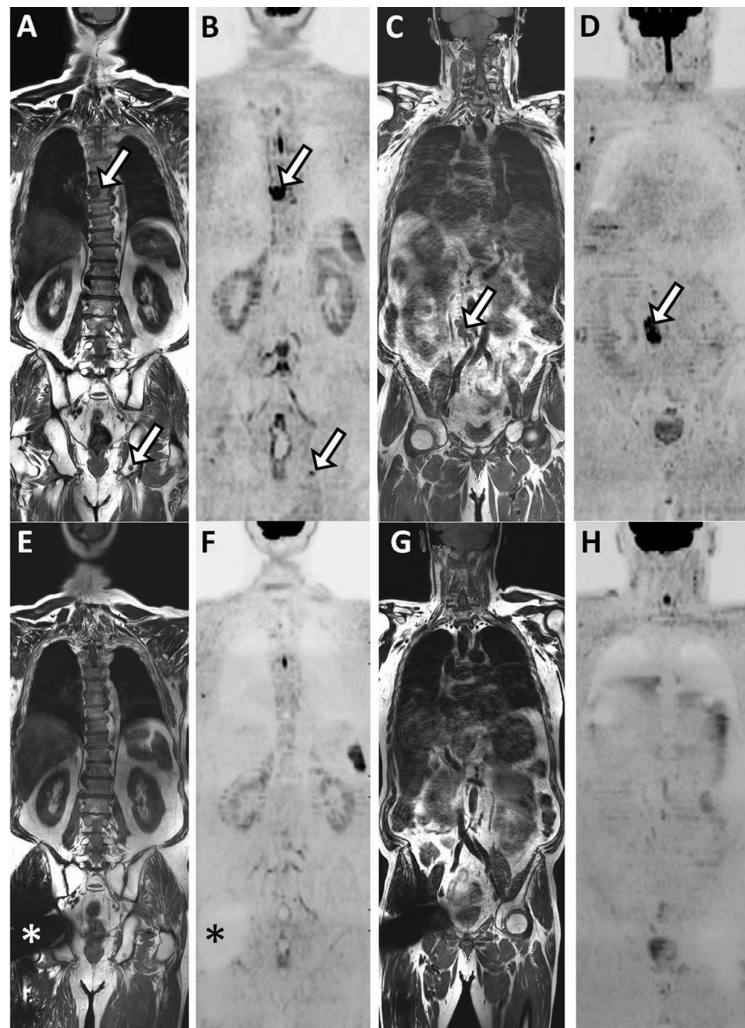


Fig. 2 – Response of bone and node metastases in a 73-yr-old man with metastatic hormone-naïve prostate cancer (response assessment category 1). Comparison of whole-body magnetic resonance imaging before and after treatment. (A,C) Coronal T1-weighted images and (B,D) DWI scans ($b = 1000 \text{ s/mm}^2$, inverted gray scale) at baseline show typical bone metastases within the T7 vertebral body and left ischiatic tuberosity (arrows in A and B) and lumbo-aortic node metastases (arrows in C and D). (E–H) Corresponding 6-mo follow-up images show complete disappearance of all metastatic foci (subtle residual marrow signals on T1-weighted images correspond to scar tissue). Right total-hip arthroplasty was performed between the time points, explaining the artifacts denoted by asterisks in E and F. DWI = diffusion-weighted imaging.

