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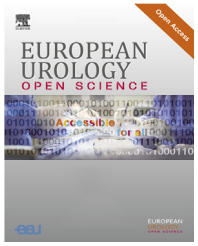

European Association of Urology

Brief Correspondence

Oligometastasis in Prostate Cancer: Can We Learn from Those "Excluded" from a Phase 2 Trial?

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Article info

Article history:
Accepted March 24, 2023

Associate Editor:
Guillaume Ploussard

Keywords:
Prostate cancer
Prostate-specific membrane antigen
Positron emission tomography
Oligometastasis
Metastasis-directed therapy

Abstract

We conducted and previously published a phase 2 trial of metastasis-directed therapy (MDT) in men with recurrence of prostate cancer at a low prostate-specific antigen level following radical prostatectomy and postoperative radiotherapy. All patients had negative conventional imaging and underwent prostate-specific membrane antigen (PSMA) positron emission tomography (PET). Patients without visible disease (n = 16) or with metastatic disease not amenable to MDT (n = 19) were excluded from the interventional study. The remaining patients with disease visible on PSMA-PET received MDT (n = 37). We analyzed all three groups to identify distinct phenotypes in the era of molecular imaging–based characterization of recurrent disease. Median follow up was 37 mo (interquartile range 27.5–43.0). There was no significant difference in time to the development of metastasis on conventional imaging among the groups; however, castrate-resistant prostate cancer-free survival was significantly shorter for patients with PSMA-avid disease not amenable to MDT (p = 0.047). Our findings suggest that PSMA-PET findings can help in discriminating diverging clinical phenotypes among men with disease recurrence and negative conventional imaging after local therapies with curative intent. There is a pressing need for better characterization of this rapidly growing population of patients with recurrent disease defined by PSMA-PET to derive robust selection criteria and outcome definitions for ongoing and future studies.

Patient summary: In men with prostate cancer with rising PSA levels following surgery and radiation, a newer type of scan called PSMA-PET (prostate-specific membrane antigen positron emission tomography) can be used to characterize and differentiate the patterns of recurrence, and inform future cancer outcomes.

Prostate-specific membrane antigen (PSMA) positron emission tomography (PET) presents challenges and opportunities in prostate cancer (PCa) [1]. This may be particularly relevant for oligometastatic disease. However, the clinical impact of PSMA-PET-only disease (molecular imaging-only metastasis, mi_onlyM), and the value of metastasis-directed therapy (MDT) in this setting have not been determined in phase-3 trials. We previously studied PSMA-PET in patients with biochemical recurrence (BCR) following radical prostatectomy (RP) and postoperative radiotherapy

https://doi.org/10.1016/j.euros.2023.03.016

(PORT) with negative conventional imaging (computed tomography [CT], bone scan) findings [2–4]. Patients with PSMA-PET-detected disease amenable to MDT continued in the study, whereas those with negative PET findings or disease not amenable to MDT were excluded. We assessed PSMA-PET-defined patterns of recurrence in all groups, including the patients "excluded", and the prognostic significance for PCa outcomes to help in identifying the existence of distinct clinical phenotypes among patients with molecular imaging–based characterization of recurrent PCa.

The PSMA MRgRT study ([^{18}F]DCFPyL PET-MR for Personalizing Prostate Cancer Subclinical Metastatic Ablative MR-guided Radiotherapy) is a single-center, single-arm, phase 2 trial with institutional review board approval (NCT03160794). The methodology has been described elsewhere [4]. Patients with BCR following RP and PORT with prostate-specific antigen (PSA) of 0.4–3.0 ng/ml, normal testosterone, and negative conventional staging (CT, bone scan) were enrolled and underwent PSMA-PET-magnetic resonance imaging/CT. Patients without metastases (group A) or with metastases not amenable to MDT (group B) were excluded from the interventional study and managed according to patient preference/physician discretion. Patients with PSMA-PET-detected disease amenable to MDT underwent SBRT or lymphadenectomy (group C). The decision to use MDT was not based on an a priori definition of the number of lesions, given the lack of prospective evidence in the molecularly defined oligorecurrent setting at the time of trial design; rather, patients were reviewed by urologic and radiation oncologists and cases were discussed at multidisciplinary tumor boards. Follow-up imaging (conventional or PSMA-PET) and the use and timing of androgen deprivation therapy (ADT), generally on detection of a PSA rise, were not mandated but at physician/patient discretion.

