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Original articles

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 $\leq$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 (κ = 0.30) but none to slight in mCRPC (κ = 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.

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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 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.

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 $\geq$1.5 cm on the short axis or soft tissue lesions $\geq$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 PSA $\leq$0.2 ng/ml in mHNPC and a decrease of $\geq$50% from the pretreatment level in mCRPC [5,7].

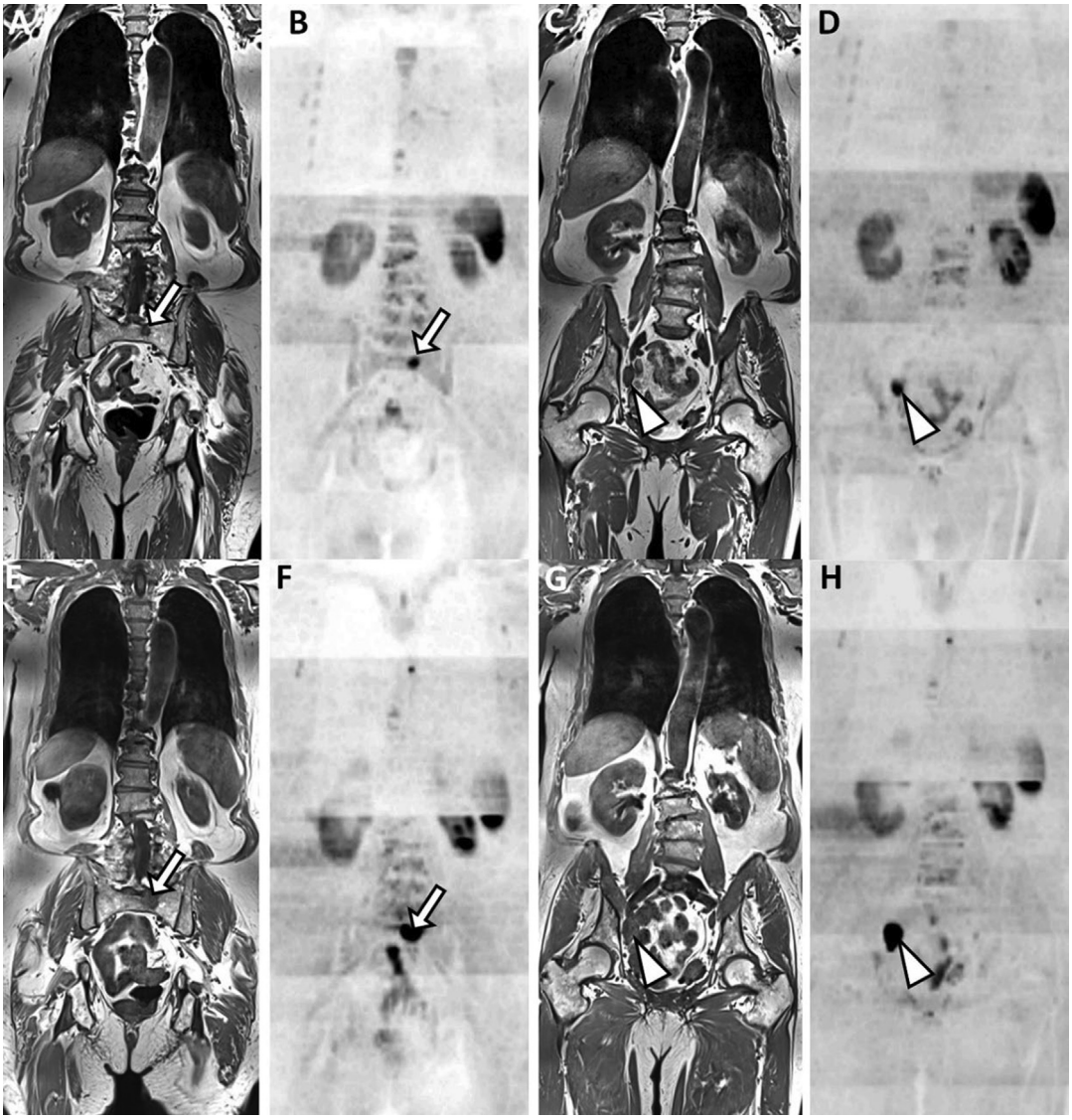

Fig. 1 – Progression of bone and node metastases in a 77-yr-old man with metastatic hormone-naïve prostate cancer (response assessment category 5). Comparison of whole-body magnetic resonance imaging before and after treatment. (A,C) Coronal T1-weighted images and (B,D) DWI scans (b = 1000 s/mm^2, inverted 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.