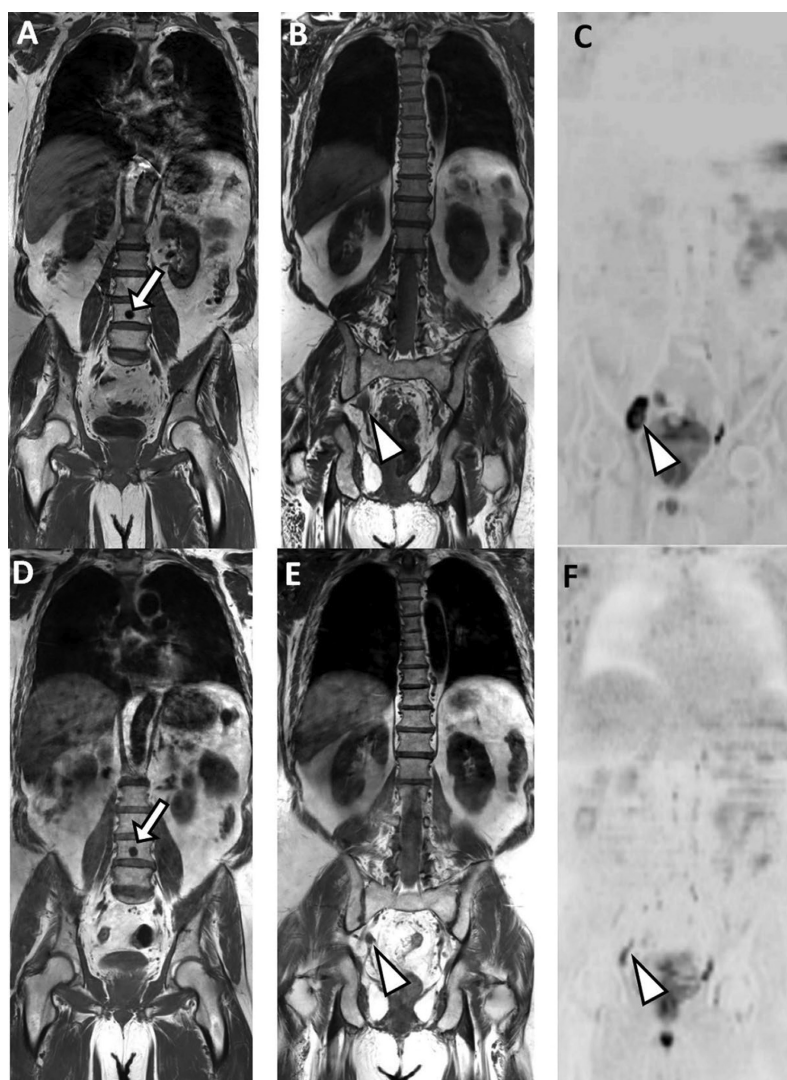


Fig. 3 – Response of nodal metastasis and stability of bone metastasis in a 75-yr-old man with metastatic castration-resistant prostate cancer (response assessment category 2). Comparison of whole-body magnetic resonance imaging before and after treatment. (A,B) Coronal T1-weighted images and (C) diffusion-weighted imaging ($b = 1000 \text{ s/mm}^2$, inverted gray scale) typical bone metastasis within the L3 vertebral body (arrow in A) and right iliac node metastases (arrowheads in B and C). (D–F) Corresponding 6-mo follow-up images show stability in the size of the L3 bone lesion (arrow in D) but almost complete disappearance of the metastatic nodes (arrowheads in E and F).

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Table 1 – Characteristics of the study population

Parameter	mHNPC	mCRPC
Patients (n)	37	51
Mean age, yr (95% CI)	69 (67–71)	63 (60–66)
Patients alive at the time of analysis, n/N (%)	24/37 (64.8)	2/51 (3.9)
Median ARPI treatment duration, mo (95% CI)	9 (4–12)	11 (9.03–17)
Median follow-up, mo (95% CI)	17 (14–21)	20 (17–25)
Patients starting a subsequent treatment (n)	14	49
Median time to subsequent treatment, mo (95% CI)	12 (5.3–18)	11 (9–15)
Median PSA at ARPI initiation, ng/ml (95% CI)	77.7 (31.3–130)	50.0 (19.6–98.7)
Median PSA at evaluation, ng/ml (95% CI)	0.96 (0.04–2.03)	17.7 (8.29–32.5)
ISUP grade group, n/N (%)		
Grade group 5	17/37 (45.9)	12/51 (23.5)
Grade group 4	10/37 (27.0)	3/51 (5.9)
Grade group 3	3/37 (8.1)	8/51 (15.7)
Grade group 2	3/37 (8.1)	16/51 (31.3)
Grade group 1	4/37 (10.8)	12/51 (23.5)
Synchronous metastasis, n/N (%)	26/37 (70.2)	15/51 (29.4)
Metachronous metastasis, n/N (%)	11/37 (29.7)	36/51 (70.6)
Low-volume disease, n/N (%) ^a	10/37 (27.0)	21/51 (41.2)
High-volume disease, n/N (%) ^a	27/37 (72.9)	30/51 (58.9)
Bone metastasis, n/N (%)	35/37 (94.6)	51/51 (100)
Node metastasis, n/N (%)	18/37 (48.6)	13/51 (25.5)
PSA response, n/N (%) ^b	16/37 (43.2)	29/51 (56.9)
PSA progression, n/N (%)	21/37 (56.8)	22/51 (43.1)
wbMRI response, n/N (%)	27/37 (72.9)	7/51 (13.7)
wbMRI progression, n/N (%)	10/37 (27.1)	44/51 (86.3)
PSA response and wbMRI response, n/N (%)	15/37 (40.5)	6/51 (11.8)
PSA progression and wbMRI progression, n/N (%)	7/37 (19)	19/51 (37.2)
wbMRI progressions and PSA response, n/N (%)	1/16 (6.3)	23/29 (79.3)

mCRPC = metastatic castration-resistant prostate cancer; mHNPC = metastatic hormone-sensitive prostate cancer; CI = confidence interval; PSA = prostate-specific antigen; wbMRI = whole-body magnetic resonance imaging; ARPI = androgen receptor pathway inhibitor; ISUP = International Society of Urological Pathology.

^a According to the CHAARTED criteria.

^b PSA responders achieved a PSA level of $\leq 50\%$ of the baseline level in mCRPC and ≤ 0.2 ng/ml in mHNPC.

Statistical significance was set at $p < 0.05$. Statsdirect version 3.3.5 statistical software was used for the analyses (<https://www.statsdirect.com/>).

3. Results

The characteristics of the two study groups are listed in Table 1.

3.1. Association between PSA and wbMRI responses

Patients with mHNPC were recruited from May 2019. Mean follow-up was 19 mo (95% CI 13.6–20.3), during which 57% (21/37) of the mHNPC group did not achieve PSA ≤ 0.2 ng/ml (Table 2). Of these patients, 33% (seven of 37) showed progression on wbMRI (RAC 4/5). A complete response was seen in only 9.5% (two of 21) of patients (RAC 1). wbMRI responders (RAC 1/2) were more frequent in the PSA responder group (+37%; $p = 0.012$; Fig. 4A).

Patients with mCRPC were recruited from July 2012. Mean follow-up was 25 mo (95% CI 19.9–29.3), during which 43% (22/51) of the mCRPC group did not achieve a PSA response. Of these patients, 82% (18/22) were also wbMRI progressors (RAC 4/5). A complete response was seen in only 3.5% (one of 29) of the patients (RAC 1). It is noteworthy that among the PSA responders, 66% (19/29) had progressing disease on wbMRI (RAC 4/5; Fig. 4B).

3.2. Agreement between PSA and wbMRI responses

In the mHNPC group, the agreement in response status between PSA and wbMRI was none to moderate ($\kappa = 0.30$, 95% CI 0.10–0.51; observed agreement 62%). In the mCRPC group, the agreement in response status between PSA and wbMRI was none to fair ($\kappa = 0.15$, 95%CI 0.07–0.37; observed agreement 55%).

