Prostate Cancer – Editor's Choice

Prostate-specific Membrane Antigen Reporting and Data System Version 2.0

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Article info

Abstract

Prostate-specific Membrane Antigen Reporting and Data System (PSMA-RADS) was introduced for standardized reporting, and PSMA-RADS version 1.0 allows classification of lesions based on their likelihood of representing a site of prostate cancer on PSMA-targeted positron emission tomography (PET). In recent years, this system has extensively been investigated. Increasing evidence has accumulated that the different categories reflect their actual meanings, such as true positivity in PSMA-RADS 4 and 5 lesions. Interobserver agreement studies demonstrated high concordance among a broad spectrum of [68]Ga- or ^{18}F-labeled, PSMA-directed radiotracers, even for less experienced readers. Moreover, this system has also been applied to challenging clinical scenarios and to assist in clinical decision-making, for example, to avoid overtreatment in oligometastatic disease. Nonetheless, with an increasing use of PSMA-RADS 1.0, this framework has shown not only benefits, but also limitations, for example, for follow-up assessment of locally treated lesions. Thus, we aimed to update the PSMA-RADS framework to include a refined set of categories in order to optimize lesion-level characterization and best assist in clinical decision-making (PSMA-RADS version 2.0).

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1. Introduction

For men affected by prostate cancer (PC), [68]Ga- or ^{18}F-labeled radiotracers for prostate-specific membrane antigen (PSMA)-directed positron emission tomography (PET)/computed tomography (CT) allow for the identification of the primary tumor, as well as local recurrence and metastatic disease. PET/CT also characterizes tumoral PSMA expression in vivo, thereby identifying patients to be treated with ^{177}Lu-labeled, PSMA-directed, therapeutic analogs [1].

Of note, there is also increasing evidence of false-positive findings on PSMA-PET/CT [2], which includes uptake in various organ compartments, for example, the skeleton (Paget's disease, Schmorl's nodes, and fibrous dysplasia), central nervous system (ganglia and stroke), gastrointestinal tract (polyp in esophagus), or lung (sarcoidosis and tuberculosis) [2,3]. Different reporting systems for PSMA-PET/CT have been proposed in recent years, including the PROMISE criteria, which are based on the tumor-node-metastasis (TNM) classification [4,5] or standardized reporting guidelines endorsed by the European Association of Nuclear Medicine (E-PSMA; Supplementary Table 1) [6]. Similar to other standardized reporting and data systems (RADS), PSMA-RADS 1.0 was introduced to help navigate pitfalls and serve as a framework for scan interpretation [7].

Initially developed to increase certainty in scan interpretation [7], PSMA-RADS 1.0 has now been investigated in a number of prospective and retrospective studies [8–17]. Based on a five-point scale, the reader can classify lesions as definitely benign/not attributable to PC (PSMA-RADS 1) or lesions with disease certainly present (RADS 5), while further categories provide guidance toward close monitoring of a single lesion or trigger additional workup, such as biopsy to confirm diagnosis (PSMA-RADS 3A-D) [7].

Limitations of PSMA-RADS 1.0 are related to its use in widespread metastatic disease and longitudinal assessments, for example, to determine the response to antitumor therapies on a lesion-based level. Thus, we aimed to provide a brief overview of the current status of PSMA-RADS version 1.0 and to propose PSMA-RADS 2.0 as an updated version.

2. Current status of PSMA-RADS version 1.0

Since its introduction in 2017 [7], PSMA-RADS has carefully been studied in a number of clinical scenarios [8–17]. This classification system has not only been proved to be useful to correctly classify lesions attributable to PC, but has also been used in the context of scan interpretation for PSMA-directed radioligand therapy (RLT), to provide guidance in clinical management triggering varying diagnostic steps, and even in machine learning algorithms [8–17].

First, moderate to high concordance rates in scan interpretation have been achieved for this system for both [68]Ga- and ^{18}F-labeled radiotracers, even for less experienced readers [12,18,19], although those findings have generally been limited to ^{68}Ga-PSMA-11 and ^{18}F-DCFPyL. A frequent cause of disagreement in one study was lung lesions [19], a relatively rare manifestation of PC. Concordance rates of PSMA-RADS with other radiotracers, such as ^{18}F-rhPSMA-7.3 and ^{18}F-PSMA-1007, have yet to be evaluated.

Of note, derived agreement rates on a lesion-based level also included whether individuals are eligible for PSMA-targeted RLT [20]. In the absence of clinical data, PSMA-RADS still achieved fair to excellent concordance among the readers [20].

Moreover, to determine the true nature of a lesion, Letang et al [9] investigated osseous PSMA-RADS 4/5 (PC lesion highly likely or certainly present) and reported on specificity of 94% and accuracy of 89%. PSMA-RADS can also be combined with quantitative metrics of lesion uptake. For example, a recent report with ^{68}Ga-PSMA-11 showed that the maximum standardized uptake value, target-to-background ratio, and PSMA-RADS 4/5 demonstrated high accuracy to correctly identify malignant bone lesions [13]. For ^{18}F-labeled PSMA ligands, however, thresholds for quantification are still awaited and have to be defined and validated. Quantified PSMA-RADS classified lesions were also robust to changes in threshold-based segmentations, and as expected, PSMA-RADS 5 showed the most intense uptake as derived by the maximum standardized uptake value [21]. In general, with the current U.S. Food and Drug Administration–approved agents, the molecular imaging PSMA expression score can be used to define the qualitative degree of uptake in lesions, with intense uptake being defined as being above the parotid gland [4].

Kuten and coworkers [10] focused on a small group of patients with primary PC and low International Society of Urological Pathology scores imaged with ^{18}F-PSMA-1007 and ^{68}Ga-PSMA-11. Of the PSMA-RAD 3B sites (defined as equivocal uptake in bone lesions), 11% turned out to be true metastases and two PSMA-RADS 4/5 lesions were true positive. In addition, using ^{18}F-PSMA-1007 (mainly in patients for recurrent PC), Vollnberg et al [22] showed that only one of 11 foci with equivocal uptake in bone lesions were truly positive metastases (as determined by biopsy), resulting in a true positive rate of 9%.

Recently, our group investigated PSMA-RADS 3A lesions (defined as equivocal uptake in soft-tissue site typical of PC involvement) in individuals with biochemical recurrence. We demonstrated that increasing prostate-specific antigen (PSA) levels may point toward the presence of true positivity in those lesions [11]. Further supporting the notion of the relevance of incorporating such lesion classifications, Yin et al [23] showed that PSMA-RADS 3A/B lesions are truly indeterminate, with PSMA-RADS 3A being more likely associated with malignancy (approximately 75% of cases).