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 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

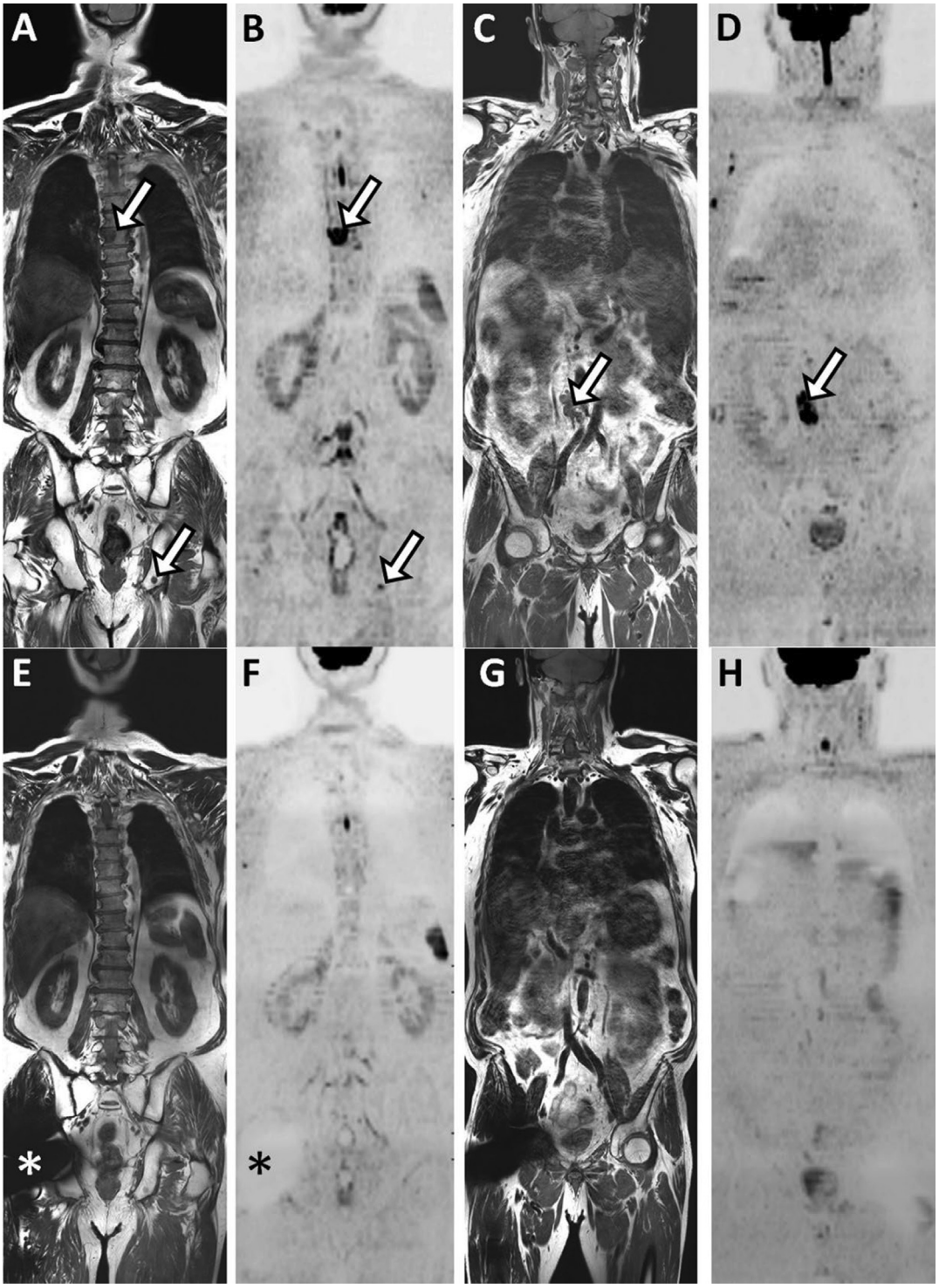

Fig. 2 – Response of bone and node metastases in a 73-yr-old man with metastatic hormone-naïve prostate cancer (response assessment category 1). Comparison of whole-body magnetic resonance imaging before and after treatment. (A,C) Coronal T1-weighted images and (B,D) DWI scans (b = 1000 s/mm^2, inverted 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.

