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Metastatic Sites' Location and Impact on Patient Management After the Introduction of Prostate-specific Membrane Antigen Positron Emission Tomography in Newly Diagnosed and Biochemically Recurrent Prostate Cancer: A Critical Review

Francesco Mattana [a,†], Lorenzo Muraglia [a,†], Pawel Rajwa [b,c], Fabio Zattoni [d], Giancarlo Marra [e], Peter K.F. Chiu [f], Isabel Heidegger [g], Veeru Kasivisvanathan [h], Claudia V. Kesch [i,j], Jonathan Olivier [k], Felix Preisser [l], Constance Thibault [m], Massimo Valerio [n], Roderick C.N. van den Bergh [o], Giorgio Gandaglia [p,q,‡], Francesco Ceci [a,r,‡,], on behalf of the European Association of Urology Young Academic Urologists Prostate Cancer Working Party*

[a] *Division of Nuclear Medicine, IEO European Institute of Oncology IRCCS, Milan, Italy;* [b] *Department of Urology, Medical University of Vienna, Vienna, Austria;* [c] *Department of Urology, Medical University of Silesia, Zabrze, Poland;* [d] *Department of Surgery, Oncology and Gastroenterology, Urology Clinic, University of Padova, Padova, Italy;* [e] *Division of Urology, Department of Surgical Sciences, AOU Città della Salute e della Scienza di Torino, Università di Torino, Turin, Italy;* [f] *SH Ho Urology Centre, Department of Surgery, The Chinese University of Hong Kong, Hong Kong;* [g] *Department of Urology, Medical University Innsbruck, Innsbruck, Austria;* [h] *Division of Surgery and Interventional Science, University College London, London, UK;* [i] *Department of Urology, University Hospital Essen, Essen, Germany;* [j] *German Cancer Consortium (DKTK)-University Hospital Essen, Essen, Germany;* [k] *Department of Urology, Lille University Hospital, Lille, France;* [l] *Department of Urology, University Hospital Frankfurt, Frankfurt am Main, Germany;* [m] *Department of Medical Oncology, European Georges Pompidou Hospital, Assistance Publique des Hôpitaux de Paris, Paris Descartes University, Paris, France;* [n] *Department of Urology, Lausanne University Hospital, Lausanne, Switzerland;* [o] *Department of Urology, Antonius Hospital, Utrecht, The Netherlands;* [p] *Unit of Urology/Division of Oncology, IRCCS Ospedale San Raffaele, Milan, Italy;* [q] *Vita-Salute San Raffaele University, Milan, Italy;* [r] *Department of Oncology and Hemato-Oncology, University of Milan, Milan, Italy*

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Abstract

Context: The introduction of prostate-specific membrane antigen positron emission tomography (PSMA-PET) had a substantial impact on the management of prostate cancer (PCa) patients with a stage migration phenomenon and consequent treatment changes.

Objective: To summarise the role of PSMA-PET to define the burden of disease through an accurate location of metastatic site(s) in PCa patients, describing the most common locations at PSMA-PET in the primary staging and recurrence setting, and to assess the clinical impact in the decision-making process.

Evidence acquisition: A comprehensive nonsystematic literature review was performed in April 2022. Literature search was updated until March 2022. The most relevant studies have been summarised, giving priority to registered clinical trials and multicentre collaborations.

Evidence synthesis: PSMA-PET showed higher diagnostic accuracy than conventional imaging both in newly diagnosed PCa and in recurrent disease. This greater accuracy led to a migration of a higher proportion of patients identified with metastatic disease. Bone metastases were reported as the most frequent site of metastatic spread in staging

† Francesco Mattana and Lorenzo Muraglia are co-first authors of this review.
‡ Giorgio Gandaglia and Francesco Ceci are co-senior authors of this review.
* Corresponding author. Division of Nuclear Medicine, IEO European Institute of Oncology IRCCS, Department of Oncology and Hemato-Oncology, University of Milan, Via Giuseppe Ripamonti, 435, 20141 Milan, Italy. Tel. +39 02 57489044.
E-mail address: francesco.ceci@ieo.it (F. Ceci).

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(up to 17%) and restaging (up to 18%). In staging, considering the suboptimal sensitivity in lymph node metastasis detection prior to radical surgery, PSMA-PET should be performed in patients with high risk or unfavourable intermediate risk only, and it is not recommended to routinely avoid pelvic lymph node dissection in case of a negative scan. In case of prostate-specific antigen relapse, PSMA-PET had higher diagnostic accuracy than other diagnostic procedures in the early detection of the sites of recurrence, thus influencing the therapy decision-making process.