Beyond studies that simply aimed to validate the PSMA-RADS system, others have shown the utility of this reporting framework within the context of clinical routine. For instance, a comparative study applied this system to determine the superiority of ^{18}F-DCFPyL to Na[18]F-PET/CT [15]. Reyes and coworkers [14] also demonstrated how PSMA-RADS can effectively guide the referring provider in clinical decision-making and revealed the impact on change in oncological management. Moreover, PSMA-RADS has also been applied to baseline PSMA-PET/CT findings in men treated with ^{177}Lu-labeled theranostic agents. Osseous tumor

volume on pretherapeutic scans was defined by PSMA-RADS 4/5, and skeletal infiltration of the tumor was less suited for predicting relevant hematotoxicity under PSMA-RLT than a simple blood collection (assessing standard hematology) [24]. Recently, this framework has been applied to deep learning, thereby providing a reliable approach for automatic lesion detection based on PSMA-RADS [8].

3. PSMA-RADS version 2.0

The introduction of PSMA-RADS 1.0 in 2017 marked one of the first efforts toward a standardized reporting system for PSMA-PET/CT [7]. Nonetheless, several limitations with this system became evident, which include the following:

1. PSMA-RADS 1A scans are relatively uncommon [21] except in low-PSA biochemical recurrence, and in some studies PSMA-RADS 1A and B were subsumed under PSMA-RADS 1 [12,20], questioning the need for separate RADS 1 subcategories.
2. Patients with a high number of suspicious lesions are more likely to have additional sites of disease without a CT correlate and with only mild to moderate uptake. According to PSMA-RADS 1.0, those findings would have been coded as PSMA-RADS 3A/B, and most likely, given the overall disease status, those lesions should be upgraded and rather considered as PSMA-RADS 4 (ie, PC highly likely).
3. PSMA-RADS 3C/3D lesions are too complex, and there is a need for simplification and extension to further clinical scenarios.
4. PSMA-RADS 4/5 lesions (ie, PC certainly present), which are reassessed after treatment, should also be categorized within the system.
5. Without treatment, stable lesions are likely benign.
6. A definition of "typical manifestation for PC involvement" is needed.

To overcome these limitations, we now propose PSMA-RADS 2.0 as follows, with changes described.
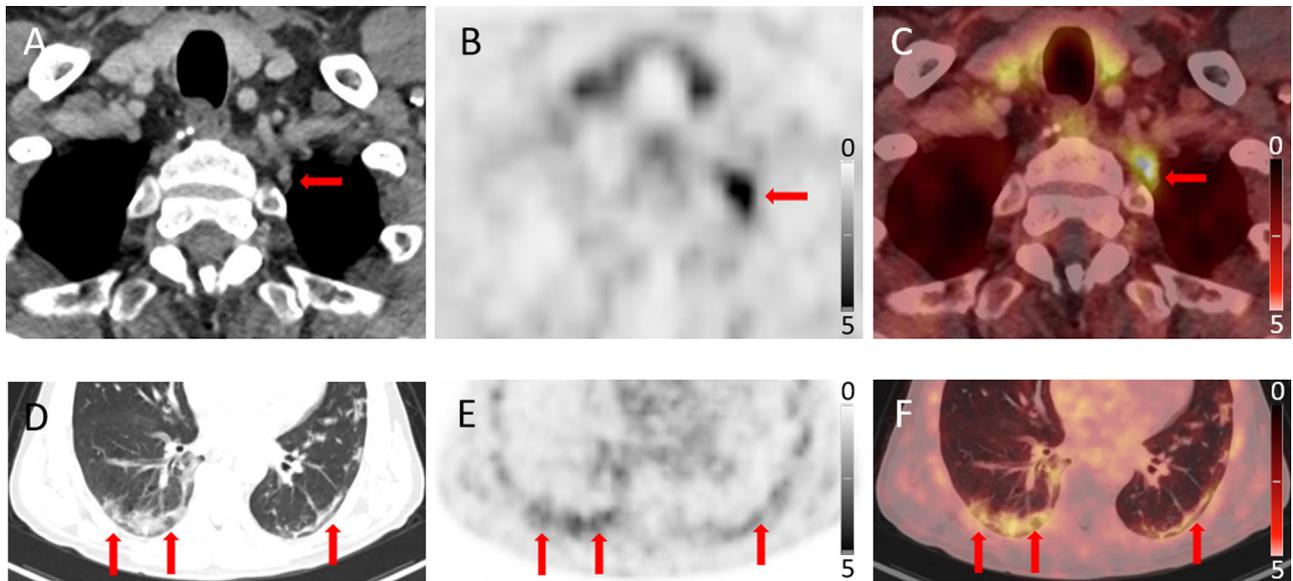
3.1. PSMA-RADS 1

PSMA-RADS 1A lesions are removed from the rating system, as these would not appear on PSMA-PET/CT and are benign by definition. Based on our clinical experience, we see no need to classify and report these lesions by PSMA-RADS, and thus, the former PSMA-RADS 1B category is now classified as PSMA-RADS 1 only (Fig. 1). As stated in PSMA-RADS 1.0, PSMA-RADS 1B lesions have focal or diffuse uptake, but are known to be benign based on their pathognomonic appearance on anatomic imaging (Fig. 2) or are biopsy-proven benign lesions. These lesions may include biopsied thyroid nodules, hepatic hemangiomas, adrenal adenomas, or ganglia that may mimic lymph nodes (Fig. 2). In PSMA-RADS 2.0, all definitively benign lesions, regardless of uptake, are categorized as PSMA-RADS 1.


Fig. 1 – PSMA-RADS 1: whole-body maximum-intensity-projection image of a patient with biochemically recurrent PC imaged with ^{18}F-PSMA-1007. No sites of abnormal uptake can be appreciated. Normal biodistribution of this agent is displayed, including intense uptake in lacrimal glands, liver, spleen, and kidneys, and low uptake in the small bowel, along with almost no urinary tract excretion of the radiotracer. PC = prostate cancer; PSMA-RADS = Prostate-specific Membrane Antigen Reporting and Data System.

3.2. PSMA-RADS 2

Relative to PSMA-RADS 1.0 [7], this category will not be modified substantively. PSMA-RADS 2 lesions are characterized by uptake that is likely benign, but these lesions have not been biopsied or definitively identified as a specific entity based on anatomic imaging. Examples of PSMA-RADS 2 lesions include focal uptake in degenerative bone lesions (Fig. 3) and minimal uptake in isolated or symmetric axillary lymph nodes (Fig. 3). We are aware of the possible overlap between PSMA-RADS 1 and 2, and the observer-dependent interpretation of different readers, most likely depending on previous experience in interpreting PSMA-PET/CT findings. Nevertheless, we believe that a distinction between PSMA-RADS 1 and 2 lesions allows the reader to