Table 2 – Association between the PSA response and whole-body magnetic resonance imaging response according to MET-RADS-P

MET-RADS-P category by group	Patients, n/N (%)	No PSA response	PSA response	p value
mHNPC				
RAC 1	2 (9.5)	9 (56.2)	0.012	
RAC 2	10 (47.6)	6 (37.5)		
RAC 3	2 (9.5)	1 (6.3)		
RAC 4/5	7 (33.3)	0 (0.0)	0.006	
Total	21/37 (56.8)	16/37 (43.2)		
mCRPC				
RAC 1	0 (0.0)	1 (3.5)	0.450	
RAC 2	2 (9.1)	4 (13.7)		
RAC 3	2 (9.1)	5 (17.2)		
RAC 4/5	18 (81.8)	19 (65.5)	0.145	
Total	22/51 (43.1)	29/51 (56.9)		

MET-RADS-P = Metastasis Reporting and Data System for Prostate Cancer; mCRPC = metastatic castration-resistant prostate cancer; mHNPC = metastatic hormone-sensitive prostate cancer; PSA = prostate-specific antigen; RAC = response assessment category.

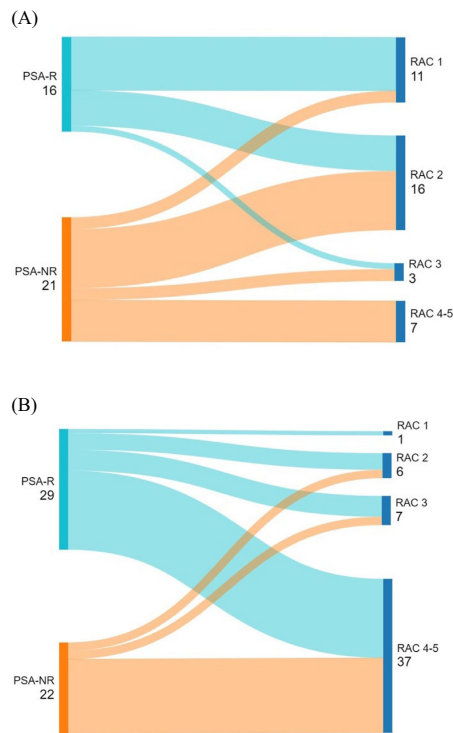


Fig. 4 – Sankey diagrams showing the concordance and discordance between response assessment via PSA and via whole-body magnetic resonance imaging using the MET-RADS-P RACs in (A) the mHNPc group ($n = 37$) and (B) the mCRPC group ($n = 51$). The widest connecting branch represent the strongest association between PSA and RAC. There is a high level of concordance between RAC and the PSA response in mHSPC, and a high level of discordance between RAC and the PSA response in mCRPC. PSA = prostate-specific antigen; R = response; NR = nonresponse; RAC = response assessment category according to MET-RADS-P; MET-RADS-P = Metastasis Reporting and Data System for Prostate Cancer; mHNPc = metastatic hormone-naïve prostate cancer; mCRPC = metastatic castration-resistant prostate cancer.

3.3. Probability of and time to subsequent treatment

In the mHNPc group, 38% (14/37) of the patients received subsequent treatment. The median time to subsequent treatment was 16 mo (95% CI 6.3–26) for PSA responders and 11 mo (95% CI 5.0–13) for patients without a PSA response. The probability of subsequent therapy was lower for PSA responders (HR 0.36; $p = 0.034$; Table 3). A similar trend was observed when using wbMRI to assess the response (HR 0.13; $p < 0.001$; Fig. 5).

In the mCRPC group, 96% (49/51) of the patients received a subsequent treatment. The median time to subsequent treatment was 16 mo (95% CI 11–25) for PSA responders and 9.0 mo (95% CI 6.0–11) for patients without a PSA

Table 3 – Cox regression results for the association between a positive response and the probability of subsequent treatment

Response type	Events, n/N (%)	HR (95% CI)	p value
mHNPc			
PSA response	14/37 (37.9%)	0.36 (0.14–0.93)	0.034
wbMRI response		0.13 (0.05–0.37)	<0.001
mCRPC			
PSA response	49/51 (96.1%)	0.64 (0.36–1.14)	0.129
wbMRI response		0.65 (0.35–1.22)	0.184

HR = hazard ratio; CI = confidence interval; mCRPC = metastatic castration-resistant prostate cancer; mHNPc = metastatic hormone-sensitive prostate cancer; PSA = prostate-specific antigen; wbMRI = whole-body magnetic resonance imaging.

response. No significant association between a positive response and the time to subsequent treatment was observed for either PSA or wbMRI assessment (all $p > 0.05$).

3.4. OS analysis

In the mHNPc group, 35% (13/37) of the patients had died, all from PC, by the time of the analysis, with median OS of 17 mo (95% CI 14–21). A nonsignificant trend for higher risk of death (HR 2.77; $p = 0.189$) was observed for those without a PSA response (Table 4). The risk of death was significantly higher for patients with wbMRI progression (HR 8.59; $p = 0.002$).

In the mCRPC group, 96% (49/51) of the patients died, all from PC, with median OS of 20 mo (95% CI 17–23). Responses were not associated with the risk of death, regardless of the criterion used (PSA, wbMRI, or PSA + wbMRI; all $p > 0.05$).

4. Discussion

Addition of an ARPI to ADT at diagnosis in mHNPc or at progression on ADT in mCRPC is the modern standard of care [1,2]. Future trials will address emerging questions. Should treatment be escalated in subsets of patients with a poor response before clear progression? Conversely, should patients with a strong response be offered a shorter treatment duration or a break?

