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Review – Prostate Cancer – Editor's Choice

Managing Nonmetastatic Castration-resistant Prostate Cancer

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Abstract

Context: Patients with nonmetastatic castration-resistant prostate cancer (nmCRPC) have rising prostate-specific antigen (PSA) and castrate testosterone levels, with no radiological findings of metastatic disease on computed tomography and bone scan. Given recent drug approvals for nmCRPC, with many other therapeutics and imaging modalities being developed, management of nmCRPC is a rapidly evolving field that merits detailed investigation.

Objective: To review current nmCRPC management practices and identify opportunities for improving care of nmCRPC patients.

Evidence acquisition: A literature search up to July 2018 was conducted, including clinical trials and clinical practice guidelines (National Comprehensive Cancer Network, European Society for Medical Oncology, European Association of Urology, Prostate Cancer Clinical Trials Working Group, Prostate Cancer Radiographic Assessments for Detection of Advanced Recurrence). Keywords included prostate cancer, nonmetastatic, castration resistance, rising PSA, and biochemical relapse.

Evidence synthesis: Recommendations regarding indications for, and frequency of, imaging and PSA testing, as well as for initiating systemic therapy in nmCRPC are based on PSA rise kinetics and symptoms. Both enzalutamide and apalutamide have been shown to significantly increase metastasis-free survival in phase III placebo-controlled randomised trials in nmCRPC patients with PSA doubling time (DT) ≤ 10 mo. The expected impact of new imaging techniques in the assessment of nmCRPC is also reviewed.

Conclusions: nmCRPC is a heterogeneous disease; while observation may be an option for some patients, enzalutamide and apalutamide may be appropriate to treat nmCRPC patients with PSA-DT ≤ 10 mo. The emergence of more accurate imaging modalities as well as circulating tumour biomarker assays will likely redefine the assessment of nmCRPC in the near future.

Patient summary: Herein, we review key literature and clinical practice guidelines to summarise the optimal management of patients with prostate cancer and rising prostate-specific antigen despite castrate testosterone levels, but with no evidence of distant metastasis on traditional imaging. New drugs are being developed for this disease setting; novel imaging and tumour biomarker blood tests are likely to define this disease state more accurately.

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1. Introduction

Despite high cure rates after prostatectomy and/or radiation therapy, a proportion of patients with prostate cancer will suffer disease relapse. Since Huggins and Hodges [1] demonstrated the androgen-dependent nature of prostate cancer in the 1940s, androgen deprivation therapy (ADT) has become the mainstay for treating advanced disease. ADT is not curative for patients with metastatic disease, but usually induces disease regression and prostate-specific antigen (PSA) declines, which may be sustained for variable periods of time and is associated with prolongation of life when used together with radiation in men with high-risk localised disease. The role of early salvage ADT after PSA rise following local treatment is still a topic for debate [2,3], but if salvage ADT is used in men with biochemical relapse the disease nearly always re-emerges despite castrate levels of testosterone, resulting in biological transformation to what is known as castration-resistant prostate cancer (CRPC); however, evolution to CRPC can occur before the actual identification of metastases on conventional imaging.

This review summarises advances in the management of nonmetastatic CRPC (nmCRPC), including emerging data from clinical trials and clinical development of novel imaging techniques. Patients with nmCRPC are asymptomatic and have variable life expectancy; hence, careful consideration must be given to whether the therapeutic benefit outweighs the risks inherent to that specific therapy and its ability to improve patient outcome.

2. Evidence acquisition

A literature search for clinical trials and clinical studies up to July 2018 was conducted, including peer-reviewed publications available through PubMed and abstracts from major scientific conferences. Keywords included “prostate cancer”, “nonmetastatic”, “castration-resistance”, “rising PSA”, “biochemical relapse”. The latest versions of the European Society for Medical Oncology, National Comprehensive Cancer Network (NCCN), European Association of Urology, Prostate Cancer Radiographic Assessments for Detection of Advanced Recurrence (RADAR) and Prostate Cancer Working Group (PCWG) guidelines were reviewed.

3. Evidence synthesis

3.1. Current definition of nmCRPC

Prostate cancer progression is a continuous process despite discrete clinical states having been defined to subclassify the disease for therapeutic interventions, with pragmatic delineated biological and clinical milestones marking these transitions [4]. Progression during ADT defines a move to the castration-resistant state, with visualisation of distant disease by imaging being the landmark for the metastatic versus the nonmetastatic state.

Currently, the most accepted definition of progression on ADT is based on PSA increases and follows the PCWG3

consensus, primarily intended to define endpoints for clinical trial design [5]: a 25% increase from the nadir (considering a starting value of ≥ 1.0 ng/ml), with a minimum rise of 2 ng/ml, in the context of castrate testosterone values (<50 ng/dl). Guidelines from the European Association of Urology acknowledge that there is no accepted universal definition of PSA relapse, but usually the evidence of two consecutive PSA rises of >0.2 ng/ml are considered suggestive of progression [6]. PSA progression following ADT can occur prior to the detection of metastases in the presence of either (1) local recurrence in the prostate bed after prostatectomy or persistent local disease after radical radiation therapy, or (2) no detectable disease in the primary site, no detected involved lymph nodes by computed tomography (CT)/magnetic resonance imaging (MRI; lymph nodes ≤ 1.5 cm in the short axis in the pelvis are not considered), or no disease in bone or visceral organs. While both scenarios technically constitute a nonmetastatic and castration-resistant state, the term nmCRPC commonly refers to the latter situation, which will be the main focus of this review (Fig. 1). It needs to be noted that the clinical trials discussed herein included nmCRPC patients regardless of the presence or absence of residual or recurrent local disease. The conventional, and most commonly utilised, diagnostic imaging studies to define the nmCRPC state include technetium-99m diphosphonate scintigraphy (bone scan [BS]) for evaluating skeletal metastases, as well as CT of the chest, abdomen, and pelvis (or MRI if CT scanning is contraindicated); the potential role of more sensitive imaging modalities including prostate-specific membrane antigen (PSMA) positron emission tomography (PET) and whole-body MRI is discussed later in this manuscript.