Conclusions: PSMA-PET detects a higher number of lesions than conventional imaging or other PET radiotracers, especially metastatic lesions unseen with other modalities. The high diagnostic accuracy of PSMA-PET leads to a significant patient upstage and thus an impact in clinical management, even if the overall impact on cancer mortality is still to be assessed.

Patient summary: Prostate-specific membrane antigen positron emission tomography (PSMA-PET) identifies metastatic lesions with higher accuracy than conventional imaging, both in primary prostate cancer and during disease recurrence. Skeletal metastasis and extrapelvic lymph nodes are the most common sites of metastatic spread. The high accuracy of PSMA-PET in the detection of metastatic disease led to a significant impact on patient management, even if the overall impact on cancer mortality is still to be assessed.

1. Introduction

Prostate-specific membrane antigen (PSMA) is considered a key target for molecular imaging in prostate cancer (PCa) patients. Several PSMA inhibitors have been proposed for positron emission tomography (PET) imaging [1], and phase III clinical studies proved the superiority of PSMA-PET to computed tomography (CT) or bone scan (BS) in patients affected by PCa in different clinical settings [2]. PSMA-PET is currently considered the standard of care in patients with biochemical relapse after radical treatment due to the potential implications for patient management and the administration of PSMA-guided therapy including metastasis-directed therapies (MDTs) [2]. Similarly, prospective trials demonstrated the superiority of PSMA-PET to conventional imaging both as a staging procedure prior to surgery and in the diagnostic/biopsy setting, as well as for the identification of candidates for radioligand therapy in advanced PCa. In this context, the results derived by clinical trials (eg, proPSMA and PRIMARY) [3,4] highlighted the advantage of having a new-generation imaging procedure to assess the disease burden more accurately prior to surgery, but also emphasise the potential role of characterising the intraprostatic lesion(s). Nonetheless, the routine use of PSMA-PET in all newly diagnosed PCa patients is not recommended by clinical guidelines due to the lack of evidence on long-term oncological control and the stage migration phenomenon, where men who were staged as M0 at conventional imaging would now be considered as M1 at advanced imaging with consequent changes in the treatment paradigm [2]. Similarly, there is a lack of evidence regarding the role of PSMA-PET as a baseline procedure prior to the administration of systemic therapies in case of metastatic disease. Thus, a clinical decision to switch to subsequent lines in advanced PCa cannot be taken relying on PSMA-PET only. Although data regarding the impact of PSMA-PET on PCa cancer-specific and overall mortality are still awaited [5], its implementation in the management of PCa patients is already of high clinical interest.

The aim of this critical review was summarising the role of PSMA-PET to define the burden of disease through an accurate location of metastatic site(s) in PCa patients, to describe the most common sites of positive spots at PSMA-PET in newly diagnosed PCa and during biochemical recurrence (BCR), and to assess its clinical impact in the decision-making process.

2. Evidence acquisition

A comprehensive literature review was performed in April 2022 with a nonsystematic approach. The search is updated until March 2022, and was performed using the Ovid platform and a comparison of the Embase and Medline databases, using the following string: (“prostate specific membrane antigen” OR “PSMA”) AND (“Positron Emission Tomography” OR PET) AND (“prostate cancer” OR PCa). The most relevant studies have been summarised, giving priority to registered clinical trials and multicentre collaborations.

Four authors (F.M., L.M., P.R., and F.Z.) performed the literature research. Disagreements have been resolved by consensus. All the original articles published in English over the past 10 yr were considered. Retrospective and prospective series, as well as randomised and nonrandomised clinical trials reporting data about metastatic sites location and impact on patient management have been considered. Abstract, narrative review, case reports or case series, editorials, and letter to editors have been excluded. In the study selection process, priority was given to randomised clinical trials, prospective academic studies, or retrospective multicentre collaborations involving high-volume centres with proven expertise in PSMA-PET. For clinical studies, all PSMA radiopharmaceuticals were considered; the most frequent PET tracer used was ^{68}Ga-PSMA-11, followed by ^{18}F-DCFPyL and ^{18}F-PSMA-1007. The literature search was

updated until March 2022. After the first literature screening, a total of 38 studies have been selected. Authors tabulated and organised relevant studies and performed a comprehensive qualitative narrative synthesis of both tabulated studies and nontabulated articles.