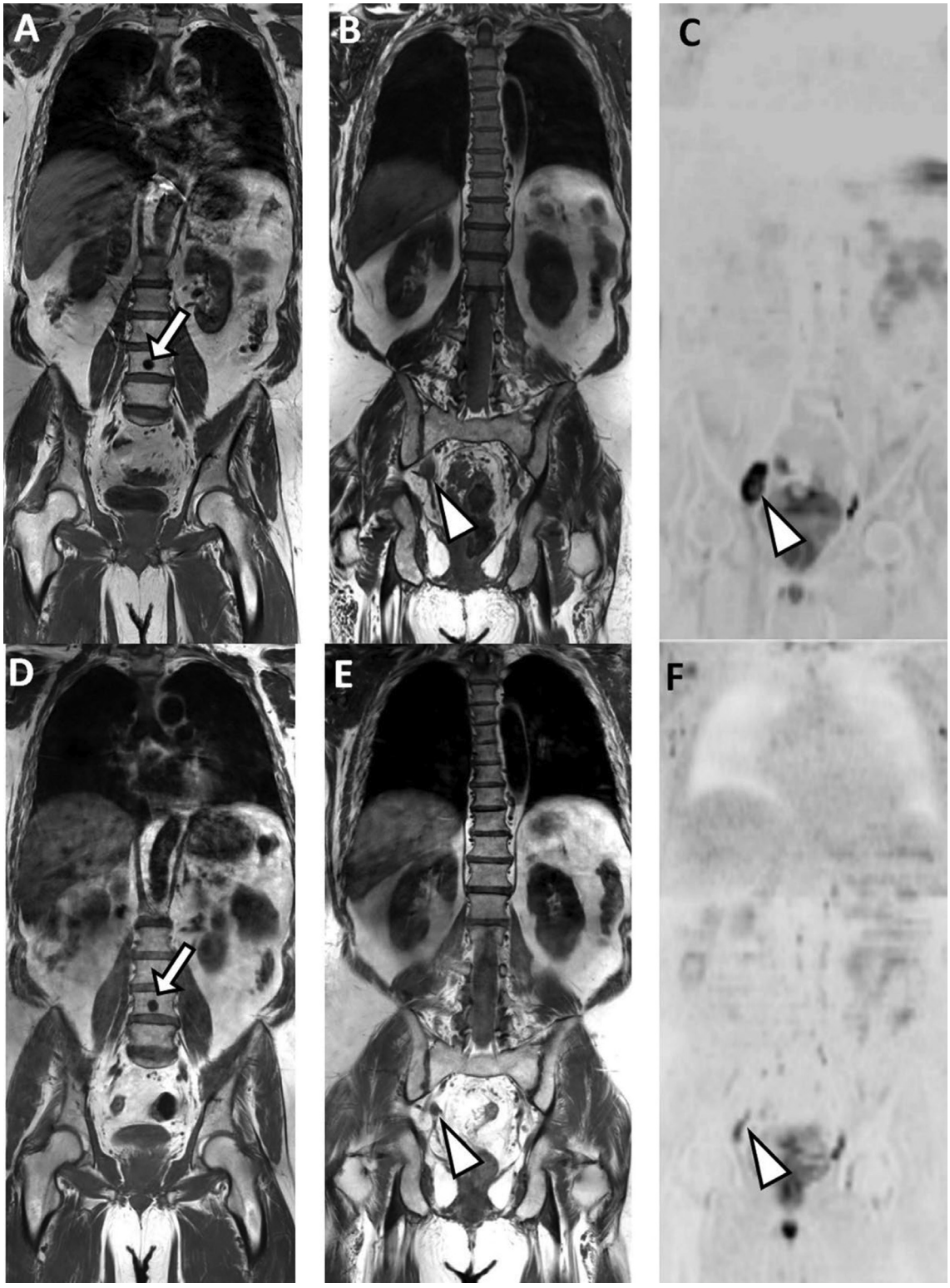

Fig. 3 – Response of nodal metastasis and stability of bone metastasis in a 75-yr-old man with metastatic castration-resistant prostate cancer (response assessment category 2). Comparison of whole-body magnetic resonance imaging before and after treatment. (A,B) Coronal T1-weighted images and (C) diffusion-weighted imaging (b = 1000 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).

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 ≤50% of the baseline level in mCRPC and ≤0.2 ng/ml in mHNPC.

and survival and cumulative probability plots were generated.

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.