Optimal disease monitoring in patients suffering from nmCRPC also remains controversial in routine clinical practice, with variable imaging re-evaluation strategies [6–9]. A consensus statement by the RADAR group suggested pursuing further BS and CT scan when the PSA level reaches 2 ng/ml, and, if this was negative, recommended repeating these again when the PSA level reaches 5 ng/ml and then again after every doubling of the PSA, based on PSA testing every 3 mo for asymptomatic men. They also recommended that this frequency should be altered for symptomatic patients, in whom clinical evolution should guide investigations regardless of PSA level [10].

Baseline PSA level, PSA velocity, and PSA doubling time (PSA-DT) have been associated with time to bone metastases, and bone metastasis-free survival (MFS) and overall survival (OS) from nmCRPC [11]; these parameters are commonly used to decide which nmCRPC patients should undergo imaging studies and the frequency of these.

3.2. Emerging options for systemic therapy

Prior to the recent prospective trials reported in 2018, it was estimated that one in three patients with nmCRPC would develop metastasis within 2 years of diagnosis, with baseline PSA and PSA rise kinetics independently predicting the risk of detection of metastasis [11]. The median survival

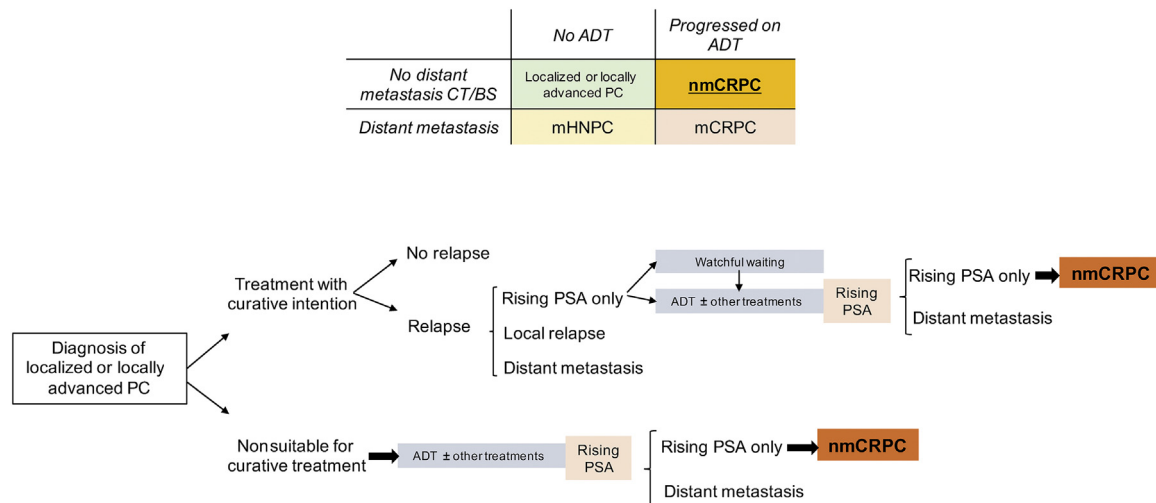


Fig. 1 – Schematic representation of disease evolution patterns to the clinical states of nonmetastatic castration-resistant prostate cancer (nmCRPC). ADT = androgen deprivation therapy; BS = bone scintigraphy; CT = computerised tomography; HNPC = hormone-naïve prostate cancer; CRPC = castration-resistant prostate cancer; mCRPC = metastatic castration-resistant prostate cancer; PC = prostate cancer; PSA = prostate specific antigen.

estimation for nmCRPC patients has clearly been impacted by the recent introduction of multiple life-extending therapies for mCRPC (abiraterone, enzalutamide, radium-223, and taxanes) and is nowadays probably beyond 4–5 yr based on the control arms of recent studies [12,13]. In recent years, several clinical trials have established the benefit of utilising abiraterone acetate and enzalutamide in earlier stages of disease [14–17]. As a result, both compounds are now used regularly in the prechemotherapy mCRPC state, with abiraterone recently being shown to also significantly impact the prognosis of patients with metastatic hormone-naïve prostate cancer. These data supported the evaluation of these drugs also in the nmCRPC setting.

3.2.1. Landmark trials in nmCRPC: PROSPER and SPARTAN

The evaluation of enzalutamide in the nmCRPC stage has recently achieved a significant milestone with the report of randomised phase III trial data. In a previous phase II study, 396 patients with either metastatic ($n = 257$) or nonmetastatic ($n = 130$) CRPC were randomised to receive enzalutamide or bicalutamide at progression on ADT. Among nmCRPC patients, the hazard ratio (HR) for radiological progression was 0.24 (95% confidence interval [CI] 0.10–0.56) favouring enzalutamide. Overall, 87.8% of nmCRPC patients were free of radiological progression after 2 years of enzalutamide therapy [18]. This was followed by a phase III, double-blind, randomised study of enzalutamide in nmCRPC (PROSPER) in 1401 patients (randomised 2:1 to enzalutamide:placebo; median PSA-DT prior to study entry = 3.6 mo) progressing on ADT with PSA-DT of ≤ 10 mo. Enzalutamide treatment resulted in significantly superior metastasis-free survival (MFS) (primary endpoint; median 36.6 mo for enzalutamide vs 14.7 mo for placebo; HR = 0.29; $p < 0.0001$; Table 1). These data led to the approval of enzalutamide by the Food and Drug Administration (FDA) for nmCRPC with PSA-DT of ≤ 10 mo in July 2018. In a preliminary analysis, differences in OS were not

significant (HR = 0.80, 95% CI 0.58–1.09, $p = 0.15$; median follow-up 22 mo); further analysis of more mature survival data are planned [19].