One of the main hurdles in developing these trials is the need for robust methods to measure tumor responses, such as imaging techniques for visualization of skeletal metastases. Investigators have historically relied on PSA responses to predict outcomes. In the SWOG-9346 trial, the risk of death after 7 mo of ADT in metastatic hormone-sensitive PC (mHSPC) was five times lower for patients who achieved PSA ≤ 0.2 ng/ml than for patients with PSA > 4.0 ng/ml after treatment [18]. The prognostic value of PSA response has also been demonstrated in patients with mHNPc treated with ADT and an ARPI [19–21]. Early PSA response is also an independent prognostic factor in patients with mCRPC treated with an ARPI [22]. A greater PSA decline within the first 3 mo of enzalutamide treatment was associated with longer OS, longer times to PSA and radiographic progression, higher objective soft-tissue response rates, and a longer time to deterioration in quality of life.

Our study cohort comprised 37 patients with mHNPc and 51 with mCRPC who were treated with ADT and an

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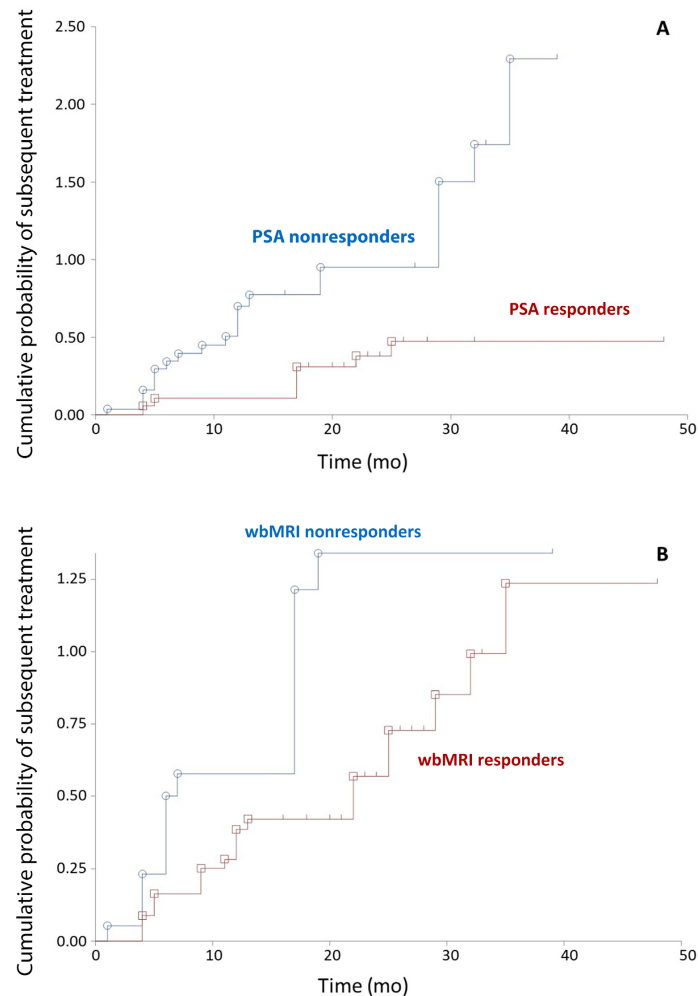


Fig. 5 – Cumulative probability of subsequent treatment according to Cox regression for patients with metastatic hormone-naïve prostate cancer stratified by (A) PSA response (≤ 0.2 ng/ml vs not) and (B) a wbMRI response according to Metastasis Reporting and Data System for Prostate Cancer evaluation. The cumulative probability of subsequent therapy is significantly lower for PSA responders ($p = 0.034$, Table 3) and for wbMRI responder ($p < 0.001$; Table 3). PSA = prostate-specific antigen; wbMRI = whole-body magnetic resonance imaging.

ARPI and underwent wbMRI at baseline and 6 or 12 mo. The PSA response rates align with published trials, with 44% 48% of the mHNPc group achieving PSA < 0.2 ng/ml and 66% 67% of the mCRPC group achieving a PSA response $> 50\%$. The hazard ratios for OS by PSA response also align with literature results [18–22] and the PSA response in the mHNPc

group was correlated with the time to subsequent treatment.

Modern imaging technologies such as wbMRI and prostate-specific membrane antigen (PSMA) positron emission tomography (PET)/CT allow objective measurement of the responses of bone, nodal, and visceral metastases to

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Table 4 – Cox regression results for the association between response category and overall survival

Response category	HR (95% CI)	p value
mHNPC		
No PSA response ^a	2.77 (0.61–12.6)	0.189
wbMRI progression	8.59 (2.27–32.5)	0.002
PSA response and wbMRI response	0.36 (0.08–1.65)	0.189
wbMRI progression and PSA response	–	–
mCRPC		
No PSA response	1.25 (0.71–2.21)	0.444
wbMRI progression	1.28 (0.68–2.40)	0.446
PSA response and wbMRI response	0.79 (0.39–1.60)	0.516
wbMRI progression and PSA response	1.30 (0.59–2.88)	0.520

HR = hazard ratio; CI = confidence interval; mCRPC = metastatic castration-resistant prostate cancer; mHNPC = metastatic hormone-sensitive prostate cancer; PSA = prostate-specific antigen; wbMRI = whole-body magnetic resonance imaging.

treatment [23]. Multiple studies and systematic reviews have demonstrated that wbMRI is effective in detecting metastatic spread and in monitoring therapy responses in patients with advanced PC [8–11,13]. The MET-RADS-P guidelines for standardization of data acquisition, interpretation, and reporting of wbMRI studies in advanced PC were published in 2017, with excellent interobserver agreement [9,24]. A pilot study using wbMRI with DWI to assess the response of bone metastases to treatment in mCRPC showed that a decrease in tumor volume and an increase in median ADC for bone metastases can potentially be used to monitor the response to olaparib in this setting [25].