Baseline demographics and clinical characteristics were summarized using descriptive statistics. Between-group baseline differences were assessed using a Kruskal-Wallis test for continuous variables and Fisher's exact test for proportions. Time-to-event analysis of survival outcomes was performed using the Kaplan-Meier method and the log-rank test was applied to compare differences between groups. Biochemical progression-free survival (bPFS) and ADT-free survival were not analyzed as they were directly impacted by nonrandomized, nonstandardized treatments (ie, patients with MDT compared to observation would be expected to have improved bPFS, and patients started on ADT because of polymetastatic disease on PSMA-PET compared to MDT would be expected to have worse ADT-free survival). Therefore, castrate-resistant PCa (CRPC) (defined as rising PSA or new metastases in setting of castrate testosterone levels)-free survival was the primary PCa-specific endpoint. No deaths were recorded. The timing of the development of metastases on conventional imaging (M1) was assessed, and termed "time-lag" to try to quantify the lapse between mi_onlyM and M1 status. All tests were two-sided; $p < 0.05$ was deemed significant. Statistical analyses were performed using R version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria).

The total cohort included 72 patients: 16 in group A (miM0), 19 in group B (mi_onlyM not amenable to MDT), and 37 in group C (mi_onlyM MDT-treated). Baseline characteristics are shown in Table 1. Groups B and C had a higher proportion of pT3b and pN1 cases, and PORT was more likely to include pelvic RT and ADT in comparison to group A. Median PSA was lowest in group A (0.8 ng/ml) and highest in B (1.4 ng/ml) ($p = 0.045$). The distribution of PSMA-PET-identified disease differed among the three groups: a higher proportion of patients in group B had prostate bed recurrence and miM1b/c disease. In groups A and B, immediate management (within 3 months) following PSMA-PET included observation ($n = 12$ and $n = 7$), discharge to other cancer centers ($n = 3$ and $n = 5$), and initiation of ADT ($n = 1$ and $n = 7$). Median follow-up was 37 mo (IQR 27.5–43.0) for the full cohort, 39 mo (IQR 26.5–41.2) for group A, 31 mo (IQR 2–37) for group B, and 40 mo (IQR 34–46) for group C.

CRPC-free survival was significantly worse in group B ($p = 0.047$; Fig. 1A), although the median was not reached (NR) across the groups. No significant associations with CRPC-free survival were found on univariable analyses, including the number and location of metastases.

Time to M1 status was comparable among the three groups ($p = 0.61$; Fig. 1B). The median time to M1 was NR (95% CI NR) in group A, 45 mo (95% CI 45–NR) in group B, and NR (95% CI 46–NR) in group C. When the analysis was limited to patients who underwent any conventional imaging during follow-up, there was still no difference among the groups ($p = 0.82$; Fig. 1C), with median time to M1 of 29 mo (95% CI 20–NR), 25 mo (95% CI 21–NR), and 28 mo (95% CI 22–NR) in groups A, B, and C, respectively. On univariable analysis, there were no significant associations with time to M1, including the number and location of metastases.

Our secondary analysis of PSMA MRgRT revealed two major findings. First, CRPC-free survival was worse for patients with mi_onlyM disease not amenable to MDT, suggesting that PSMA-PET allows for discrimination of diverging clinical trajectories among patients who were considered a homogeneous cohort up to now. However, importantly, CRPC-free survival differences between groups may also have been impacted by treatments that were nonstandardized, as those with mi_onlyM disease not amenable to MDT were more likely to receive ADT following PSMA-PET in comparison to the other groups.