3. Evidence synthesis

3.1. Staging prostate cancer with PSMA-PET: distribution of metastatic sites

Accurate staging of PCa is crucial to correct planning of curative-intent therapeutic strategies after disease diagnosis. PSMA-PET could be considered to stage high-risk localised or locally advanced PCa. A cross-sectional abdominopelvic imaging study for lymph node (LN) evaluation, such as CT, and a BS are still considered the staging pathway of reference and generally performed in clinical practice. According to the European Association of Urology (EAU) guidelines [2], PSMA-PET is more accurate for staging than CT and BS in high-risk disease (level of evidence 1b). However, even if PSMA-PET is performed as an imaging study with high diagnostic accuracy, data regarding long-term oncological control generated by the stage migration phenomenon are still missing.

Four studies (n = 4) reporting the distribution sites of positive spots at PSMA-PET were identified (Table 1). In a cohort of 691 consecutive high-risk PCa patients who performed PSMA-PET as a staging procedure, Klingenberg et al. [6] observed a disease with nodal involvement (N1/M1a) in 31% of patients, while skeletal involvement (M1b) was observed in 17%. The reported risk of advanced disease for potential clinically confined cancer (cT2a, cT2b, and cT2c) was almost equal (24%, 28%, and 22%, respectively). Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy for LN metastasis (LNM) detection were 31%, 97%, 69%, 85%, and 83%, respectively. However, there is heterogeneity regarding validation criteria commonly used to confirm PSMA-PET findings, thus reflecting heterogeneous results concerning its diagnostic performance among different studies (Table 1). A composite standard of truth has recently been accepted by the Food and Drug Administration (FDA) [7,8]. These reference standards were defined as (1) evaluable histopathology results from prostatectomy, salvage pelvic LN dissection, or targeted biopsy; (2) correlative follow-up imaging findings using ^{18}F-fluciclovine or ^{11}C-choline PET, or focused magnetic resonance imaging (MRI) or CT; or (3) if neither of the above was available or informative, confirmed prostate-specific antigen (PSA) response up to 9 mo after radiation initiation (without concomitant androgen deprivation therapy [ADT]) of all PET-positive lesions. PSA response was defined as a PSA decline of $\geq$50% from baseline.

In this clinical setting, a randomised controlled phase III trial has recently been published, comparing PSMA-PET with the standard of care (CT and BS). The proPSMA [3] trial reported higher specificity and PPV for LNM and bone metastasis localisation. Sensitivity remains suboptimal but significantly higher if compared with conventional imaging. First-line PSMA-PET (n = 148 patients) detected pelvic nodal disease (N) in 20% of cases, extrapelvic nodes (M1a) in 9%, bone metastases (M1b) in 10%, and visceral metastases (M1c) in 1%. Considering that 30% of the patients presented local or distant metastasis, PSMA-PET had a 27% (95% confidence interval [CI] 23–31, p < 0·001) absolute greater area under the curve (AUC) for accuracy when compared with conventional imaging (92% [88–95%] vs 65% [60–69%]), higher sensitivity (85% [74–96%] vs 38% [24–52%]), higher impact on clinical management (28% [21–36%] vs 15% [10–22%]; p = 0.008), and lower percentage of inconclusive findings (7% [4–13%] vs 23% [17–21%]). Following first-line PSMA-PET, 14% patients shifted from curative to palliative-intent treatment, 11 (7%) had a change in radiotherapy technique, and 11 (7%) in surgical technique. In patients with fewer than three distant metastases on first-line imaging who crossed over to second-line imaging, conventional imaging had a high or medium effect in 5% (95% CI 2–10%) compared with 27% (20–35%) with PSMA-PET.

Table 1 – Distribution of metastatic sites in intermediate-high risk staging setting

Study reference and design	Radiotracer	D'Amico risk assessment	Median Initial PSA (ng/ml)	No. of patients	Change in management	Distribution of metastatic sites
Hofman [3] proPSMA Prospective	^{68}Ga-PSMA	High risk	10	302	28%	M1a 9% M1b 10% M1c 1%
Klingenberg [6] Prospective	^{68}Ga-PSMA	High risk	NA	691	NA	M1a 16% M1b 17% M1c 2%
Pienta [7] OSPREY Prospective	^{18}F-DCFPyl	High risk	9.7	268	NA	M1 12%
Hope [9] Prospective	^{68}Ga-PSMA	Intermediate risk 18% High risk 81%	11.1	277 (overall n = 764)	NA	Surgery cohort: M1a 1% M1b 3% M1c 1%
Hope [9] Prospective	^{68}Ga-PSMA	Intermediate risk 24% High risk 75%	11.9	487 (overall n = 764)	NA	Nonsurgery cohort: M1a 10% M1b 13% M1c 4%

NA = not available; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen.