The proportion of patients with a MET-RADS-P response in our study is low, even among patients with a deep PSA response. Among the PSA responders, only 56% (nine of 16) in the mHNPC group and < 1% 3.5% in the mCRPC (one of 29) in the mCRPC group achieved an imaging response. The clinical significance of such residual metastatic disease is unknown but suggests that intensified hormonal treatment cannot eradicate PC. This is unsurprising and in line with several studies on neoadjuvant treatment before radical prostatectomy. For example, minimal residual disease was achieved in only 38% of the patients treated with degarelix and apalutamide in the ARNEO trial [26].

Importantly, wbMRI progression was seen in 66% of the patients who had a PSA response in the mCRPC group. This is not surprising, as nearly a quarter of 265 patients with radiographic progression and evaluable PSA levels in the enzalutamide arm of the PREVAIL trial had no rise in PSA [27]. Discordance between PSA and imaging responses has also been described in the ⁶⁸Ga-PSMA PET setting [28]. The discordance between PSA and imaging responses reinforces the clonal theory of castration resistance, according to which prostate cancer comprises two pools of AR-dependent and AR-independent cells. ADT and ARPIs selectively eradicate the AR-dependent PSA-expressing cells. This induces selective outgrowth of AR-independent cells, leading to further progression [29].

Han et al [30] performed a systematic review and meta-analysis of ten studies assessing the concordance of response evaluation using PSMA PET/CT findings and PSA levels after systemic treatment, and the association between PSMA PET/CT and OS in mCRPC. Two studies

reported a decrease in PSMA-derived tumor volume, which was associated with better OS. It is noteworthy that PSMA PET/CT and PSA response results were discordant in nearly a quarter of the patients with mCRPC; further studies are warranted to establish the clinical meaning of this discordance. This finding also suggests that different imaging modalities could be complementary; for example, for patients with PSMA-negative disease, wbMRI could allow better characterization of lesions showing metabolic and anatomic metastasis.

Much more reassuring is the observation that no wbMRI progression was observed among patients with mHNPC who experienced a PSA response to ≤ 0.2 ng/ml, as these patients are candidates for de-escalation strategies. The prognostic value of a partial response versus a complete response requires further study in a larger series.

Two recent prospective trials investigated the value of wbMRI in assessing treatment responses in metastatic PC, but neither of them used the MET-RADS-P criteria. Dalla Volta et al [31] used wbMRI to evaluate the bone response rate in 126 patients with mHSPC treated with ADT + enzalutamide. The wbMRI response was defined on the basis of lesion size, ADC, signal on b800 DWI, and the fat fraction. Complete and partial responses on imaging were correlated with lower risk of death. The authors did not evaluate the correlation between imaging and other parameters, such as PSA, for response assessment. The iPROMET study evaluated the correlation between changes in MRI parameters and response or time to progression in 55 patients with mCRPC treated with ARPIs [32]. Response was defined as either a response according to RECIST version 1.1 and/or a 50% decrease in PSA. A decrease in tumor volume and an increase in fat fraction in lesions on wbMRI after treatment were the most significant indicators of a longer response. Multivariate analysis revealed that higher-volume bone disease, lower fat fraction, and lower ADC were associated with a higher risk of progression.

Our results show that the MET-RADS-P RACs can be used in daily practice to monitor patients alongside PSA for more accurate assessment of treatment responses. In our small trial, MET-RADS-P results were correlated with OS and time to subsequent treatment in mHSPC and complemented the PSA response results in mCRPC. We recommend incorporation of MET-RADS-P in clinical studies for evaluation of its impact on oncological outcomes and for standardized reporting, which would allow comparison of results from different trials. The main limitation of our study is the small sample size, as this was a proof-of-concept study to design future clinical trials. The short follow-up period probably explains the short OS in the mHNPC cohort.

5. Conclusions

Our study confirms that the wbMRI response to modern hormonal therapy regimens in mHNPC and mCRPC can complement the PSA response assessment in a large subset of patients. This stresses the need to incorporate new imaging technologies in future escalation and de-escalation trials to better select patients and monitor treatment efficacy.

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Study concept and design: All authors.

Acquisition of data: Van Damme, Tombal, Van Nieuwenhove, Pasoglou, Lecouvet.

Analysis and interpretation of data: Van Damme, Tombal, Michoux, Padhani, Lecouvet.

Drafting of the manuscript: All authors.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.euo.2024.10.009>.

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9. Discussion and Future Directions

The landscape of PCa management has undergone a radical transformation over the past decade. Once a disease primarily monitored with serum biomarkers and bone scintigraphy, PCa is now managed in an era of biological precision, in which functional and molecular imaging play a central role ^{16,193}. The advent of modern imaging modalities (MIMs), notably WB-MRI and PSMA-PET/CT, has challenged long-standing diagnostic conventions. These technologies provide unprecedented insights into tumour biology, metastatic distribution, and treatment-response dynamics ¹⁸⁹.

Historically, therapeutic response in metastatic PCa has been monitored using PSA kinetics, alongside anatomical imaging and clinical evaluation. Although PSA remains valuable, it fails to capture the biological complexity of treatment resistance, particularly as tumours evolve towards androgen receptor (AR)-independent phenotypes. Consequently, many patients experience PSA-silent progression, with radiological or symptomatic progression despite stable or declining PSA levels. This discordance, well documented in trials such as PREVAIL, VISION, and, more recently, CAPitello-281, underscores the need for objective imaging biomarkers capable of quantifying disease burden and biological activity beyond PSA ^{159,194,195}.