Second, we found no difference in time to M1 by disease status on PSMA-PET. This is an important finding given that M1 status is a validated surrogate of survival [5,6], while the significance of M0/mi_onlyM disease within the spectrum of recurrent PCa and its surrogacy for survival [7,8] remain unknown. Interestingly, time to M1 was shorter when the analysis was restricted to patients who underwent conventional imaging during follow-up. While this may stem from selection bias, the patient population was homogeneous at enrolment, and it is likely that the true time-lag is between the results for the overall and the restricted subset. In addition, optimal management for patients with mi_onlyM PCa is unknown, including whether these patients should receive systemic therapies that are the standard of care for M1 PCa [9].

Table 1 – Baseline patient characteristics

Parameter	Full cohort (*n* = 72)	PSMA-PET^{-} (*n* = 16)	PSMA-PET^{+} w/o MDT (*n* = 19)	PSMA-PET^{+} w/ MDT (*n* = 37)	*p* value
Age at diagnosis (yr) [a]	61 (57–65)	62.5 (59–65.5)	60 (59–65)	60 (56–65)	0.53
RP Gleason score, *n* (%)					0.81
6	5 (7)	1 (6)	2 (11)	2 (6)	
3 + 4	25 (35)	5 (31.5)	8 (44)	12 (32)	
4 + 3	26 (36)	5 (31.5)	5 (28)	16 (43)	
8–10	13 (18)	4 (25)	2 (11)	7 (19)	
Data missing	3 (4)	1 (6)	2 (6)	0	
pT category, *n* (%)					0.76
pT2	23 (32)	7 (44)	6 (33)	10 (27)	
pT3	1 (1)	0 (0)	0 (0)	1 (3)	
pT3a	23 (32)	6 (38)	5 (28)	12 (32)	
pT3b	24 (34)	3 (19)	7 (39)	14 (38)	
Data missing	1	0	1	0	
pN category, *n* (%)					0.48
pNx	11 (15)	3 (19)	2 (11)	6 (16)	
pN0	55 (77)	13 (81)	13 (72)	29 (78)	
pN1	5 (7)	0 (0)	3 (17)	2 (5)	
Data missing	1	0	1	0	
Time from RP to end of RT (mo) [a]	11 (5.0–34.8)	29.5 (5–50)	13 (6–40)	7 (5–17)	0.075
Timing of RT, *n* (%)					0.16
Adjuvant	20 (28)	4 (25)	2 (11)	14 (38)	
Salvage	50 (69)	12 (75)	16 (84)	22 (59)	
Neoadjuvant	2 (3)	0 (0)	1 (5)	1 (3)	
RT treatment volume, *n* (%)					0.8
Prostate bed	9 (12)	1 (6)	3 (16)	5 (14)	
Bed+ pelvis	63 (88)	15 (94)	16 (84)	32 (86)	
RT + ADT, *n* (%)					0.47
No	59 (84)	15 (94)	14 (78)	30 (83)	
Yes	11 (16)	1 (6)	4 (22)	6 (17)	
Data missing	2	0	1	1	
Duration of ADT with RT (mo) [a]	6 (6,10)	6 (6,6)	7 (6,15)	6 (6,10.5)	0.68
Age at enrollment (yr) [a]	69.5 (63.8–73)	72 (68.5–74)	71 (67.5–75)	68 (63–71)	0.02
Time from RP to PSMA-PET (mo) [a]	84 (60–114.2)	91.5 (74.8–133.5)	93 (76–142.5)	75 (48–96)	0.062
Time from RT to PSMA-PET (mo) [a]	70 (37.5–89)	70 (43.2–91)	77 (51.5–110)	61 (36–80)	0.43
PSA at enrollment (ng/ml) [a]	1.0 (0.6–1.8)	0.8 (0.5–1.2)	1.4 (0.8–2.5)	1.0 (0.7–1.8)	0.045
Number of metastases, *n* (%)					<0.001
0	16 (22)	16 (100)	0 (0)	0 (0)	
1	20 (28)	0 (0)	2 (11)	18 (49)	
2	12 (17)	0 (0)	4 (21)	8 (22)	
3	6 (8)	0 (0)	1 (5)	5 (14)	
4	5 (7)	0 (0)	2 (11)	3 (8)	
5	3 (4)	0 (0)	0 (0)	3 (8)	
6	2 (3)	0 (0)	2 (11)	0 (0)	
7	3 (4)	0 (0)	3 (16)	0 (0)	
>7	5 (7)	0 (0)	5 (26)	0 (0)	
Number of metastases (*n*) [a]	1.5 (1–3.2)	0 (0–0)	6 (2–7.5)	2 (1–3)	<0.001
Disease state/location on PSMA-PET, *n* (%)					
miT0N0M0	16 (22)	16 (100)	0 (0)	0 (0)	<0.001
miTr	4 (5)	0 (0)	4 (21)	0 (0)	
miN1a	15 (21)	0 (0)	0 (0)	15 (41)	
miN1b	28 (39)	0 (0)	11 (58)	17 (46)	
miM1a	2 (3)	0 (0)	0 (0)	2 (5)	
miN1 + M1a	0 (0)	0 (0)	0 (0)	0 (0)	
miM1b	5 (7)	0 (0)	2 (10.5)	3 (8)	
miM1c	2 (3)	0 (0)	2 (10.5)	0 (0)	