Apalutamide (ARN-509) was the first drug approved by the FDA for nmCRPC. Initially, a phase II single-arm study first evaluated apalutamide (a nonsteroidal androgen receptor [AR] inhibitor) in CRPC, including 51 nmCRPC patients with a high PSA level of >8 ng/ml and/or PSA-DT ≤ 10 mo. A majority of these cases (80%) were enrolled after having received ADT and at least one antiandrogen. The PSA50% response rate (primary endpoint) was 89% [20]. In 2018, a placebo-controlled double-blinded randomised phase III trial (SPARTAN), enrolling 1207 patients (median PSA-DT prior to study entry = 4.5 mo, inclusion criteria PSA-DT ≤ 10 mo), demonstrated superiority for apalutamide over placebo in MFS (median 40.5 vs 16.2 mo; HR = 0.28; $p < 0.0001$). Apalutamide was superior to placebo in all prespecified secondary endpoints, including time to metastasis, progression-free survival, and time to symptomatic progression ($p < 0.001$ for all comparisons). A first survival analysis showed an HR of 0.7 (95% CI 0.47–1.04, $p = 0.07$; median follow-up 20.3 mo) for apalutamide, although longer follow-up is needed [12].

The 2018 NCCN guideline update already includes the option of apalutamide as systemic therapy for PSA-DT ≤ 10 mo; it needs to be noted that this last update of the NCCN guidelines preceded the FDA approval of enzalutamide in this setting. Observation without therapeutic intervention should also be considered, particularly for PSA-DT ≥ 10 mo and/or when the patient is frail or unlikely to benefit due to limited life expectancy. Alternative secondary hormone therapy manoeuvres considered by the NCCN guidelines for patients with rapid PSA-DT include the addition or withdrawal of first-generation AR inhibitors, and the use of ketoconazole, corticosteroids, or oestrogens, although there is a lack of randomised trial data to support that these interventions would impact patient outcome [7,21].

Table 1 – Comparison of clinical trial design, endpoints, and main results of the two principal trials reported in nmCRPC: SPARTAN and PROSPER

		SPARTAN	PROSPER
Trial design	Key inclusion criteria	• nmCRPC by CT/BS • Rising PSA • Testosterone ≤ 50 ng/dl • Baseline PSA ≥ 2 ng/ml • PSA-DT ≤ 10 mo	• nmCRPC by CT/BS • Rising PSA • Testosterone ≤ 50 ng/dl • Baseline PSA ≥ 2 ng/ml • PSA-DT ≤ 10 mo
	Stratification factors	• PSA-DT > 6 vs ≤ 6 mo • Prior use of bone-sparing agents • Nodal disease (N0 vs N1) at trial entry	• PSA-DT > 6 vs ≤ 6 mo • Prior use of bone-sparing agents
	Primary endpoint	MFS, defined as time from randomisation to the first detection of distant metastasis on imaging or death from any cause	MFS, defined as time from randomisation to radiographic progression or death within 112 d of treatment discontinuation
	Key secondary endpoints	Time to metastasis, PFS, PFS2, time to symptomatic progression, overall survival	Time to PSA progression, time to first use of a new antineoplastic agent, time to chemotherapy, overall survival
Population	Experimental arm	Apalutamide + continued ADT ($n = 806$) Median PSA-DT 4.4 mo	Enzalutamide + continued ADT ($n = 933$) Median PSA-DT 3.8 mo
	Control arm	Placebo + continued ADT ($n = 401$) Median PSA-DT 4.5 mo	Placebo + continued ADT ($n = 468$) Median PSA-DT 3.6 mo
Efficacy	Primary endpoint—MFS exper. vs placebo	40.5 vs 16.5 mo HR 0.28 (95% CI 0.23–0.35), $p < 0.001$	36.6 vs 14.7 mo HR 0.29 (95% CI 0.24–0.35), $p < 0.001$
	Time to PSA progression	Median not reached for apalutamide group vs 3.7 mo for placebo group HR 0.06 (95% CI 0.05–0.08)	37.2 vs 3.9 mo HR 0.07 (95% CI 0.05–0.08), $p < 0.0001$
	Progression-free survival	40.5 vs 14.7 mo HR 0.29 (95% CI 0.24–0.36)	Not reported
	Interim analysis	Median not reached for apalutamide group vs 39 mo for placebo group	Median not reached for either group after median follow-up time of 22 mo
	Overall survival	HR 0.70 (95% CI 0.47–1.04), $p = 0.07$	HR 0.80 (95% CI 0.58–1.09), $p = 0.15$

ADT = androgen deprivation therapy; BS = bone scan; CI = confidence interval; CT = computed tomography; DT = doubling time; exper. = experiment; HR = hazard ratio; MFS = metastasis-free survival; nmCRPC = nonmetastatic castration-resistant prostate cancer; PFS = progression-free survival; PSA = prostate-specific antigen.

3.2.2. Other trials evaluating AR signalling targeting agents in nmCRPC

IMAAGEN was a phase II single-arm trial evaluating the antitumour activity of abiraterone acetate in nonmetastatic, post-ADT prostate cancer with rising PSA. With 122 evaluable patients, the primary endpoint analysis identified an 87% PSA50% decline rate. Preliminary analysis estimated that median time to radiographic evidence of disease progression on abiraterone for nmCRPC was 41.4 mo (95% CI 27–not reached) [22]. No randomised phase 3 trial testing abiraterone acetate has been conducted in men with nmCRPC.