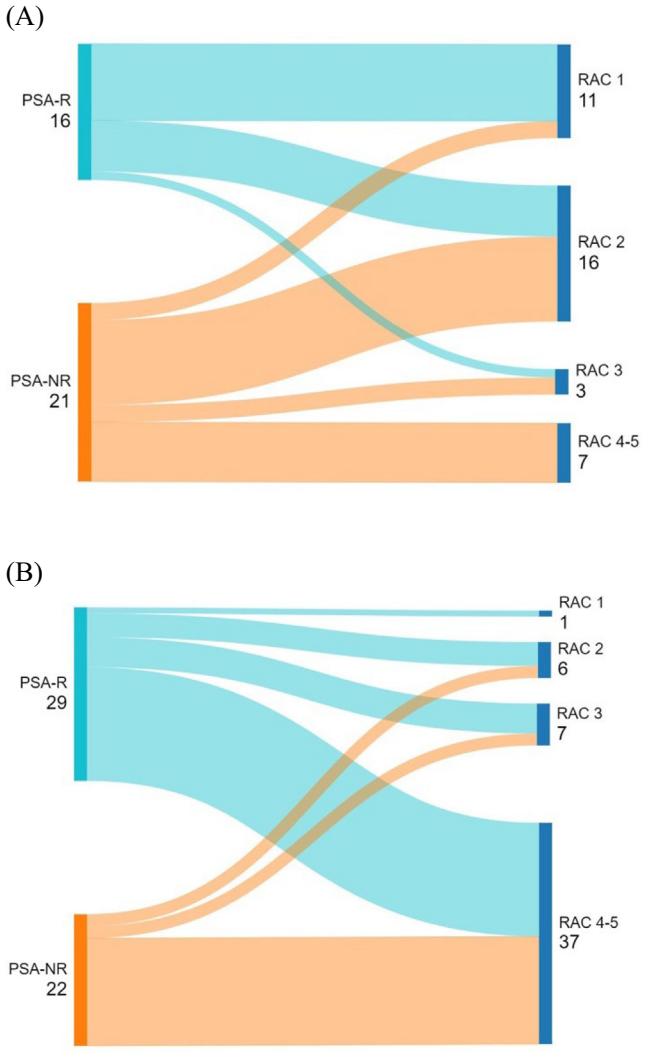

Fig. 4 – Sankey diagrams showing the concordance and discordance between response assessment via PSA and via whole-body magnetic resonance imaging using the MET-RADS-P RACs in (A) the mHNPC group ($n = 37$) and (B) the mCRPC group ($n = 51$). The widest connecting branch represent the strongest association 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 response. No significant association between a positive response and the time to subsequent treatment was observed for either PSA or wbMRI assessment (all $p > 0.05$).

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.