Fig. 2 – PSMA-RADS 1: two patients with biochemically recurrent PC. (A-C) Intense uptake on transaxial ^{18}F-PSMA-1007 PSMA-PET/CT in a paravertebral structure (arrows), which might be misinterpreted as a lymph node. Instead, this is a typical finding of a cervicothoracic, PSMA-avid ganglion. (D–F) Diffuse uptake pattern in peripheral fibrous changes and ground glass opacities in both lungs (arrows). This patient has recently recovered from a COVID-19 infection and demonstrated non-specific ^{18}F-PSMA-1007 uptake in the lower lung. CT = computed tomography; PC = prostate cancer; PET = positron emission tomography; PSMA-RADS = Prostate-specific Membrane Antigen Reporting and Data System.
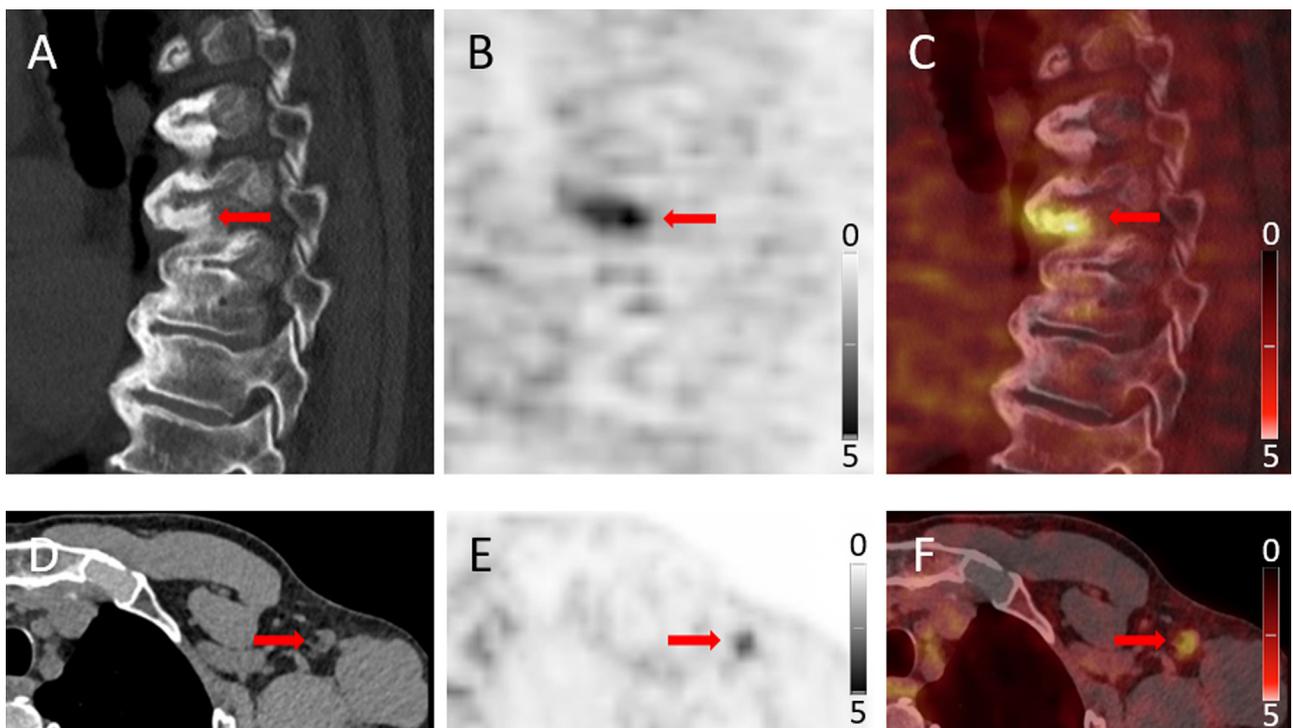
Fig. 3 – PSMA-RADS 2: two patients with biochemically recurrent PC and likely benign findings. The first patient had pronounced degenerative changes in the thoracic spine with spondylophyte formation. (A) Sagittal CT, (B) sagittal ^{18}F-PSMA-1007 PET, and (C) fused images revealed intense uptake in a ventral spondylophyte (arrows), most likely caused by degenerative changes. (E) Axial ^{18}F-PSMA-1007 PET (and (F) axial fused images show mild uptake in a nonenlarged axillary lymph node on (D) axial CT (arrows). Such findings in the axilla (or in hilar or mediastinal lymph nodes) are often non-specific or indicate chronic inflammatory process. Especially if distributed symmetrically, these are not suggestive of PC in the context of biochemical recurrence. CT = computed tomography; PC = prostate cancer; PET = positron emission tomography; PSMA-RADS = Prostate-specific Membrane Antigen Reporting and Data System.

indicate even subtle nuances toward benign findings or an increasing likelihood of malignancy in their reports.

3.3. General note on "typical" manifestations for the following RADS categories

For the following RADS classifications, lesions can be attributed with the term "typical" (for PC involvement). In this context, the pretest probability for typical manifestations of PC involvement increases based on clinical factors that have provided an independent predictive value for positive findings on PSMA-PET/CT, including elevated PSA levels, shorter PSA doubling times, concurrent androgen deprivation therapy, and higher-grade groups [25–27]. Beyond these clinical parameters, distribution patterns have been described, which also help the reader identify a site of disease as typical (provided in the order of decreasing detection rate): PC in the pelvis only, extrapelvic disease (with nodal/soft tissue lesions), skeletal involvement, or both (extrapelvic together with bone lesions) [28]. Nonetheless, the individual clinical context is of importance for rendering a lesion as a typical PC manifestation on PSMA-PET/CT.
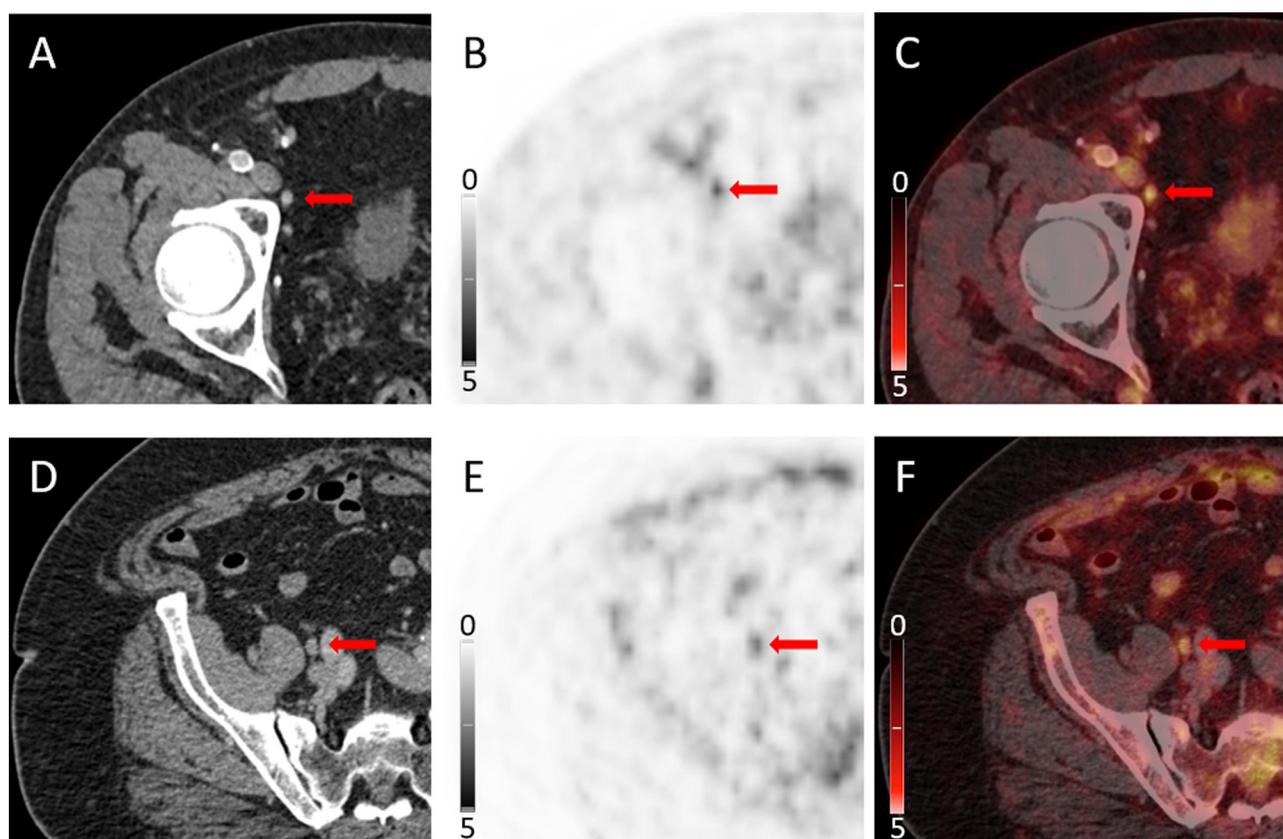
3.4. PSMA-RADS 3