The efficacy of darolutamide (ODM-201, BAY-1841788, a novel AR inhibitor) in men with high-risk nmCRPC is also being evaluated in the ARAMIS phase III trial (NCT02200614)—a double-blind, placebo-controlled study that has now completed accrual.

A single-arm phase II trial evaluated orteronel (TAK-700), a CYP17A inhibitor, in nonmetastatic prostate cancer. The trial population had short baseline PSA-DT (median 2.4 mo), indicating a high-risk population [23]. Median time to PSA progression and first detectable metastases were 13.8 and 25.4 mo, respectively, with six of 38 patients meeting the primary endpoint of PSA 0.2 after 3 mo of therapy [24]. The development of orteronel was halted after randomised phase III studies failed to demonstrate prolongation of OS in the mCRPC state.

3.3. Challenges of PSA testing: what does rising PSA really mean?

PSA is a peptidase and a downstream target gene of AR, and glucocorticoid receptor, signalling. Curiously, it is neither an antigen nor prostate specific, being expressed in other tissues, including the female breast gland, at lower concentrations. In healthy conditions, it is primarily secreted by epithelial prostate cells, but its transcriptional regulation by AR makes it a biomarker of AR signalling in tumours, resulting in its application in prostate cancer management. Whether PSA is just a messenger or also has a direct impact on prostate cancer pathogenesis is still unclear.

In the setting of nmCRPC, when no disease is detectable by conventional imaging tests, PSA testing indirectly monitors tumour AR signalling activity, which can correlate with disease burden. However, it must be noted that PSA declines are not proven surrogate biomarkers of survival outcome and that downregulation of AR signalling does not always represent tumour cell elimination, and indeed it is well recognised that some aggressive prostate cancers are low PSA secretors [25,26]. In the nmCRPC state, more data are needed to demonstrate that slowing of PSA velocity, or achievement of a greater PSA decline in the nmCRPC state, is associated with meaningful benefit in terms of extending survival or improving quality of life. In the SPARTAN trial, a 50% PSA decline was associated with a significant reduction

in the risk of clinical deterioration, based on patient-reported outcomes and health-related quality-of-life questionnaires [27]. PSA-DT in nmCRPC has, however, been associated with prognosis; trials evaluating inhibition of bone turnover with the endothelin antagonist atrasentan [28] and RANK ligand inhibition with denosumab [29] evaluated PSA changes in the nmCRPC state and their association with outcome. Briefly, neither drugs demonstrated an improvement in OS, although denosumab significantly prolonged bone-metastasis-free survival (HR = 0.85 [95% CI 0.73–0.98], $p = 0.028$) compared with placebo. In the atrasentan trial, PSA-DT was longer in the active treatment arm than in the placebo arm ($p = 0.031$), but this did not translate into significant prolongation of time to progression (671 vs 764 d; $p = 0.288$) or OS (HR = 0.92 [95% CI 0.77–1.10], $p = 0.22$). Importantly, an analysis of the placebo arm in the denosumab trial correlated PSA-DT with patient outcome, identifying a higher relative risk of bone metastasis or death for patients with PSA-DT shorter than 8 mo [30].

3.4. Clinical trial endpoints and clinical benefit in nmCRPC

3.4.1. MFS and clinical benefit

Measuring the magnitude of clinical benefit derived from a therapy in patients with no radiological evidence of metastatic disease and clinical symptoms has been a major challenge for developing novel therapeutic strategies in nmCRPC. The recent PROSPER and SPARTAN trials, as well as the ongoing ARAMIS trial, have used prolongation of time to metastatic disease visible by CT and BS as a primary endpoint (MFS).

The approval granted by the FDA to apalutamide and enzalutamide in nmCRPC is the first ever based on MFS benefit in prostate cancer and sets a precedent for a paradigm change in prostate cancer clinical trials. While certainly the true clinical benefit of delaying an asymptomatic radiographic event is yet to be fully defined, MFS as an intermediate endpoint supported by secondary analyses can now be assumed to accelerate FDA approval of prostate cancer drugs, compared to waiting for the gold-standard OS data. It remains to be seen whether other regulators will view MFS in the same light.

When evaluating trials conducted in the adjuvant setting, an improvement in 5-yr MFS has been shown to be a surrogate for OS in patients with intermediate- and high-risk, and clinically localised prostate cancer [31]. However, these data cannot be extrapolated to nmCRPC. Conceptually, MFS in the localised hormone-naïve cancer setting involves prevention of the development of any metastasis after a therapy with curative intent, but in the nmCRPC setting, MFS involves delaying of the appearance of a greater (ie, visible on imaging) burden of established metastatic disease probably already present but occult due to insensitive conventional imaging. Exploratory landmark analysis in patients who developed metastases after 6, 9, and 12 mo in the SPARTAN trial suggests that an association between MFS and OS may be also present in nmCRPC (Spearman's correlation coefficient: 0.62; $p < 0.0001$) [32], but determination of OS surrogacy for MFS in nmCRPC will

probably require a meta-analysis of individual patient data from all nmCRPC phase 3 trials.

Notably, MFS was associated with improvements in health-related quality of life in seven of 10 scoring systems analysed in the PROSPER study [27]. Apalutamide also resulted in a 55% reduction in the risk of symptomatic progression (skeletal events, pain progression, or other clinically relevant symptoms) in the SPARTAN trial. Quality-of-life data after treatment discontinuation is expected to assess whether delaying time to metastasis detection associates with significant deferment in symptom development.

3.4.2. What are the benefits and risks of treating nmCRPC rather than mCRPC?

An unmet need in clinical trials for nmCRPC is evaluating not only the clinical benefits of an intervention, but also the additional benefit derived from pursuing such interventions at the nmCRPC stage rather than at a later time point. The implications of treatment intensification in the asymptomatic nmCRPC stage also need to account particularly for the long-term toxicities of earlier and therefore longer drug administration, as well as the associated economic implications. In the PROSPER study, 5% and 3% of patients in the enzalutamide cohort suffered grade 3 hypertension and fatigue, respectively, compared with 2% and 1% in the placebo group. In the SPARTAN trial, grade 3–4 rash (5.2% vs 0.3%), falls (1.7% vs 0.8%), and fractures (2.7% vs 0.8%) were more common in the apalutamide arm.