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 $\leq$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

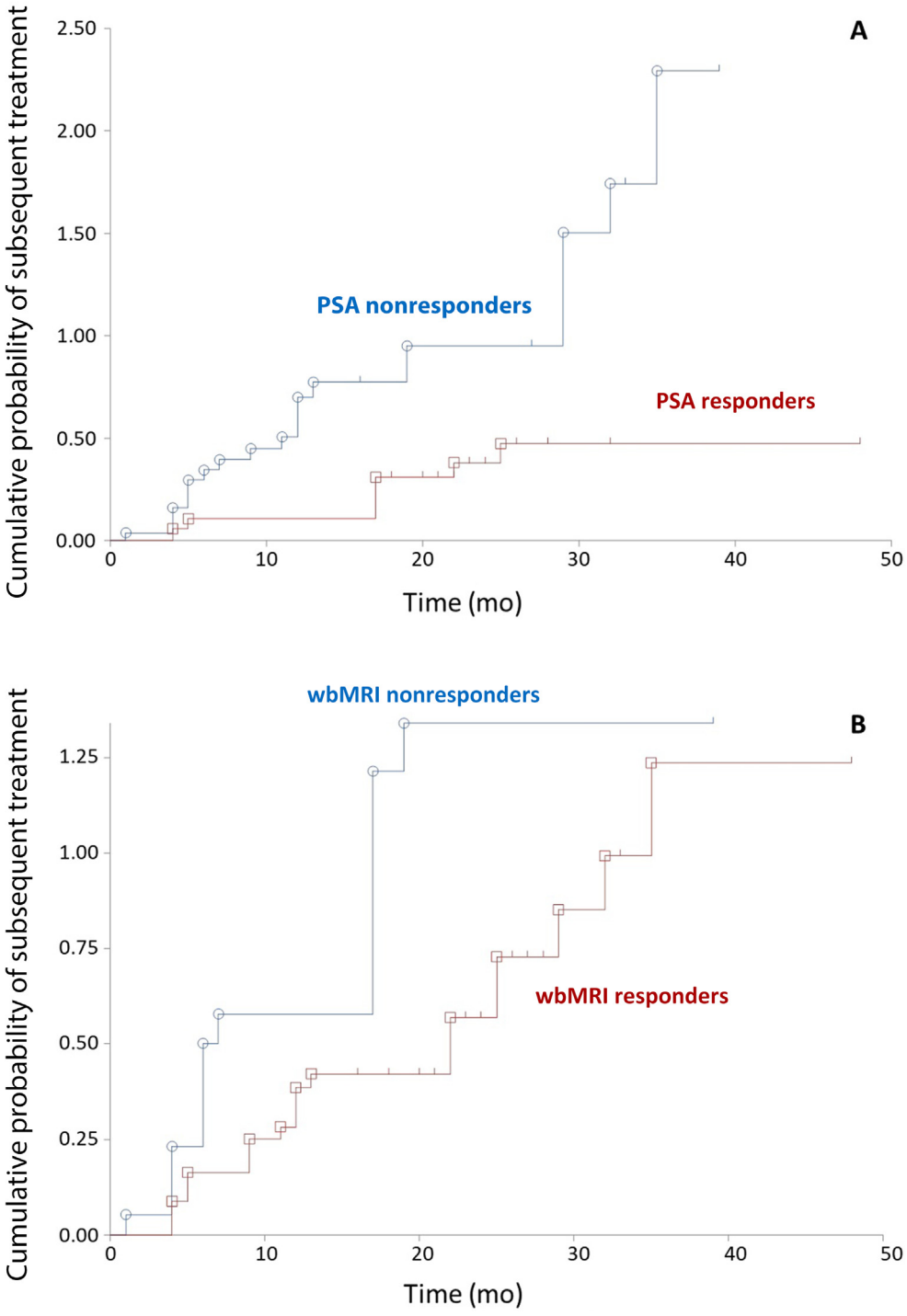

Fig. 5 – Cumulative probability of subsequent treatment according to Cox regression for patients with metastatic hormone-naïve prostate cancer stratified by (A) PSA response (≤0.2 ng/ml vs not) and (B) a wbMRI response according to Metastasis Reporting and Data System for Prostate Cancer evaluation. 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 Pea 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

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 ^{68}Ga-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 $\leq$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.

Author contributions: Frederic E. Lecouvet 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: 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.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Michoux, Padhani.
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Appendix A. Supplementary material

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