When compared with PSMA-RADS 1.0 [7], PSMA-RADS 3 was subject to the most profound modifications, mainly to reduce complexity of this category and to make its use more intuitive. All PSMA-RADS 3A-D lesions have now in common that these require either further workup or follow-up to determine their true natures.

PSMA-RADS 3A and 3B represent uptake in either soft tissue (Fig. 4, RADS 3A) or bone (Fig. 5, RADS 3B). Both categories may be suggestive of PC. Such lesions usually include small lymph nodes at sites typical for PC with focal but low uptake (PSMA-RADS 3A) or bone lesions with focal uptake that could represent a metastasis (PSMA-RADS 3B). The lymph node sites that would be "typical" for PC will be context dependent, with miN1 disease according to the miTNM staging system from PROMISE being typical in patients who are undergoing primary staging or at the time of first recurrence [4]. In more advanced patients, the common iliac, retroperitoneal, retrocrural, mediastinal, hilar, and supraclavicular nodes (ie, miM1a) are also typical [29]. When possible and targetable, biopsy would be preferred for further characterization if it would impact subsequent patient management.

For all findings that cannot be biopsied or investigated with another imaging modality, a disease site may be corroborated by additional serial imaging that establishes evidence of progression or response at that site [23]. If there is evidence of disease progression (ie, increasing uptake or growth of findings on CT), this may lead to recategorization

Fig. 4 – PSMA-RADS 3A: two patients with rising PSA levels and equivocal uptake in parailiacal lymph nodes. (A and D) Axial CT, (B and E) axial ^{18}F-PSMA-1007 PET, and (C and F) axial fused images revealed small (short-axis diameter, <0.8 cm) left parailiacal lymph nodes (arrows). The degree of uptake is only slightly above the background, leaving this finding indeterminate. In general, biopsy of these lymph nodes may be considered. Otherwise, follow-up imaging in 3–6 mo may be recommended. PET = positron emission tomography; PSA = prostate-specific antigen; PSMA-RADS = Prostate-specific Membrane Antigen Reporting and Data System.
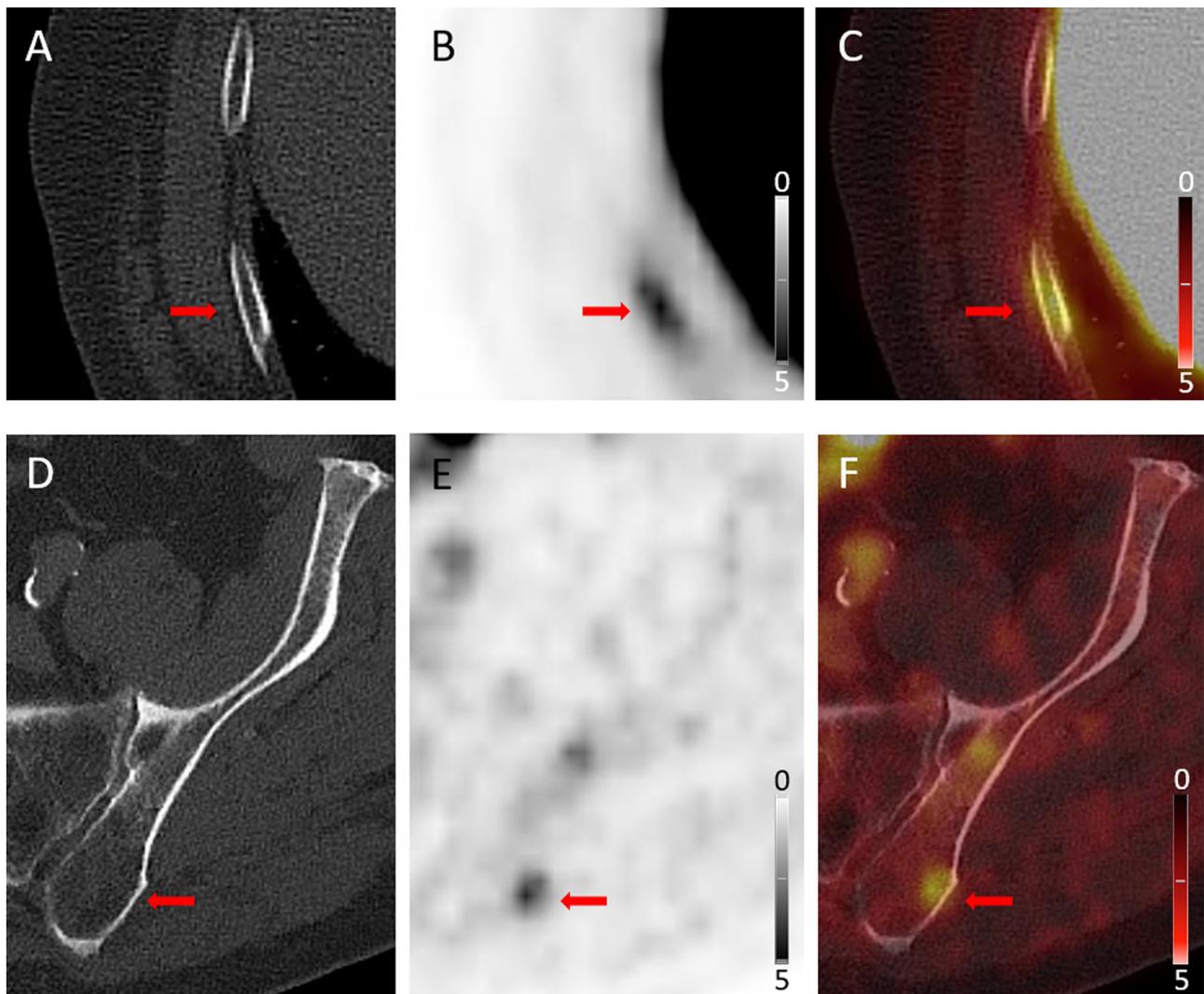
Fig. 5 – PSMA-RADS 3B: two patients with recurrent PC and equivocal uptake in bone lesions. (B) Axial ¹⁸F-PSMA-1007 PET and (C) axial fused images showed low focal uptake in a rib without a corresponding lesion in the (A) axial bone window on CT (arrows). (E) Axial ¹⁸F-PSMA-1007 PET and (F) axial fused images with low focal uptake in the left iliac bone without an anatomical correlate in the (D) axial bone window on CT (arrows). Given the high frequency of nonspecific bone uptake with ¹⁸F-PSMA-1007 [38] such lesions can be difficult to categorize and, depending on the clinical context, a score of PSMA-RADS 2 may be appropriate, at times. These focal low-level uptake sites lacking anatomic correlates render these findings indeterminate for early metastatic disease versus benign processes such as traumatic changes or small sites of fibrous dysplasia. Biopsy is often difficult; follow-up imaging may be considered. CT = computed tomography; PC = prostate cancer; PET = positron emission tomography; PSMA-RADS = Prostate-specific Membrane Antigen Reporting and Data System.