PSMA-PET = prostate-specific membrane antigen positron emission tomography; MDT = metastasis-directed therapy; IQR = interquartile range; RP = radical prostatectomy; RT = radiotherapy; ADT = androgen deprivation therapy; PSA = prostate-specific antigen. miTr = prostate bed recurrence; miN1a = single pelvic nodal recurrence; miN1b = multiple pelvic nodal recurrence; miM1a = extrapelvic nodal recurrence; miM1b = bone recurrence; miM1c = non-nodal or bone distant recurrence.

[a] Results presented as median (interquartile range).

There are limitations to our work. First, treatments for patients in groups A and B were nonstandardized and not study-mandated. This heterogeneity may have resulted in an inhomogeneous cohort of patients. However, the study enrolled patients in a well-defined uniform scenario (eg, M0 BCR after maximal local therapies) and therefore it seems reasonable to suggest that both the PSMA-PET distribution of disease and the subsequent treatments could have contributed to the divergence into separate cohorts. For similar reasons, we refrained from analyzing bPFS and ADT-free survival, as these are directly impacted by somewhat arbitrary practices. Second, not all patients underwent conventional imaging during follow-up, limiting the sample size for the time-lag analysis. However, to the best of our

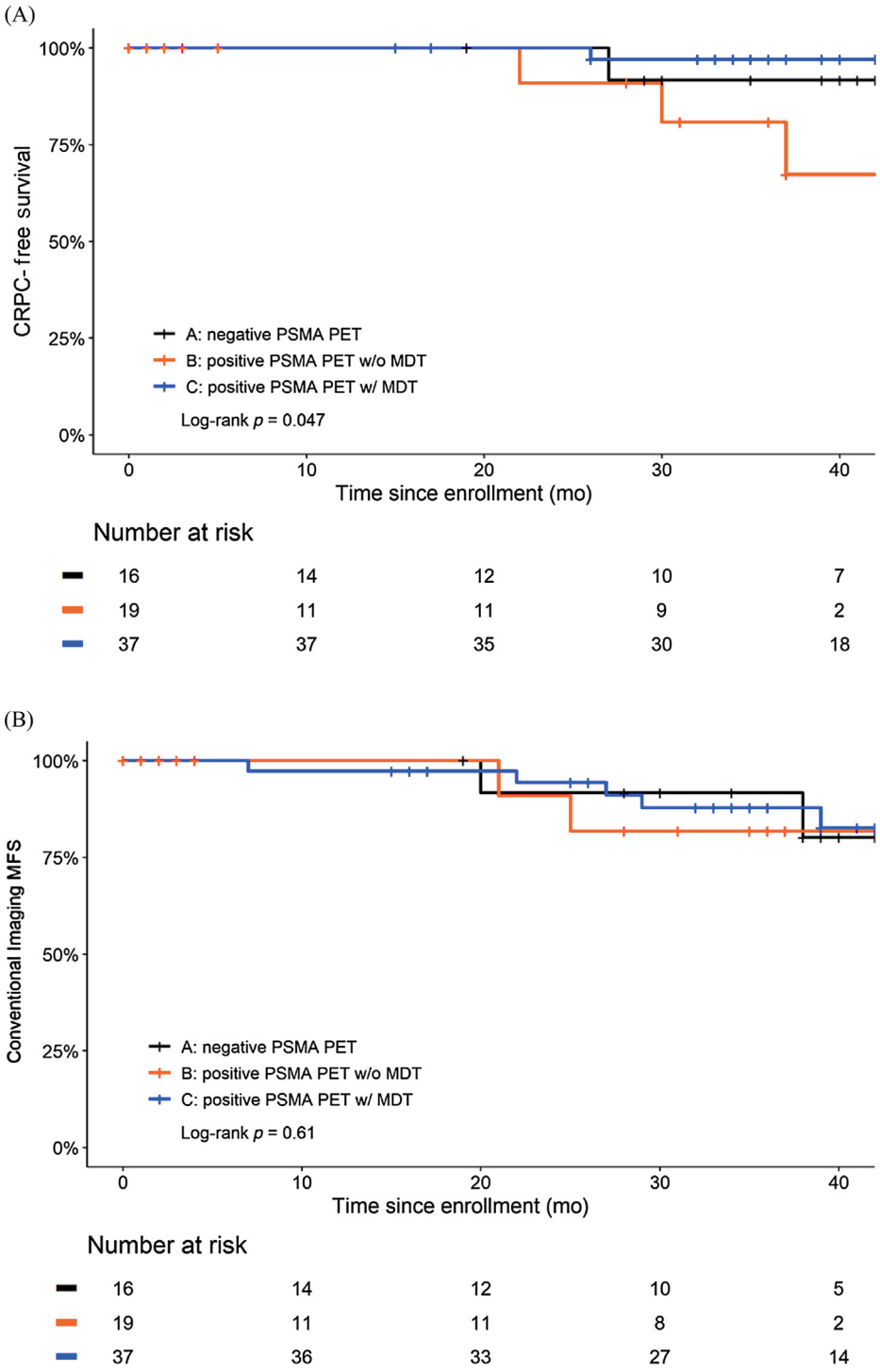

Fig. 1 – Kaplan-Meier curves for (A) CRPC-free survival, (B) time-lag from PSMA-PET detection to conventional imaging positivity in the entire cohort, and (B) time-lag from PSMA PET detection to conventional imaging positivity in patients undergoing conventional imaging during follow-up. CRPC = castration-resistant prostate cancer; MDT = metastasis-directed therapy; MFS = metastasis-free survival; PET = positron emission tomography; PSMA = prostate-specific membrane antigen.

knowledge, this is the first study assessing the potential time-lag between PSMA-PET detection to M1 status, which has important implications for prognostication, management, and trial design.

In conclusion, in patients with BCR and negative conventional imaging after curative-intent therapies, the extent of PSMA-avid disease on PET is associated with worse CRPC-free survival. However, the presence or extent of recurrent disease on PSMA-PET does not seem to correlate with time-lag to M1, which we estimate may be between 2 and 5 years. More research is needed to unveil clinical heterogeneity within the mi_onlyM disease state and determine whether this emerging entity behaves similarly and has the same surrogacy for survival as M1 disease.