WB-MRI and PSMA-PET/CT have each emerged as powerful, complementary tools addressing these limitations. Their respective advantages, WB-MRI's functional and quantitative tissue characterisation and PSMA PET's molecular specificity and sensitivity, define a new standard of disease monitoring that transcends the dichotomy between anatomic and biochemical assessment⁶².

9.1. Whole-body MRI: From anatomic to biological monitoring

WB-MRI provides a comprehensive, radiation-free assessment of bone, lymph node, and visceral diseases in a single scan. Its multiparametric approach, combining T1-weighted, fat-suppressed, and diffusion-weighted imaging (DWI),

quantifies changes in marrow composition and cellular density ³⁰. The development of the METastasis Reporting and Data System for PCa (MET-RADS-P) marks a significant advance towards standardisation, establishing protocols for acquisition, anatomical coverage, and structured reporting. MET-RADS-P extends beyond qualitative interpretation: it encourages quantitative evaluation using apparent diffusion coefficient (ADC) and fat fraction (FF) maps, which reflect microstructural changes in tumour cellularity and marrow fat content. These quantitative biomarkers are emerging as early indicators of treatment response, often preceding morphological regression ³⁵.

Multiple studies have shown that WB-MRI-derived progression correlates with survival outcomes, particularly in mHNPC ¹⁶⁸. In our prospective study, MET-RADS-P-defined progression independently predicted OS and time to subsequent treatment, outperforming PSA-based criteria. The strength of WB-MRI lies in its ability to visualise biological heterogeneity, capturing coexisting regressing and progressing lesions across skeletal and visceral compartments. This feature is particularly relevant in mCRPC, where selective clonal evolution leads to mixed responses within the same patient. WB-MRI thus enables a spatially resolved assessment of therapeutic efficacy, detecting emerging resistant clones that may not yet influence systemic biomarkers. The identification of isolated progression sites can inform metastasis-directed therapy (MDT), adaptive treatment intensification, or enrolment in molecularly guided clinical trials ⁶⁵.

Despite these advantages, the widespread integration of WB-MRI faces persistent barriers. Variability in scanner hardware, diffusion sequence parameters, and post-processing workflows undermines inter-site reproducibility. Quantitative parameters such as ADC remain sensitive to acquisition settings, necessitating harmonisation initiatives akin to those for standardised uptake values (SUVs) in PET. Furthermore, interpretative expertise remains a limiting factor. The complexity of WB-MRI datasets requires radiologists with subspecialised training in oncologic imaging. The incorporation

of AI and radiomics promises to alleviate these constraints by automating lesion segmentation, extracting texture-based biomarkers, and predicting treatment outcomes. In this context, WB-MRI is evolving from a primarily anatomical modality into a biological imaging platform, integrating quantitative, radiomic, and potentially radiogenomic information. Future directions include the development of response-adaptive imaging biomarkers trained on multicentric data harmonised through MET-RADS-P ¹⁸⁹.

9.2. PSMA-PET/CT: The molecular frontier of PCa imaging

PSMA-PET/CT exploits PSMA overexpression in PCa cells, providing a direct molecular signature of disease burden. Its exceptional sensitivity, detecting sub-centimetre nodal and skeletal lesions, has redefined staging across all phases of disease. In the metastatic setting, PSMA-PET enables quantitative assessment of whole-body tumour burden using volumetric indices, such as PSMA tumour volume (PSMA-TV) and total lesion PSMA expression (TL-PSMA). These parameters correlate with prognosis and treatment response, offering a molecular biomarker analogous to tumour metabolic volume in FDG-PET for other cancers ¹⁸². PSMA-PET has shown promising utility for response monitoring during AR-targeted therapy, radionuclide therapy (Lu-177-PSMA), and chemotherapy. The PROMISE and PSMA-RADS frameworks standardise lesion interpretation and facilitate longitudinal assessment. However, challenges remain: PSMA expression can be downregulated in dedifferentiated or neuroendocrine-transformed tumours, leading to false-negative scans despite clinical progression. Consequently, PSMA-PET-negative but metabolically active disease may require complementary imaging with WB-MRI or FDG-PET ^{51,53}.

Beyond lesion detection, PSMA PET enables measurement of radiomic signatures and the spatial and textural heterogeneity of PSMA uptake, which may be associated with tumour aggressiveness and AR-signalling status. When combined with WB-MRI quantitative parameters (ADC, FF), these radiomic

features form the basis of multi-parametric hybrid imaging biomarkers capable of distinguishing indolent from aggressive disease phenotypes.

9.3. Hybrid and AI-augmented imaging: The future of integration

The emergence of simultaneous PET/MRI systems represents the logical convergence of the two most advanced modalities in PCa imaging. PET/MRI enables the acquisition of PSMA-targeted molecular data alongside high-resolution anatomical and functional MRI sequences, producing perfectly co-registered datasets. This fusion enables simultaneous assessment of tumour metabolism, receptor expression, and microstructural integrity. PET/MRI could thus serve as the definitive response-monitoring platform, combining PSMA-TV and SUV-based molecular burden quantification; ADC and FF metrics of microenvironmental remodelling; and dynamic contrast- or diffusion-based perfusion metrics reflecting vascular normalisation.