to PSMA-RADS 4 or 5. Stable lesions without treatment may be benign and could then be scored with a PSMA-RADS score of 1 or 2. In inconclusive cases, we would leave it to the discretion of the interpreting imaging specialist to recommend additional follow-up.

Relative to PSMA-RADS 1.0 [7], it is at the discretion of the reader whether in highly metastatic patients (more than five lesions), PSMA-RADS 3A or 3B lesions should be reassigned and upgraded to PSMA-RADS 4, as in extensive disease, such findings with equivocal uptake are most likely also attributable to PC. In lesions with high clinical relevance triggering clinical decision-making, biopsy may be considered.

PSMA-RADS 3C lesions are still defined as intense uptake at a site that is highly atypical for all but advanced stages of PC. As these lesions may be caused by an underlying malig-

nancy that is not PC, further investigation is required, preferably biopsy. An example would be a focal soft tissue uptake in a patient with a low PSA level who is being evaluated for biochemical recurrence (Fig. 6) for further treatment decisions.

The definition for PSMA-RADS 3D lesions has been simplified to all abnormal and suspicious lesions on CT that do not show uptake of PSMA ligand, that is, not higher than background (Fig. 7). As such, relative to PSMA-RADS 1.0, this category is now no longer restricted to lesions that are exclusively suspicious for malignancy, as other reasons may have also caused missing radiotracer uptake, for example, infectious disease. As these lesions may also represent a variety of other malignancies, including neuroendocrine-differentiated PC or lung carcinoma, or other diseases requiring treatment, further workup is needed (immediate biopsy
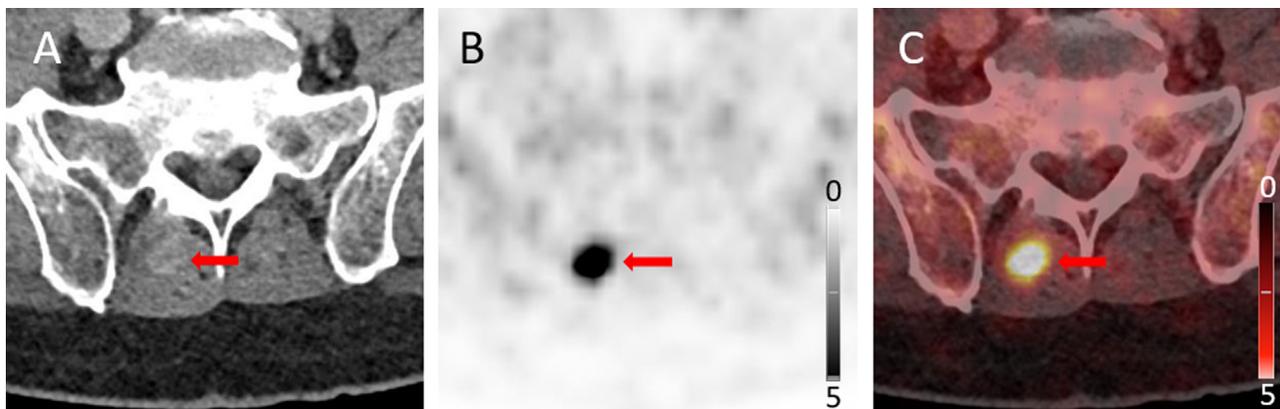
Fig. 6 – PSMA-RADS 3C: intense focal uptake in a soft tissue lesion of a patient with biochemically recurrent PC. (A) Axial CT, (B) axial ^{18}F-PSMA-1007 PET, and (C) axial fused images show exceptionally high uptake in a soft tissue lesion with intense uptake of radiotracer in the lower spine muscles on the right. Patient's low PSA level was discordant with this finding. Biopsy of lesion revealed a metastasis of clear cell renal cell carcinoma that had surgically been removed 13 yr earlier. CT = computed tomography; PC = prostate cancer; PET = positron emission tomography; PSA = prostate-specific antigen; PSMA-RADS = Prostate-specific Membrane Antigen Reporting and Data System.
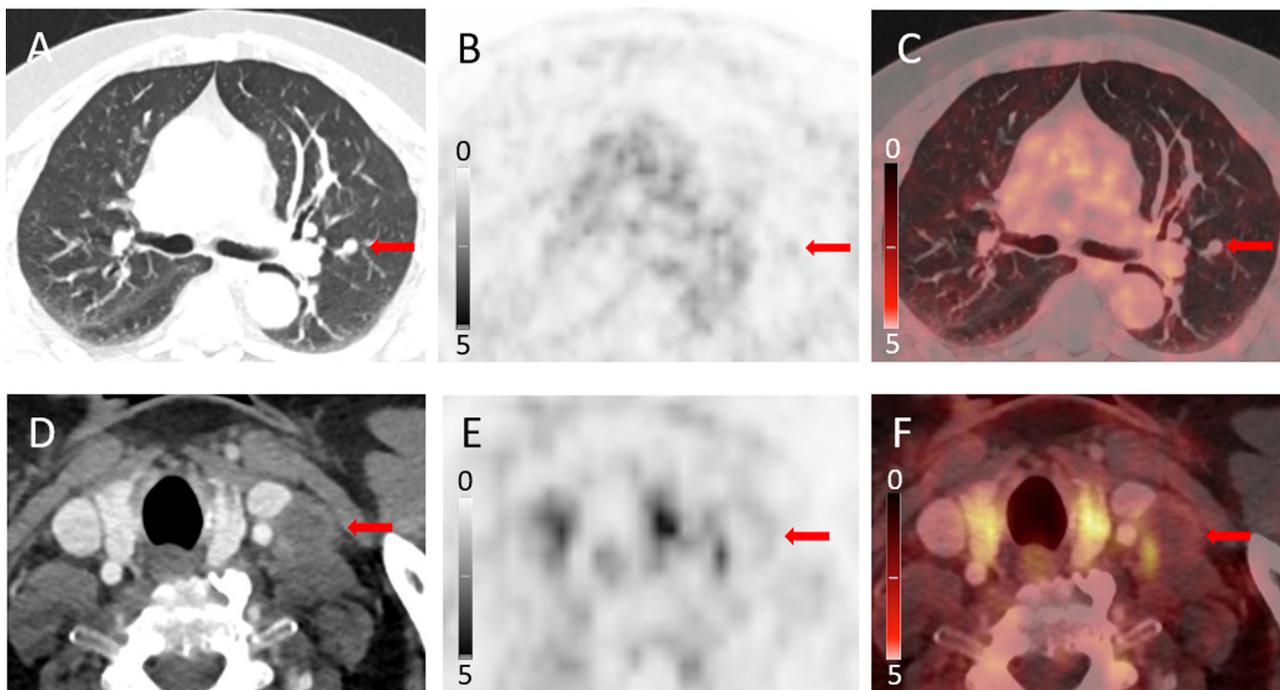
Fig. 7 – PSMA-RADS 3D: two patients with biochemically recurrent PC and non–radiotracer-avid abnormalities in CT. (A) Axial lung window CT, (B) axial ^{18}F-PSMA-1007 PET, and (C) axial fused images showed a 1 cm right upper lobe nodule without significant uptake (arrows). Despite equivocal findings on additional ^{18}F-FDG PET/CT (not shown), the nodule was surgically removed. Histology revealed an atypical carcinoid of the lung. (D) Axial CT, (E) axial ^{18}F-PSMA-1007 PET, and (F) axial fused images show a 2 cm lymph node adjacent to the left thyroid and the blood vessels (Virchow's lymph node) and without significant uptake (arrows). The lymph node was surgically removed and histology revealed an infection with mycobacteria other than tuberculosis. CT = computed tomography; PC = prostate cancer; PET = positron emission tomography; PSMA-RADS = Prostate-specific Membrane Antigen Reporting and Data System.