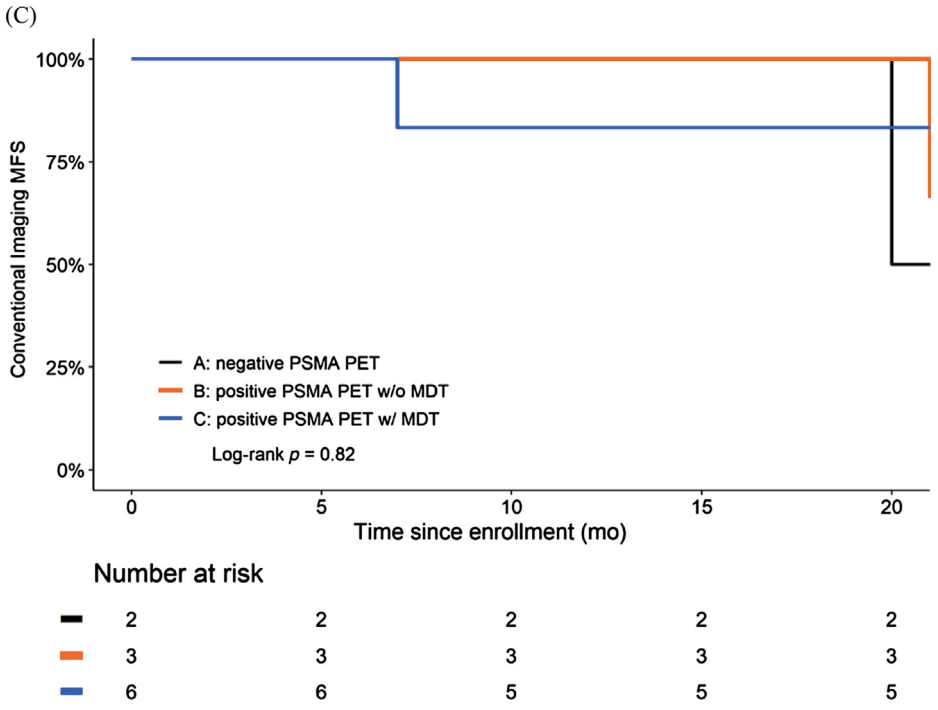

Fig. 1 (*continued*)

Author contributions: Rachel M. Glicksman 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: Glicksman, Metser, Berlin.
Acquisition of data: Glicksman, Murad, Ramotar.
Analysis and interpretation of data: Glicksman, Murad, Santiago, Liu, Ramotar, Metser, Berlin.
Drafting of the manuscript: Glicksman, Berlin.
Critical revision of the manuscript for important intellectual content: Glicksman, Murad, Santiago, Liu, Ramotar, Metser, Berlin.
Statistical analysis: Santiago, Liu.
Obtaining funding: Glicksman, Berlin.
Administrative, technical, or material support: None.
Supervision: Berlin.
Other: None.

Financial disclosures: Rachel M. Glicksman certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Rachel M. Glicksman has received honoraria from Bayer, TerSera, Tolmar, and Knight Therapeutics, and research funding from Astellas, outside of the submitted work. Ur Metser is a consultant for Point Biopharma outside of the submitted work. The remaining authors have nothing to disclose.

Funding/Support and role of the sponsor: This study received funding via a Terry Fox Canadian Comprehensive Cancer Centre Network pilot project from the Terry Fox Research Institute, and AbbVie Canadian Association of Radiation Oncology) Uro-Oncologic Radiation Award, the Astellas Prostate Cancer Innovation Fund (University of Toronto), and The Princess Margaret Cancer Foundation. The sponsors played no direct role in the study.

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