Early studies indicate that combined PET/MRI metrics improve response prediction and correlate more strongly with overall survival than PET or MRI alone. Moreover, hybrid systems significantly reduce radiation exposure compared with PET/CT, making them suitable for serial monitoring in long-term management. ¹⁹⁶⁻¹⁹⁸

9.4. Radiomics, AI, and digital biomarkers

The convergence of radiomics and AI-driven analytics will redefine how imaging contributes to precision oncology. High-dimensional radiomic features extracted from WB-MRI and PSMA PET images capture complex patterns invisible to human observers. Machine learning algorithms trained on these data can predict PSA response, time to castration resistance, or survival outcomes ^{199,200}. The integration of imaging genomics (radiogenomics), linking imaging phenotypes to genomic alterations such as AR-V7, PTEN, or BRCA2 mutations, promises to transform WB-MRI and PSMA PET into non-invasive surrogates of molecular

profiling. In clinical practice, this would enable real-time monitoring of clonal evolution, guiding therapy adaptation long before clinical progression becomes apparent ²⁰⁰.

9.5. From research to clinical translation: Structural and economic challenges

Despite technological progress, structural inequities and economic barriers limit the widespread adoption of modern imaging. The cost of PSMA ligands and hybrid imaging infrastructure remains prohibitive across many healthcare systems. Even in high-income countries, access to PSMA PET and WB-MRI is often restricted to academic or tertiary centres, creating geographical disparities in care. Reimbursement policies vary widely. In many regions, PSMA PET and WB-MRI are not yet incorporated into national cost models, limiting use to research protocols or select patient groups. This lack of standard reimbursement prevents routine integration into treatment algorithms and restricts participation in multicentre trials ^{17,201}.

To overcome these challenges, international harmonisation efforts must prioritise: establishing validated multicentric acquisition standards (e.g., MET-RADS-P 2.0, PROMISE 2.0); creating centralised image repositories for federated AI training; and advocating for value-based reimbursement models that recognise the cost-effectiveness of early, accurate disease monitoring. Ultimately, the long-term economic advantage of MIMs lies not in reducing cost per scan, but in optimising therapeutic sequencing, avoiding ineffective treatments, and enabling precision-guided therapy ²⁰².

9.6. Regulatory validation and qualification as clinical trial endpoints

A critical next step towards integrating WB-MRI and PSMA PET into the therapeutic development continuum is their regulatory qualification as validated imaging biomarkers by agencies such as the U.S. Food and Drug Administration and the European Medicines Agency. Despite compelling evidence of their

diagnostic and prognostic utility, both modalities currently lack formal regulatory endorsement as surrogate endpoints in clinical trials. This gap limits their use for drug approval, therapeutic response monitoring, and adaptive trial design. For regulatory validation, imaging biomarkers must demonstrate analytical validity (technical consistency and reproducibility), clinical validity (strong correlation with clinical outcomes such as progression-free or overall survival), and clinical utility (evidence that their use improves decision-making or patient outcomes). Achieving this requires multicentre harmonisation of acquisition protocols, standardised interpretation frameworks (MET-RADS-P, PROMISE, PSMA-RADS), and robust quality control pipelines. The long-term vision is for WB-MRI and PSMA PET to become qualified regulatory endpoints, analogous to RECIST for solid tumours or PERCIST for FDG-PET ^{189,203}.

Such recognition would enable these modalities to serve as objective, quantifiable biomarkers in pivotal registration trials, thereby accelerating the evaluation of novel systemic therapies. Regulatory acceptance would also incentivise payer reimbursement, foster wider accessibility, and anchor these techniques as central tools within the evolving paradigm of precision oncology.

9.7. The future of response assessment in advanced PCa

The next decade will likely witness a paradigm shift in how therapeutic efficacy is measured. Traditional frameworks (RECIST 1.1 and PSA-based criteria) will be replaced by integrative response assessment models combining clinical, biochemical, and imaging biomarkers. WB-MRI and PSMA PET will play complementary roles in this ecosystem.

WB-MRI is poised to become a central tool in the biological monitoring of advanced PCa. As a primary biomarker of functional response, quantitative variations in ADC and FF values can serve as early indicators of cytoreduction and marrow normalisation, preceding conventional morphological changes. Its ability to characterise spatial heterogeneity across metastatic sites allows

precise mapping of mixed or focal responses, thereby guiding metastasis-directed and adaptive therapeutic strategies. The radiation-free nature of WB-MRI makes it ideally suited for longitudinal monitoring in patients receiving prolonged hormonal or radioligand therapy, enabling repeated assessment without cumulative exposure. Furthermore, advances in AI and radiomics are expanding the prognostic potential of WB-MRI by automating lesion segmentation, extracting high-dimensional features of tissue microstructure, and generating predictive models that stratify patients by risk of progression and survival outcomes. Collectively, these attributes position WB-MRI as a reproducible, quantitative, and biologically informative modality capable of capturing both global and localised treatment effects across the disease course¹³.

PSMA-PET/CT is emerging as a cornerstone of molecular monitoring for advanced PCa, offering unparalleled sensitivity for detecting and characterising disease at the microscopic level. It enables molecular residual disease detection, identifying subclinical tumour deposits that remain invisible to conventional imaging. As a theranostic platform, PSMA PET extends beyond diagnosis to directly guide and monitor targeted radionuclide therapies such as ¹⁷⁷Lu-PSMA and ²²⁵Ac-PSMA, creating a closed loop between imaging and treatment. Its capacity for quantitative treatment monitoring through serial measurements of PSMA tumour volume (PSMA-TV) and total lesion PSMA uptake (TL-PSMA) provides a robust molecular analogue of tumour burden, allowing objective correlation with clinical outcomes²⁰³. Furthermore, predictive imaging genomics derived from PSMA uptake heterogeneity may reveal underlying biological features such as androgen receptor signalling status or neuroendocrine differentiation, offering early insight into mechanisms of treatment resistance. Collectively, these capabilities position PSMA PET as both a sensitive molecular biomarker and a functional companion to therapeutic decision-making, bridging diagnosis, therapy selection, and longitudinal response evaluation within a unified imaging framework.