or close follow-up imaging). Nonetheless, context is of importance, for example, in a patient with low expression in the primary with CT correlate, this finding would then still be classified as PSMA-RADS 5. If there are multiple disease sites coded as PSMA-RADS 4/5, but a single suspicious lesion on CT without any uptake, the latter finding would then be rated as PSMA-RADS 3D. Lung lesions, however, may be without relevant uptake due to partial-volume effect and have been identified as a frequent cause of disagreement, thereby affecting the interobserver concordance rate on PSMA-RADS [19]. The pulmonary system, however, is a less common metastatic site in men with PC [30], and thus, lung nodules without PSMA positivity may also represent other malignancies [31], thereby requiring further workup.

3.5. PSMA-RADS 4

The definition of PSMA-RADS 4 lesions has not been changed. These lesions are characterized by high focal uptake at sites typical for PC, while anatomic correlate is missing (eg, nonenlarged lymph nodes <1 cm on CT or bone lesion with intense uptake but no clear morphologic correlate; Fig. 8). PSMA-RADS 4 lesions have a high likelihood of being malignant. Nonetheless, different anatomical imaging modalities have varying levels of power to identify disease sites. Thus, their clinical relevance should be considered in particular for PSMA-RADS 4 lesions, for example, when dynamic contrast-enhanced (or diffusion-weighted) magnetic resonance is applied as part of hybrid imaging [32].

3.6. PSMA-RADS 5

PSMA-RADS 5 lesions are still considered almost certainly PC. These disease sites are characterized by high focal

uptake with definite anatomic confirmation (eg, enlarged lymph nodes or sclerotic bone lesion) at sites typical for PC (Fig. 9).

PSMA-RADS 5T (T for treatment) is introduced and includes previously identified metastases that have been treated (eg, initially classified PSMA-RADS 5 lesions, such as irradiated skeletal metastases, which are then examined on follow-up PSMA-PET/CT; Fig. 10). Such lesions do not necessarily show intense uptake, but should still be considered as (treated) sites of disease. PSMA-RADS 5T then also includes lesions that completely disappear under treatment, that is, complete resolution of initially classified malignant findings with only non-specific remnants upon follow-up.