Further phase III studies assessed PSMA-PET accuracy in correctly detecting metastatic LNs using a histopathological analysis as reference standards. One of the largest prospective FDA-registered studies enrolled 764 patients, with 277 patients being eligible for a primary endpoint analysis and thus referred to radical prostatectomy and pelvic LN dissection, with histopathological validation [9]. In the per-patient analysis, PSMA-PET holds sensitivity of 44%, specificity of 97%, and a PPV of 88%. Interestingly, in the subcohort of patients not referred to surgery (nonsurgery cohort), skeletal metastases (M1b) have been observed in 18% of patients, while non-nodal visceral metastases (M1c) have been reported in 14%.

The OSPREY trial [7] enrolled 252 patients studied with ^{18}F-DCFPyL-PET and described sensitivity that ranged from 31% to 42% among three independent readers with high specificity (median 98%). Notably, these diagnostic performances differ from proPSMA results. Among 126 patients treated with radical prostatectomy, only 83 received histopathological validation. The diagnostic accuracy for this subgroup of patients was not reported, but lower sensitivity than the overall reported 85% might be expected, considering the data derived from literature. Recently, a meta-analysis reported overall sensitivity of 59% for PSMA-PET to detect pelvic LN involvement (range 23–100%) [10]. Patients' selection (high-risk vs high-risk and unfavourable intermediate-risk PCa), study design (prospective vs retrospective, consecutive vs nonconsecutive patients), sample size, and incidence of nodal metastasis in the selected cohort [11] are parameters related to this broad variability. Reader experience might also affect the overall diagnostic accuracy: equivocal findings on PSMA-PET, even if with a lower incidence than conventional imaging, remain challenging [12]. At present, a standardised reporting system (E-PSMA) has been published by the European Association of Nuclear Medicine developed to improve scan interpretation reproducibility [1]. However, external validation of these criteria is still awaited. Hence, the potential improvement on the diagnostic accuracy derived by the application of this reporting system still needs to be confirmed.

The higher NPV for nodal disease detection might contribute to select patients in which bilateral pelvic lymphadenectomy might be avoided. Roscigno et al. [13] retrospectively evaluated 630 consecutive intermediate- and high-risk PCa patients, reporting that nodal metastases were present in 133 patients. Out of these patients, 64 (48%), 58 (44%), 53 (40%), 16 (12%), and 20 (15%) had nodal metastases in the internal iliac, external iliac, obturator, common iliac, and presacral regions, respectively. Metastases in common iliac nodes were always associated with concomitant involvement of lower pelvic chains, confirming the theory of nodal metastasis ascending pathway. An extended pelvic lymphadenectomy (ePLND) would have removed all pathological nodes in 73% of patients only. Yaxley et al. [14] investigated the predictive value of preoperative PSMA-PET on LNM, concluding that by omitting ePLND based on negative preoperative PSMA-PET, nodal metastasis would have been missed in 20% of men. On the contrary, data from the proPSMA study and by Kulkarni et al. [15] showed a high NPV for PSMA-PET, missing LNM in 5% and 13%, respectively, in a high-risk setting.

Finally, according to the most updated literature, it is not recommended to routinely avoid pelvic LN dissection in case of negative PSMA-PET.

The results presented in this section about metastatic site location have been summarised in Table 1 and Figure 1.

3.2. *Staging prostate cancer with PSMA-PET: impact on clinical management*

The higher accuracy of PSMA-PET than that of conventional imaging generates a migration of patients towards different stages, generally leading to disease upstage. However, this more accurate staging is not sufficient to fully support its implementation as a standard of care procedure prior to primary therapy [3,6], as its clinical net benefit should be assessed through the impact on treatment decisions and survival outcomes. While there is still a lack of strong evidence on the survival benefits due to the introduction of PSMA-PET in the management of newly diagnosed PCa, as PSMA-PET is still a novel technique, several studies analysed the impact of PSMA-PET on the decision-making process [3,16–18]. In the proPSMA trial, first- and second-line PSMA-PET changed intent management in 28% and 27% of patients, respectively. Conventional imaging impacted the management in 15% (first line) and 8% (second line) of patients only [3]. Furthermore, the lower incidence of equivocal findings in PSMA-PET than in CT/BS (23% vs 7%) strengthens its reliability in daily clinical practice.

Real-world evidence from another prospective phase III trial [9] showed that urologists changed their management from radical prostatectomy to nonsurgical treatment options due to disease upstaging on molecular imaging. In detail, only 14% of D'Amico intermediate- and high-risk patients who underwent surgery had cN1 disease in PSMA-PET, while 52% with cN1 on PSMA-PET underwent different treatments. While the immediate impact on clinical management is evident, no data are supporting the hypothesis that sparing the patient from surgery will improve the overall survival. However, MDT can be offered to oligometastatic patients and a PSMA-guided therapy is a feasible approach [5].