Health-economic issues also need to be considered; there is an urgent need for studies analysing the impact of earlier treatment on healthcare costs, taking into consideration drug costs and the benefits of delaying disease progression, as well as drug- and disease-related adverse events, and the economic benefit of improving quality of life. These studies are necessary but challenging as costs and “willingness-to-pay” thresholds differ between countries and healthcare systems. A similar issue is being faced with the recent successful pivotal trials of abiraterone and docetaxel in the hormone-naïve metastatic prostate cancer setting [33].

Assessing the impact of earlier versus later intervention can be fully validated only by conducting prospective trials with direct comparison of these strategies, where the impact on survival and quality of life of pursuing the same therapeutic strategy at nmCRPC or mCRPC is compared. In the meantime, a more mature analysis of OS data from the PROSPER and SPARTAN trials, where a proportion of patients in the placebo arms received enzalutamide later in the course of the disease could, at least in part, be informative. For now, the trend towards an improvement in OS as a supportive secondary endpoint indicates that at least there is no suggestion of truncation of survival with early use of these agents.

3.4.3. Can we define a concept of “molecular residual disease” or micrometastatic state using circulating tumour cell counts and ctDNA? (Anatomical M0 vs biological M0)

Several studies have indicated the prognostic utility of circulating tumour cell counts, and more recently also of ctDNA, and the utility of a change in these parameters as a response biomarker for metastatic prostate cancer

[34–36]. The burden of circulating tumour material in patients with localised prostate cancer seems to be very low with current detection techniques [37], but if present, detection of disseminated tumour cells may be associated with a greater risk of metastatic disease [38]. Identification of “molecularly detectable residual disease” from circulating tumour material or bone micrometastasis in nmCRPC could help stratify nmCRPC patients based on the risk of relapse and for treatment intensification. A particular challenge for the use of ctDNA in prostate cancer is the lack of highly recurrent truncal mutations that would enable very focused assessment (eg, ctDNA assessment of only KRAS and TP53 in pancreatic adenocarcinoma).

3.5. New imaging modalities will redefine the classification of prostate cancer

Clinical trial data for nmCRPC also have to be interpreted in light of the diagnostic tools used to classify patients as

nonmetastatic. The current standard imaging techniques for evaluation of distant metastasis in patients with rising PSA are CT and BS, and these have limited accuracy to detect prostate cancer dissemination to lymph nodes and bone. CT has limited sensitivity for the detection of metastatic lymph nodes (42% [95% CI 26–56%] in a pooled analysis of 18 clinical studies) [39]. A recent meta-analysis has shown that BS has a sensitivity of 79% and specificity of 82% for detecting bone metastases at single-patient level [40]. Development of more sensitive molecular and functional imaging is likely to help define the true extent of disease, detect small foci of relapse, and shrink the size of the true nmCRPC population. It is critical that more sensitive imaging assays undergo the same level of scrutiny as predictive biomarker and drug development strategies to enable their clinical qualification. Critically, the clinical relevance of identifying metastatic lesions not detected by CT and BS requires further evaluation in clinical trials as axioms from nmCRPC trials cannot be extrapolated if the

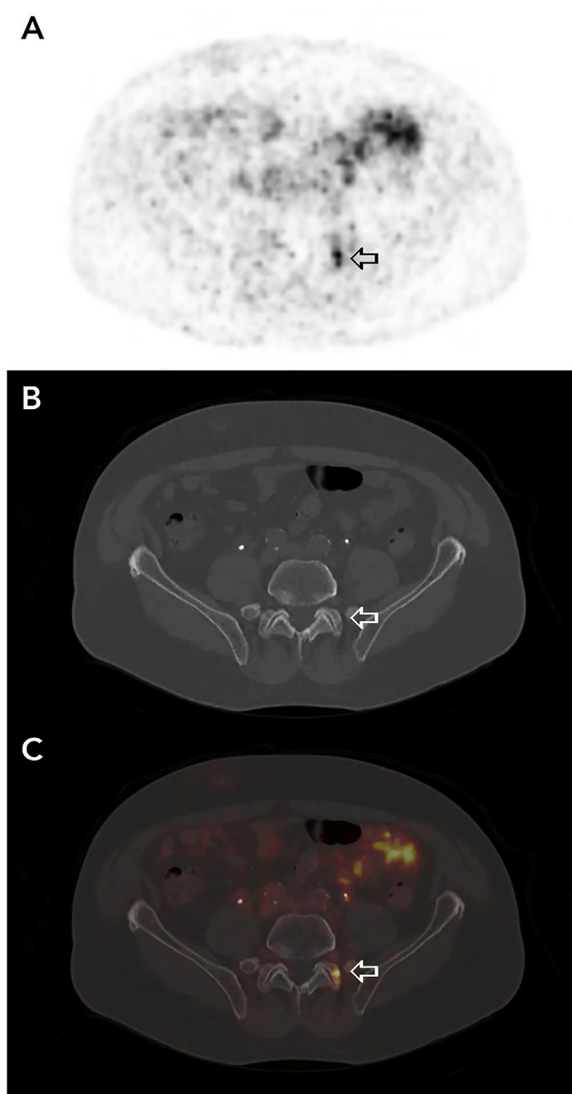


Fig. 2 – Axial section of Ga-68-PSMA-PET (A) identifying a small sacral bone metastasis in a patient with rising PSA on ADT with no metastatic disease detected by CT (B) or bone scan. (C) PET/CT fusion images, with the arrow pointing at the metastatic deposit. CT = computed tomography; PET = positron emission tomography; PSA = prostate specific antigen; PSMA = prostate-specific membrane antigen.

definition of nmCRPC changes is based on these more sensitive imaging modalities (eg, PSMA PET and whole-body MRI).