The optimal strategy for imaging in advanced PCa will not prioritise one modality over the other, but rather integrate PSMA PET and WB-MRI within a unified, multimodal response framework. The advent of hybrid PSMA PET/MRI systems operationalises this integration, enabling simultaneous acquisition of molecular and functional biomarkers within a single examination. Such technology not only enhances diagnostic precision and reduces patient burden but also provides a standardised platform for adaptive, biomarker-driven clinical trials, where imaging-derived biological endpoints can inform real-time treatment modification ¹⁸⁹.

This convergence represents a paradigm shift from sequential imaging to biologically integrated monitoring, forming the cornerstone of next-generation precision oncology.

9.8. A vision for clinical trials and precision oncology

Future pivotal studies should embed modern imaging endpoints prospectively. Imaging-informed strategies can be compared to conventional monitoring in randomised designs, evaluating whether earlier intervention based on imaging-detected progression improves survival or quality of life. Trials such as VISION, PSMAfore, ENZA-P, or PSMAAddition already illustrate this transition, incorporating PSMA imaging as both inclusion and response criteria ^{179,194,204,205}.

Beyond efficacy trials, imaging data will drive digital twin models, virtual representations of individual patients that simulate disease evolution under different therapies. These models will rely on longitudinal WB-MRI and PSMA PET biomarkers to predict treatment outcomes, enabling clinicians to dynamically personalise therapy pathways

10. Conclusion

This thesis has examined the impact of modern imaging modalities on the management of prostate cancer across the disease spectrum, with particular emphasis on whole-body MRI (WB-MRI) and PSMA-targeted PET imaging. The body of evidence reviewed demonstrates that these techniques substantially outperform conventional imaging in the detection of metastatic disease, characterisation of tumour burden, and identification of recurrence at earlier stages. Importantly, however, the clinical consequences of highly sensitive imaging extend well beyond improved diagnostic accuracy. The introduction of modern imaging profoundly reshapes disease classification, prognostication, and treatment decision-making. In particular, imaging-driven stage migration complicates the interpretation of historical datasets and limits comparability between clinical trials conducted across different imaging eras. These considerations underscore the need to contextualise clinical outcomes within the imaging framework used and caution against the assumption that earlier detection necessarily translates into improved long-term clinical benefit ^{19,193}.

A central theme of this thesis is the evolution of imaging from a predominantly diagnostic modality to a quantitative biomarker that informs treatment response and disease dynamics. In advanced prostate cancer, particularly in bone-predominant disease, conventional response criteria fail to adequately capture biologically meaningful changes. The integration of functional and quantitative imaging parameters, such as diffusion-weighted imaging metrics, marrow fat fraction, and PET-derived volumetric and uptake-based indices, offers a more objective assessment of tumour viability and therapeutic efficacy. Nonetheless, substantial variability in image acquisition, interpretation criteria, and reporting standards continues to limit widespread clinical adoption. Accordingly, this work highlights the critical importance of standardisation initiatives, including MET-RADS and PROMISE, as foundational steps toward reproducible, imaging-based endpoints in both clinical practice and research ^{35,51}.

Adherence to harmonised imaging protocols remains both a technical challenge and a major barrier to the integration of advanced imaging into routine oncological care. Although MET-RADS-P provides a robust framework for WB-MRI interpretation, its implementation is inconsistent across institutions and healthcare systems, reflecting broader disparities in infrastructure and expertise. Scanner heterogeneity, differences in coil configuration, variability in acquisition parameters, and divergent post-processing workflows all contribute to marked variability in image quality and diagnostic output. This heterogeneity undermines not only clinical reproducibility but also the feasibility of pooling imaging data across centres for multicentre clinical trials. PSMA PET/CT faces similar challenges. Despite the development of structured reporting systems such as PROMISE and PSMA-RADS, local reporting practices persist in many centres, resulting in inconsistent lesion characterisation and staging. This fragmentation introduces interpretive discontinuities across the care pathway, from initial diagnosis to treatment response assessment, and complicates multidisciplinary decision-making ¹⁸⁹.

The implications for biomarker development are a prominent focus of this thesis. Historically, therapeutic response in metastatic prostate cancer has been monitored primarily through PSA kinetics, supplemented by anatomical imaging and clinical assessment. While PSA remains a valuable biomarker, it inadequately reflects the biological complexity of treatment resistance, particularly as tumours evolve towards androgen receptor (AR)-independent phenotypes. As a result, a significant proportion of patients experience PSA-silent progression, with radiological or symptomatic disease progression occurring despite stable or declining PSA levels. This discordance, well documented in trials such as PREVAIL, VISION, and more recently CAPItello-281, highlights the need for objective imaging biomarkers capable of quantifying disease burden and biological activity beyond PSA alone ^{159,194,195}. Quantitative imaging biomarkers, including ADC values, marrow fat fraction, and PSMA tumour volume, show considerable promise for disease burden assessment and response evaluation; however, in the

absence of harmonised acquisition protocols and validated thresholds, their role remains exploratory ¹⁸⁹.

WB-MRI and PSMA-PET/CT have therefore emerged as powerful and complementary modalities that address many of these limitations. Their respective strengths, functional and quantitative tissue characterisation for WB-MRI, and molecular specificity and sensitivity for PSMA-PET, together define a new paradigm of disease monitoring that transcends the traditional dichotomy between anatomical and biochemical assessment ⁶².

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