3.7. Overall RADS score

Similar to SSTR-RADS [33,34], an overall RADS score (ORS) is emphasized in the updated version of PSMA-RADS 2.0, given the expanding use of imaging to define patients
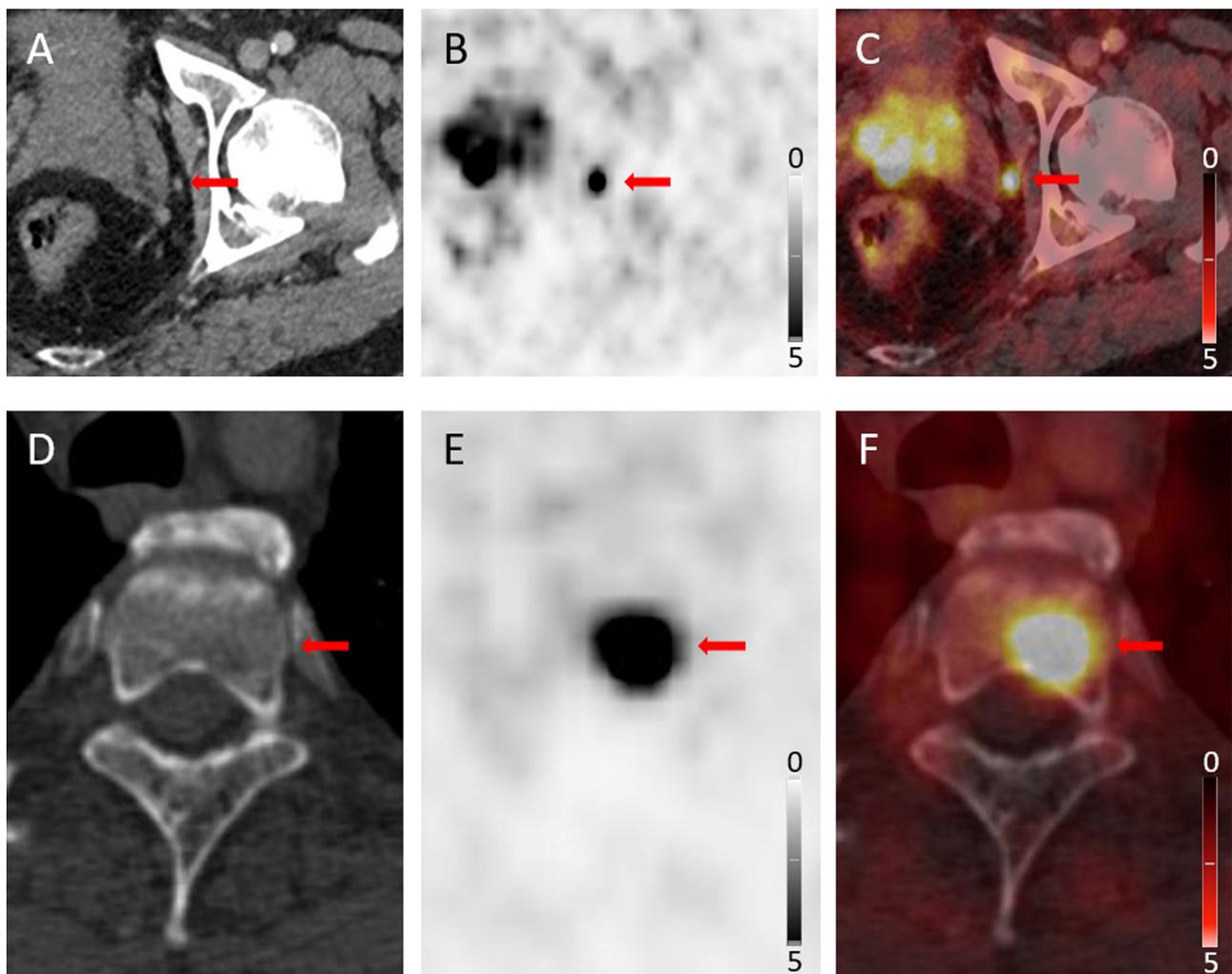
Fig. 8 – PSMA-RADS 4: two patients with biochemically recurrent PC and focal intense uptake without definitive findings on conventional imaging. (A) Axial CT, (B) axial ¹⁸F-PSMA-1007 PET, and (C) axial fused images showed high focal uptake consistent with metastatic PC (arrows). However, because the short-axis diameter of lymph node was 0.3 cm (ie, <1.0 cm), this findings would have been considered benign on CT alone. (E) Axial ¹⁸F-PSMA-1007 PET (F) and axial fused images showed an intensive focal uptake consistent with metastatic PC (arrows), but no anatomic correlates in corresponding (D) axial bone window CT. Considering the typical location of osseous lesion in the spine, this finding is most likely attributable to PC. CT = computed tomography; PC = prostate cancer; PET = positron emission tomography; PSMA-RADS = Prostate-specific Membrane Antigen Reporting and Data System.
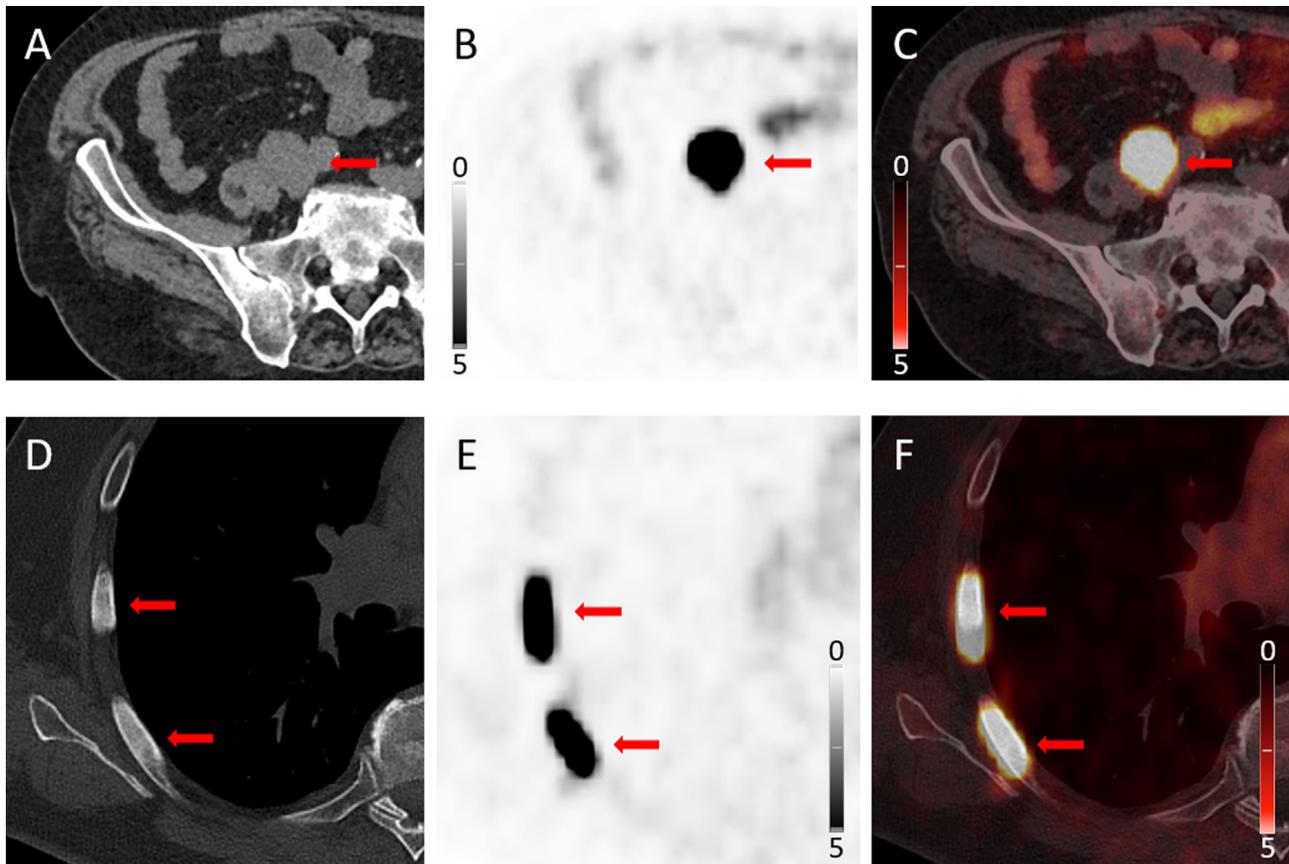
Fig. 9 – PSMA-RADS 5: two patients with biochemically recurrent PC and focal intensive uptake with corresponding findings on conventional imaging. (A) Axial CT, (B) axial ^{18}F-PSMA-1007 PET, and (C) axial fused images showed intensive focal uptake in an enlarged right iliac lymph node consistent with metastatic PC (arrows). (E) Axial ^{18}F-PSMA-1007 PET and (F) axial fused images showed an intensive focal uptake in two ribs and sclerotic changes in corresponding (D) axial bone window CT (arrows). These findings are consistent with metastatic PC. CT = computed tomography; PC = prostate cancer; PET = positron emission tomography; PSMA-RADS = Prostate-specific Membrane Antigen Reporting and Data System.