PSMA-PET is a useful tool for treatment planning and guiding surgery or radiation therapy [18–21]. Grubmüller et al. [17] found that PSMA-PET/MRI had sensitivity of 85% and specificity of 85% for detecting organ-confined disease, possibly allowing for nerve-sparing surgery. In total 29% of surgeons changed their surgical approach according to PSMA-PET/MRI results. In patients referred to radiotherapy as the primary intervention [18], the intended treatment planned prior to the PET scan was adapted in approximately 60% of cases [4,22]. Moreover, PSMA-PET allows an accurate detection of metastatic lesions at presentation and has the potential to guide MDT, as it is an emerging treatment modality in low-volume metastatic patients, potentially improving the oncological outcomes [22–24]. Results about the impact of PSMA-PET in the initial management of PCa are summarised in Table 1.

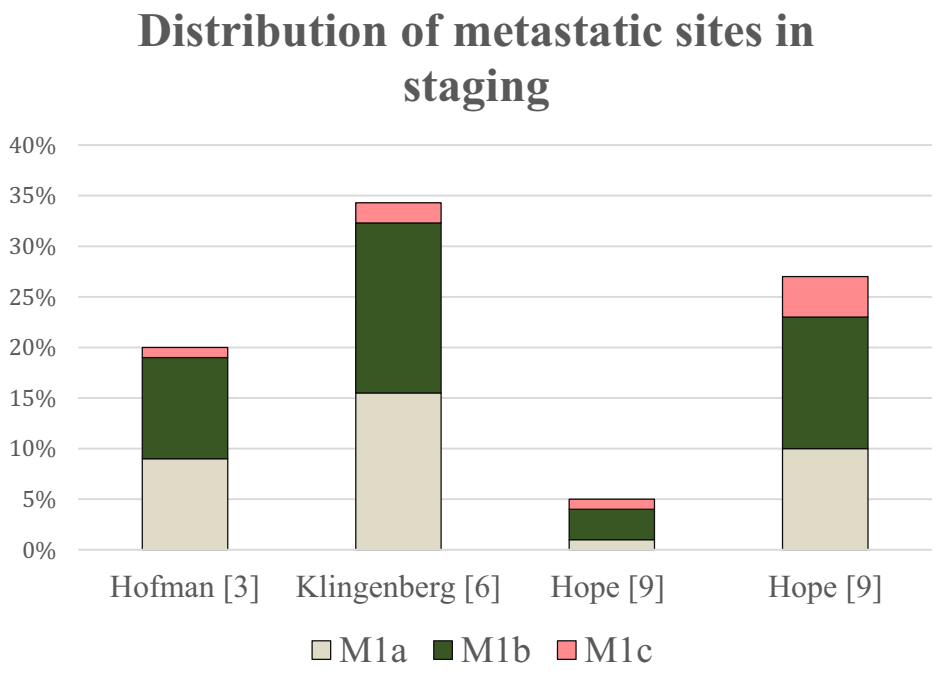

Fig. 1 – Distribution of metastatic sites (M1a, M1b, and M1c), among the studies selected, in high-risk prostate cancer patients referred to PSMA-PET in staging. Only studies reporting data about metastatic site location were selected. Distributions are expressed as positivity rates (percentage of patients presenting metastatic lesions in PSMA-PET vs total number of patients). PET = positron emission tomography; PSMA = prostate-specific membrane antigen.

3.3. Restaging prostate cancer with PSMA-PET during BCR: distribution of metastatic sites

BCR occurs in up to 50% of PCa patients within 10 yr from radical therapy and is defined as a rise in PSA levels (>0.2 ng/ml after radical prostatectomy and >2 ng/ml above the nadir after radiotherapy). The EAU guidelines suggest the use of PSMA-PET in all proven cases of BCR if the results are likely to influence the treatment strategy, thus letting the clinicians take the final decision on whether to refer the patient to PSMA-PET or not in case of recurrence [25]. In this setting, PSMA-PET can address subsequent treatment (eg, MDTs) to delay the initiation of ADT. Several prospective registry studies [26] confirmed the superiority of PSMA-PET imaging to conventional imaging and other PET tracers (eg, choline or fluciclovine). Furthermore, PSMA-PET generally holds higher inter-reader agreement than other diagnostic procedures [3], and it is currently available a structured reporting system (E-PSMA) to improve its repeatability and reproducibility among different centres [1].