Pelvic multiparametric magnetic resonance imaging (mpMRI) with anatomical and functional sequences is also changing traditional approaches to prostate cancer diagnosis [41] and is more sensitive at detecting local relapse after radical prostatectomy [42]. For the detection of distant metastases in the nmCRPC setting, whole-body coverage may be needed. Whole-body MRI is more sensitive at detecting bone metastases than BS and CT approaches [43]. Diffusion-weighted imaging (DWI) is a functional MRI technique studying the random movement of water molecules within a tissue; DWI with whole-body MRI accurately depicts disease in solid organs with high sensitivity for bone metastasis detection [44], although this is less sensitive in detecting the involvement of small lymph nodes.

PET with a wide variety of radiopharmaceuticals has also been utilised to assess nodal and bone infiltration by prostate cancer. The most commonly used radiopharmaceutical for any type of cancer assessment, ^{18}F -fluorodeoxyglucose (FDG), performs poorly in metastatic prostate cancer detection probably due to the lack of glucose avidity in hormone-sensitive and/or small prostate cancer lesions [45]. PET/CT with ^{11}C -choline has been reported to have a sensitivity of 73% and specificity of 88% for detecting postprostatectomy, clinically suspected, recurrent disease [46]. Nevertheless, in a study of patients with rising PSA after prostatectomy, mpMRI was reported to be superior at detecting local recurrence, while ^{11}C -choline PET/CT was superior at detecting pelvic nodal metastases; both were equally accurate for detecting pelvic bone metastasis [47].

Other PET tracers under evaluation include NaF; F-18-fluciclovine, more developed in the context of detecting recurrences for imaging in the hormone-naïve setting [48]; and ^{68}Ga -PSMA. PSMA-PET/CT seems more sensitive than other radiotracers at detecting metastases, although concerns remain about heterogeneous PSMA expression in prostate cancers [49–51] (Fig. 2). In retrospective analyses of 1007 consecutive cases with biochemical recurrence scanned with ^{68}Ga -PSMA PET/CT, 79.5% had a least one lesion indicating recurrent disease [52]. The probability of positive PSMA-PET increased significantly with higher PSA levels, an association identified in other studies [53]. Only 24% of these patients had previously received ADT. Prior to direct extrapolation of data to the nmCRPC space, we need to better understand how AR signalling, ADT, and the development of castration resistance modulate PSMA expression, with studies of PSMA-PET/CT in nmCRPC [54,55].

These novel imaging modalities are increasingly available to clinicians, primarily in academic centres, but axioms from recent nmCRPC trials cannot be extrapolated if the definition of nmCRPC changes. It is critical that the clinical relevance of identifying metastatic lesions by PET/CT or whole-body MRI, not detectable by CT and BS, undergoes proper scrutiny in clinical trials so that these new imaging modalities are clinically qualified to guide clinical decisions.

4. Conclusions

Nonmetastatic CRPC is a heterogeneous state defined by rising PSA and insensitive imaging. The emergence of improved imaging including PSMA-PET/CT and whole-body MRI, and novel circulating tumour biomarker assays can redefine the prostate cancer management landscape. Interpretation of clinical trial data in this setting will need to account for this, as past data based on established imaging cannot be extrapolated to future practice. Apalutamide and enzalutamide have been shown to significantly increase time to detectable metastases by BS and CT scan. Although further indicators of clinical benefit are awaited, these data are impacting the landscape of prostate cancer care.

Author contributions: Johann S. de Bono had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Mateo, Fizazi, de Bono.

Acquisition of data: Mateo.

Analysis and interpretation of data: All authors.