In this critical review, we considered studies exploring cohorts of biochemically recurrent patients. In the selected studies, the median PSA value at the time of the scan ranged from 0.32 to 2.1 ng/ml, and the median PSA doubling time (PSAdt) ranged from 4 to 11.18 mo. Metastasis detection at any site (M1) ranged from 8.8% to 40%, and the most frequent metastatic site was the bone: M1b stage was reported in 7.8% to 18% of patients analysed. The results presented in these studies have been summarised in Table 2 and Figure 2. In this scenario, by detecting more lesions in earlier stages, PSMA-PET has the potential to improve patients' outcome. However, information derived by randomised control trials, specifically designed to assess the impact of PSMA-PET on survival surrogate endpoints (eg, BCR-free survival), is still pending [5].

A prospective, single-arm, registry clinical trial assessing the accuracy of PSMA-PET in localising recurrent PCa has been published by Fendler et al. [27]. Considering a subpopulation of 223 BCR patients who had a lesion validation, authors observed different PSMA-PET performance at different PSA level thresholds, resulting in a positivity rate of 38% in patients with PSA <0.5 ng/ml and 97% in patients with PSA >5 ng/ml ($p < 0.001$). The PPV value was 84% (95% CI 0.75–0.90), with most false positive findings detected in the prostate bed. The sensitivity was 92% (95% CI 0.84–0.94) on a per-patient basis and 90% (95% CI 0.82–0.95) on a per-lesion basis, and extrapelvic disease was detected in 40% of patients. Another prospective multicentre collaboration coordinated by the International Agency for Atomic Energy (IAEA) [28] investigated the PSMA-PET positivity rate in a large cohort of patients ($n = 1004$). The main findings were the following: positivity rates stratified for a Gleason score were 61% for International Society of Urological Pathology (ISUP) grade score $\leq$3 and ranging from 66% to 87% for ISUP grade score $\geq$4; positivity rates stratified according to anatomical regions were 21% in pelvic LN (N1) and 27% in any metastatic sites (M1a, b, c); overall positivity rate was positively influenced by higher PSA levels, a shorter PSAdt, a higher Gleason score, and radiotherapy as the primary treatment; and disease management changed in 56.8% of cases, suggesting a very promising potential of a PSMA-guided salvage therapy. These results were consistent with the findings of other studies on this topic. Ceci et al. [29] demonstrated that PSMA-PET was able to identify

Table 2 – Distribution of metastatic sites in first biochemical recurrence setting

Study reference and study design	Radiopharmaceutical	No. of patients	Median PSA at PET scan (ng/ml)	Median PSA doubling time (mo)	Change in management	Distribution of metastatic sites
Calais [5] Prospective	^{68}Ga-PSMA	102	0.22	NA	NA	N 20% M1a 3% M1b 8% M1c 1% M1 9%
Calais [26] Prospective	^{68}Ga-PSMA	50	0.48	4	NA	N 30% M1 16% M1a 6% M1b 8% M1c 4%
Fendler [27] Prospective	^{68}Ga-PSMA	635	2.1	6	NA	Tr/N 35% M1a/c 17% M1b 16% M1 40%
Cerci [28] Prospective	^{68}Ga-PSMA	1004	1.55	11.18	57%	N 24% M1a NA M1b 10% M1c NA M1 27%
Ceci [29] Prospective	^{68}Ga-PSMA	332	0.61	5.8	NA	Tr/N 25% M1a NA M1b NA M1c NA M1 29%
Deandreis [32] Prospective	^{68}Ga-PSMA	223	0.65	9.3	35%	Tr/N 23% M1a 9% M1b 10% M1c 3% M1 17%
Fendler [34] Prospective	^{68}Ga-PSMA	382	1.86	6.3	48–52%	Tr/N 33% M1a 17% M1b/c 23% M1 40%
Farolfi [35] Retrospective analysis of a prospective cohort	^{68}Ga-PSMA	119	0.32	NA	88%	N 18% M1a 3% M1b 18% M1c 0% M1 19%
Calais [40] Retrospective	^{68}Ga-PSMA	270	0.44	NA	19%	N 31% M1a 4% M1b 9% M1c 1% M1 25%
Ceci [43] Prospective	^{68}Ga-PSMA	176	0.62	9.8	30%	N 19% M1a 10% M1b 13% M1c 3% M1 22%

NA = not available; PET = positron emission tomography; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen.

the site of recurrence in 64% of patients with PSA persistence after radical prostatectomy and in 45% of patients with first-time BCR after radical prostatectomy, of whom 90% were oligorecurrent (five or fewer lesions) and ideal candidates for salvage therapy. Moreover, these results suggested that many patients were not identified as metastatic at initial staging, especially in case of persistent PSA after surgery, thus confirming the leading role of PSMA-PET in high-risk PCa prior to primary therapy. In a large retrospective international multicentre analysis, Bianchi et al. [30] validated a clinical-based nomogram developed to predict the PSMA-PET positivity rate in the recurrent setting [31]. The authors confirmed that the original nomogram retained excellent performance characteristics (AUC = 0.82) in the external validation, and PSA, PSAdt, and the clinical setting (clinical indication to request the PET scan) were the most important predictors.

These results have also been confirmed by other prospective studies [32], and the importance of PSMA-PET scans performed in early stages to detect oligorecurrent and/or oligometastatic disease has been highlighted as well. Finally, these studies highlighted that the presence of metastatic lesions (M1a, M1b, or M1c) can be detected in up to 20–30% of patients presenting with early recurrence, namely, in patients with first-time BCR or PSA persistence after primary treatment.

3.4. Restaging prostate cancer with PSMA-PET during BCR: impact on clinical management

The decision to offer additional therapies in recurrent PCa is challenging. The rate of stage migration derived from the use of PSMA-PET in this setting generates important consequences on patients' management, and the proper patient

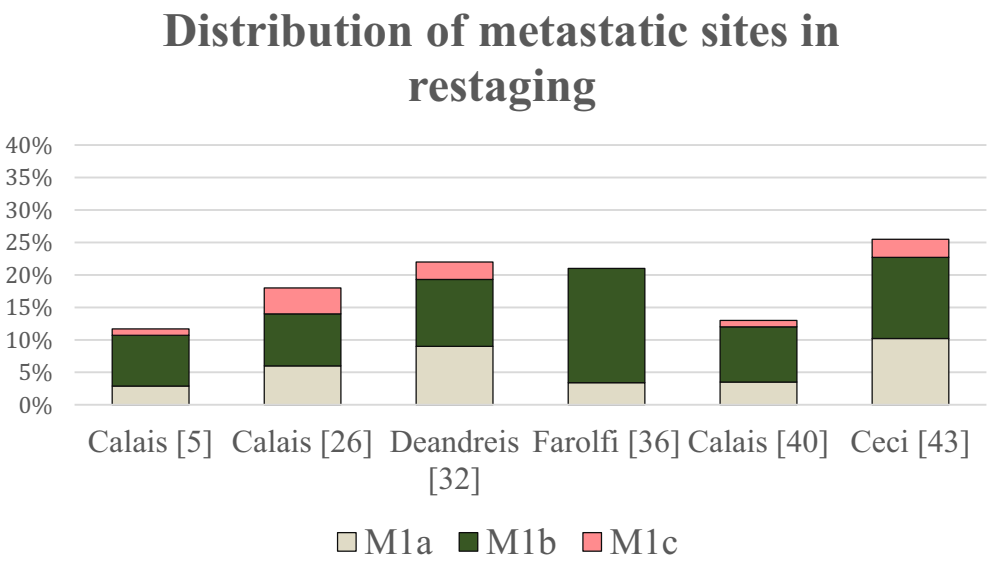

Fig. 2 – Distribution of metastatic sites (M1a, M1b, and M1c), among the studies selected, in prostate cancer patients who underwent PSMA-PET for PSA relapse after primary therapy. Only studies reporting data about metastatic site location were selected. Distributions are expressed as positivity rates (percentage of patients presenting with metastatic lesions in PSMA-PET vs total number of patients). PET = positron emission tomography; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen.

selection is essential to ensure favourable outcomes. Men with recurrent/persistent disease reflect different clinical settings and represent a highly heterogeneous population, carrying different prognoses and different profiles of disease aggressiveness. Therefore, selection of the most suitable candidates for additional therapies is crucial. Different sites of recurrence can be identified by PSMA-PET, even if its diagnostic accuracy is still suboptimal in case of less aggressive recurrence at low PSA levels [29]. Clinical management changes are frequent, and at least half of patients will change the intended planned treatment after a PSMA-PET scan [33]. EAU recommends performing PSMA-PET in case of PSA recurrence when the scan influences the treatment decisions. However, patients identified with oligometastatic disease at PSMA-PET during the first BCR can be treated with MTD or ADT, without definitive evidence in favour of the PSMA-guided approach.