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References

- [1] Huggins C, Hodges CV. Studies on prostatic cancer. I. The effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. *Cancer Res* 1941;1:293–7.
- [2] Duchesne GM, Woo HH, Bassett JK, et al. Timing of androgen-deprivation therapy in patients with prostate cancer with a rising PSA (TROC 03.06 and VCOG PR 01-03 [TOAD]): a randomised, multicentre, non-blinded, phase 3 trial. *Lancet Oncol* 2016;17:727–37.
- [3] Carrie C, Hasbini A, de Laroche G, et al. Salvage radiotherapy with or without short-term hormone therapy for rising prostate-specific antigen concentration after radical prostatectomy (GETUG-AFU 16): a randomised, multicentre, open-label phase 3 trial. *Lancet Oncol* 2016;17:747–56.
- [4] Attard G, Parker C, Eeles RA, et al. Prostate cancer. *Lancet* 2016;387:70–82.
- [5] Scher HI, Morris MJ, Stadler WM, et al. Trial design and objectives for castration-resistant prostate cancer: updated recommendations from the Prostate Cancer Clinical Trials Working Group 3. *J Clin Oncol* 2016;34:1402–18.
- [6] Mottet N, Bellmunt J, Briers E, Bolla M, Bourke L, Cancer EESGoP. EAU–ESTRO–ESUR–SIOG guidelines on prostate cancer. In: Office EG, editor. <https://uroweb.org/guideline/prostate-cancer/2018>.
- [7] NCCN. NCCN guidelines, prostate cancer (v2.2018). https://www.nccn.org/professionals/physician_gls/PDF/prostate.pdf2018.
- [8] Parker C, Gillessen S, Heidenreich A, Horwich A, Committee EG. Cancer of the prostate: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2015;26:69–77.
- [9] Gillessen S, Attard G, Beer TM, et al. Management of patients with advanced prostate cancer: the report of the advanced prostate cancer consensus conference APCCC 2017. *Eur Urol* 2018;73:178–211.
- [10] Crawford ED, Stone NN, Yu EY, et al. Challenges and recommendations for early identification of metastatic disease in prostate cancer. *Urology* 2014;83:664–9.
- [11] Smith MR, Kabbinnar F, Saad F, et al. Natural history of rising serum prostate-specific antigen in men with castrate nonmetastatic prostate cancer. *J Clin Oncol* 2005;23:2918–25.
- [12] Smith MR, Saad F, Chowdhury S, et al. Apalutamide treatment and metastasis-free survival in prostate cancer. *N Engl J Med* 2018;378:1408–18.
- [13] Madan RA, Gulley JL, Schlom J, et al. Analysis of overall survival in patients with nonmetastatic castration-resistant prostate cancer treated with vaccine, nilutamide, and combination therapy. *Clin Cancer Res* 2008;14:4526–31.
- [14] Fizazi K, Tran N, Fein L, et al. Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. *N Engl J Med* 2017;377:352–60.
- [15] James ND, de Bono JS, Spears MR, et al. Abiraterone for prostate cancer not previously treated with hormone therapy. *N Engl J Med* 2017;377:338–51.
- [16] Ryan CJ, Smith MR, Fizazi K, et al. Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naïve men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. *Lancet Oncol* 2015;16:152–60.
- [17] Beer TM, Armstrong AJ, Rathkopf DE, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. *N Engl J Med* 2014;371:424–33.
- [18] Penson DF, Armstrong AJ, Concepcion R, et al. Enzalutamide versus bicalutamide in castration-resistant prostate cancer: the STRIVE trial. *J Clin Oncol* 2016;34:2098–106.
- [19] Hussain M, Fizazi K, Saad F, et al. Enzalutamide in men with nonmetastatic, castration-resistant prostate cancer. *N Engl J Med* 2018;378:2465–74.
- [20] Smith MR, Antonarakis ES, Ryan CJ, et al. Phase 2 study of the safety and antitumor activity of apalutamide (ARN-509), a potent androgen receptor antagonist, in the high-risk nonmetastatic castration-resistant prostate cancer cohort. *Eur Urol* 2016;70:963–70.
- [21] Lodde M, Lacombe L, Fradet Y. Salvage therapy with bicalutamide 150 mg in nonmetastatic castration-resistant prostate cancer. *Urology* 2010;76:1189–93.
- [22] Ryan CJ, Crawford ED, Shore ND, et al. IMAAGEN trial safety and efficacy update: Effect of abiraterone acetate and low-dose prednisone on prostate-specific antigen and radiographic disease progression in patients with nonmetastatic castration-resistant prostate cancer. *J Clin Oncol* 2016;34(suppl):5061.
- [23] Saad F, Fizazi K, Jinga V, et al. Orteronel plus prednisone in patients with chemotherapy-naïve metastatic castration-resistant prostate cancer (ELM-PC 4): a double-blind, multicentre, phase 3, randomised, placebo-controlled trial. *Lancet Oncol* 2015;16:338–48.
- [24] Hussain M, Corn PG, Michaelson MD, et al. Phase II study of single-agent orteronel (TAK-700) in patients with nonmetastatic castration-resistant prostate cancer and rising prostate-specific antigen. *Clin Cancer Res* 2014;20:4218–27.
- [25] Wenisch JM, Mayr FB, Spiel AO, Radicioni M, Jilma B, Jilma-Stohlawetz P. Androgen deprivation decreases prostate specific antigen in the absence of tumor: implications for interpretation of PSA results. *Clin Chem Lab Med* 2014;52:431–6.
- [26] Halabi S, Armstrong AJ, Sartor O, et al. Prostate-specific antigen changes as surrogate for overall survival in men with metastatic castration-resistant prostate cancer treated with second-line chemotherapy. *J Clin Oncol* 2013;31:3944–50.
- [27] Attard G, Saad F, Tombal B, et al. Health-related quality of life (HRQoL) deterioration and pain progression in men with non-metastatic castration-resistant prostate cancer (M0 CRPC): results from the PROSPER study. *J Clin Oncol* 2018;36:5010.
- [28] Nelson JB, Love W, Chin JL, et al. Phase 3, randomized, controlled trial of atrasentan in patients with nonmetastatic, hormone-refractory prostate cancer. *Cancer* 2008;113:2478–87.
- [29] Smith MR, Saad F, Coleman R, et al. Denosumab and bone-metastasis-free survival in men with castration-resistant prostate cancer: results of a phase 3, randomised, placebo-controlled trial. *Lancet* 2012;379:39–46.
- [30] Smith MR, Saad F, Oudard S, et al. Denosumab and bone metastasis-free survival in men with nonmetastatic castration-resistant prostate cancer: exploratory analyses by baseline prostate-specific antigen doubling time. *J Clin Oncol* 2013;31:3800–6.
- [31] Xie W, Regan MM, Buyse M, et al. Metastasis-free survival is a strong surrogate of overall survival in localized prostate cancer. *J Clin Oncol* 2017;35:3097–104.