In the CONDOR trial involving 208 patients with BCR and negative standard imaging, PSMA-PET was able to change the intended management in the 64% of evaluated patients [34]. Similarly, Farolfi et al. [35] explored a cohort of patients at a very early stage of recurrence (PSA <0.5 ng/ml) and observed a change in the intended treatment in one-third of patients. These results further support the hypothesis that PSMA-PET is a valid procedure in the management of patients with recurrent PCa and low PSA levels after primary treatment, and support the implementation of this imaging procedure in the routine clinical practice [8]. In the very early stage of recurrence, PSMA-PET may allow personalised salvage radiotherapy (SRT) plans, adapting the irradiated volumes and thus leading to a potential individualised therapy [35]. In these patients, a change in the planned treatment volumes can be observed in up to one-third of patients, with a potential positive impact on progression-free survival [36]. Detection of the site of recurrence is crucial for successful treatment planning. In the event of an exclusive locoregional recurrence, long-term ADT could be avoided or at least delayed by SRT or salvage LN dissection [37]. However, a negative PSMA-PET scan should not delay the early administration of SRT, as the sensitivity of PSMA-PET for the detection of micrometastases is low and, therefore, early SRT should be offered anyway [38]. Conversely, in case of distant metastases detected, MDT as well as androgen receptor targeted therapy (abiraterone, enzalutamide, apalutamide, or darolutamide) should be considered instead [39].

During the first BCR, SRT is the treatment of choice in most patients. In a retrospective international multicentre study, Calais et al. [40] demonstrated that PSMA-PET had a major impact on a significant number of patients investigated prior to the radiotherapy planning, as 20% of patients had at least one PSMA-PET–positive lesion not covered by the clinical target volume. A randomised, controlled clinical trial investigating the outcomes of patients undergoing SRT with or without planning based on PSMA-PET findings is currently on-going [41].

Finally, the overall impact of PSMA-PET on the oncological outcomes of patients who received this new-generation imaging in case of disease recurrence is still to be determined. Interestingly, in a retrospective study by Wenzel et al. [42], PSMA-PET locoregional positivity has been associated, at 5 yr of follow-up, with shorter metastasis-free survival (MFS) in a group of 155 patients who underwent the scan prior to SRT, while PSMA-PET negativity has shown comparable MFS to patients who had not performed the scan. Moreover, in the Cox-regression modelling, positive PSMA-PET has been confirmed as an independent predictor of unfavourable MFS. Similar results have recently been published by Ceci et al. [43]. The authors reported prospective data about the incidence of clinically relevant events

during follow-up in patients who performed PSMA-PET for PSA relapse after radical treatment, using the event-free survival (EFS) as the primary endpoint median (median follow-up of 35.4 [interquartile range: 26.5–40.3] mo). Low PSA and long PSAdt were significant predictors of EFS. Furthermore, a lower incidence of events was also observed in patients having negative PSMA-PET, since longer EFS was significantly more probable in case of a negative scan (hazard ratio 1.53; 95% CI 0.91–2.55; $p = 0.108$).

These findings suggest that PSMA-PET can be used as prognostic biomarkers as well, helping to identify patients at a higher versus lower risk of disease relapse and leading to cost-effective management of patients in early stages of disease recurrence. The results presented in this section about metastatic site location have been summarised graphically in Table 2 and Figure 2.

4. Conclusions

PSMA-PET detects a higher number of lesions than conventional imaging or other PET radiopharmaceuticals. Bone is the most frequent site of metastatic spread (M1b) followed by extrapelvic LNs (M1a), both in primary PCa and during disease recurrence. Although visceral involvement is reported with a lower incidence, it is still higher than that of conventional imaging, with a significant impact on patient's management as non-nodal visceral involvement is associated with a poorer outcome.

The high diagnostic accuracy of PSMA-PET generally leads to patients' upstaging and generates a migration of patients towards different clinical settings (nonmetastatic hormone-sensitive prostate cancer [HSPC] to metastatic HSPC or nonmetastatic castration-resistant prostate cancer [CRPC] to metastatic CRPC). Overall, approximately half of patients who performed PSMA-PET will change their therapeutic strategy according to new-generation imaging results. In case of positive PSMA-PET during recurrence, a personalised therapy approach can be adopted, with MDT generally preferred over ADT only in case of oligometastatic disease.

Finally, the clinical significance of this high diagnostic accuracy is still debated as data regarding cancer-specific mortality are still awaited. Considering the presence of new drugs able to improve patients' survival in the non-metastatic setting (according to CT or BS), data from ongoing phase III randomised controlled trials are crucial to understand whether the PSMA-guided approach holds significance in delaying the castration-resistant condition and in improving patients' overall survival.

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Study concept and design: Ceci, Gandaglia.

Acquisition of data: Mattana, Muraglia, Raiwa, Zattoni.

Analysis and interpretation of data: Mattana, Muraglia, Raiwa, Zattoni, Ceci, Gandaglia.

Drafting of the manuscript: Mattana, Muraglia, Raiwa, Zattoni, Ceci, Gandaglia.

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