- [32] Smith MR, Mehra M, Nair S, Lawson J, Small EJ. Association of metastasis-free survival (MFS) and overall survival (OS) in nonmetastatic castration-resistant prostate cancer (nmCRPC). *J Clin Oncol* 2018;36(suppl):5032.
- [33] Ramamurthy C, Correa A, Handorf E, Beck R, Geynisman D. Cost-effectiveness analysis of abiraterone acetate (AA) versus docetaxel (D) for the management of metastatic hormone naïve prostate cancer (mHNPc). *J Clin Oncol* 2018;36:6514.
- [34] de Bono JS, Scher HI, Montgomery RB, et al. Circulating tumor cells predict survival benefit from treatment in metastatic castration-resistant prostate cancer. *Clin Cancer Res* 2008;14:6302–9.
- [35] Thalgott M, Rack B, Maurer T, et al. Detection of circulating tumor cells in different stages of prostate cancer. *J Cancer Res Clin Oncol* 2013;139:755–63.
- [36] Mehra N, Dolling D, Sumanasuriya S, et al. Plasma cell-free DNA concentration and outcomes from taxane therapy in metastatic castration-resistant prostate cancer from two phase III trials (FIRST-ANA and PROSELICA). *Eur Urol*. In press. <http://ds.doi.org/10.1016/j.eururo.2018.02.013>.
- [37] Chalfin HJ, Glavaris SA, Malihi PD, et al. Prostate cancer disseminated tumor cells are rarely detected in the bone marrow of localized patients undergoing radical prostatectomy across multiple rare cell detection platforms. *J Urol* 2018;199:1494–501.
- [38] Morgan TM, Lange PH, Porter MP, et al. Disseminated tumor cells in prostate cancer patients after radical prostatectomy and without evidence of disease predicts biochemical recurrence. *Clin Cancer Res* 2009;15:677–83.
- [39] Hovels AM, Heesakkers RA, Adang EM, et al. The diagnostic accuracy of CT and MRI in the staging of pelvic lymph nodes in patients with prostate cancer: a meta-analysis. *Clin Radiol* 2008;63:387–95.
- [40] Shen G, Deng H, Hu S, Jia Z. Comparison of choline-PET/CT, MRI, SPECT, and bone scintigraphy in the diagnosis of bone metastases in patients with prostate cancer: a meta-analysis. *Skelet Radiol* 2014;43:1503–13.
- [41] Kasivisvanathan V, Rannikko AS, Borghi M, et al. MRI-targeted or standard biopsy for prostate-cancer diagnosis. *N Engl J Med* 2018;378:1767–77.
- [42] Sandgren K, Westerlinck P, Jonsson JH, et al. Imaging for the detection of locoregional recurrences in biochemical progression after radical prostatectomy—a systematic review. *Eur Urol Focus*. In press. <https://doi.org/10.1016/j.euf.2017.11.001>.
- [43] Pasoglou V, Larbi A, Collette L, et al. One-step staging of high-risk prostate cancer using magnetic resonance imaging (MRI): toward an upfront simplified “all-in-one” imaging approach? *Prostate* 2014;74:469–77.
- [44] Lecouvet FE, El Mouedden J, Collette L, et al. Can whole-body magnetic resonance imaging with diffusion-weighted imaging replace Tc 99m bone scanning and computed tomography for single-step detection of metastases in patients with high-risk prostate cancer? *Eur Urol* 2012;62:68–75.
- [45] Salminen E, Hogg A, Binns D, Frydenberg M, Hicks R. Investigations with FDG-PET scanning in prostate cancer show limited value for clinical practice. *Acta Oncol* 2002;41:425–9.
- [46] Reske SN, Blumstein NM, Glatting G. [11C]choline PET/CT imaging in occult local relapse of prostate cancer after radical prostatectomy. *Eur J Nucl Med Mol Imaging* 2008;35:9–17.
- [47] Kitajima K, Murphy RC, Nathan MA, et al. Detection of recurrent prostate cancer after radical prostatectomy: comparison of 11C-choline PET/CT with pelvic multiparametric MR imaging with endorectal coil. *J Nucl Med* 2014;55:223–32.
- [48] Nanni C, Zanoni L, Pultrone C, et al. (18)F-FACBC (anti1-amino-3-(18)F-fluorocyclobutane-1-carboxylic acid) versus (11)C-choline PET/CT in prostate cancer relapse: results of a prospective trial. *Eur J Nucl Med Mol Imaging* 2016;43:1601–10.
- [49] Afshar-Oromieh A, Zechmann CM, Malcher A, et al. Comparison of PET imaging with a (68)Ga-labelled PSMA ligand and (18)F-choline-based PET/CT for the diagnosis of recurrent prostate cancer. *Eur J Nucl Med Mol Imaging* 2014;41:11–20.
- [50] Morigi JJ, Stricker PD, van Leeuwen PJ, et al. Prospective comparison of 18F-fluoromethylcholine versus 68Ga-PSMA PET/CT in prostate cancer patients who have rising PSA after curative treatment and are being considered for targeted therapy. *J Nucl Med* 2015;56:1185–90.
- [51] Schwenck J, Rempp H, Reischl G, et al. Comparison of (68)Ga-labelled PSMA-11 and (11)C-choline in the detection of prostate cancer metastases by PET/CT. *Eur J Nucl Med Mol Imaging* 2017;44:92–101.
- [52] Afshar-Oromieh A, Holland-Letz T, Giesel FL, et al. Diagnostic performance of (68)Ga-PSMA-11 (HBED-CC) PET/CT in patients with recurrent prostate cancer: evaluation in 1007 patients. *Eur J Nucl Med Mol Imaging* 2017;44:1258–68.
- [53] Verburg FA, Pfister D, Heidenreich A, et al. Extent of disease in recurrent prostate cancer determined by [(68)Ga]PSMA-HBED-CC PET/CT in relation to PSA levels, PSA doubling time and Gleason score. *Eur J Nucl Med Mol Imaging* 2016;43:397–403.
- [54] Hope TA, Truillet C, Ehman EC, et al. 68Ga-PSMA-11 PET imaging of response to androgen receptor inhibition: first human experience. *J Nucl Med* 2017;58:81–4.
- [55] Meller B, Bremmer F, Sahlmann CO, et al. Alterations in androgen deprivation enhanced prostate-specific membrane antigen (PSMA) expression in prostate cancer cells as a target for diagnostics and therapy. *EJNMMI Res* 2015;5:66.