who are candidates for PSMA-targeted therapies. This score is defined by the highest PSMA-RADS score of any of the individual target lesion and will provide an overall scan impression [20]. For instance, if a lesion has been classified as PSMA-RADS 3A and another lesion as PSMA-RADS 5, the ORS would be defined by the latter category, that is, PSMA-RADS 5. For 5T, however, ORS would also be 5T if only one single lesion is identified on follow-up PET/CT. If there are still multiple lesions from different categories on follow-up scans, 5T would be ignored and the highest lesions would still dominate the ORS, as PSMA-RADS 2.0 aims to increase awareness for findings that trigger further workup or can be interpreted as malignant.

Table 1 provides an overview of PSMA-RADS version 2.0, while Supplementary Table 2 can be used as a simplified pocket reference.

4. Future perspectives and conclusions

The updated PSMA-RADS version (2.0) includes that all definitively benign lesions, regardless of uptake, are categorized as PSMA-RADS 1, and that PSMA-RADS 3A/B and 3D may be reclassified to PSMA-RADS 4 in case of widespread metastatic disease (more than five malignant findings).

PSMA-RADS 3D has been further extended and now refers to any lesion on anatomic imaging without uptake that may require further characterization (and not exclusively to findings suggestive of malignancy). PSMA-RADS 5 now incorporates effectively treated metastases after antiprostatic therapy (5T). Further, we have emphasized ORS, that is, the highest PSMA-RADS score of any of the individual target lesion, thereby providing a categorized overall scan impression. Lastly, we have incorporated elements of the PROMISE criteria to better define some aspects of the anatomy.

We believe that the modifications made to PSMA-RADS fundamentally strengthen this reporting system and will also allow conduction of future studies, for example, to determine the relevance for PSMA-RADS 3D lesions. For instance, if biopsies triggered by PSMA-RADS 3D confirm second cancers or neuroendocrine PC, expected changes in management would be substantial. Among others, this would apply to leukemia and lymphoma, which are among the most commonly recorded second malignancies following the initial diagnosis of PC, independent from external beam radiation therapy (as part of the treatment plan for the prostate) [35].

A key area of study using the updated scoring system will be the longitudinal monitoring of patients scheduled for antitumor therapies by also categorizing treated lesions (PSMA-RADS 5T). Among others, this will now help us clas-
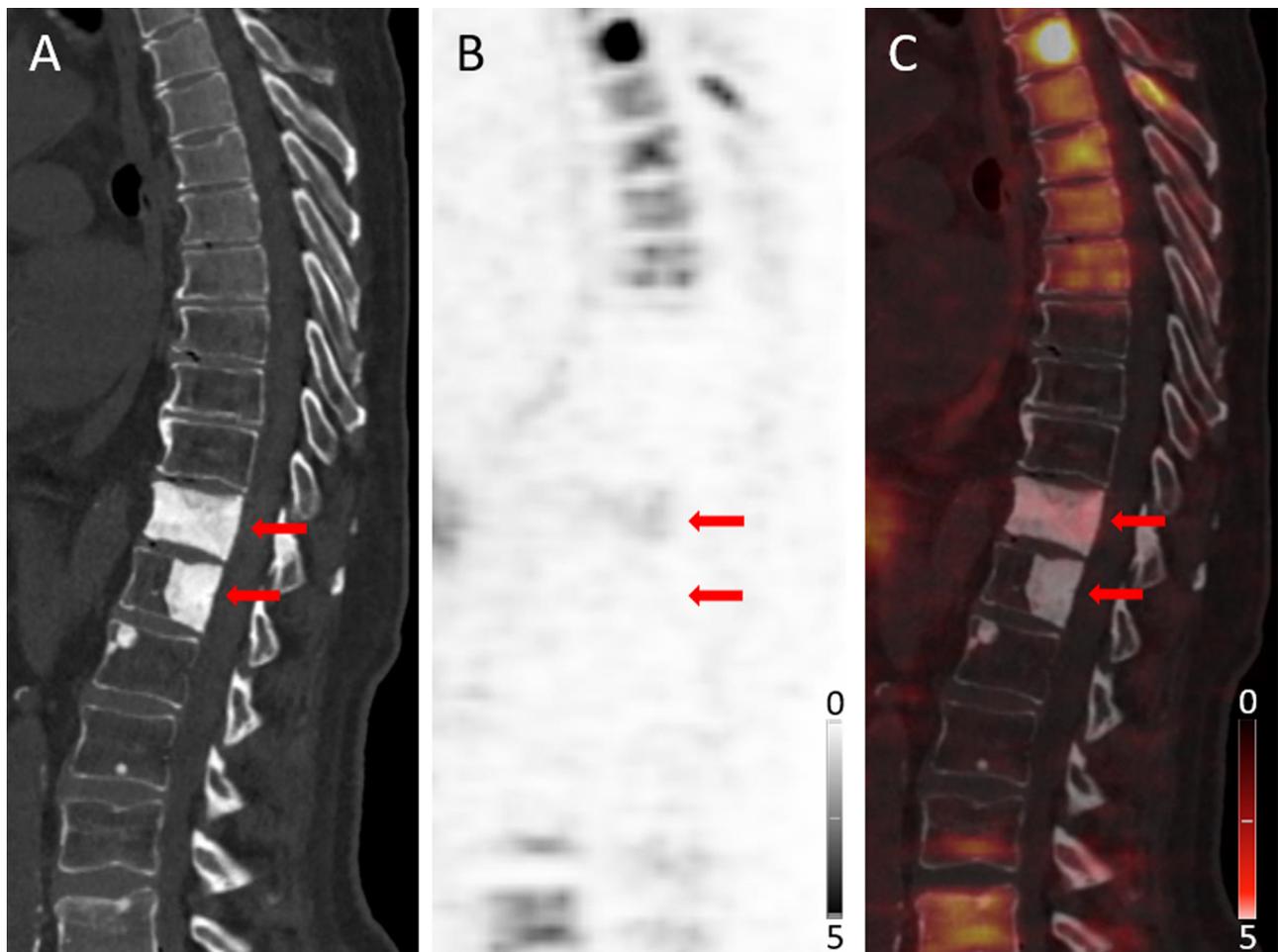
Fig. 10 – PSMA-RADS 5T: (A) sagittal bone window CT, (B) sagittal ^{18}F-PSMA-1007 PET, and (C) sagittal fused images revealed multiple metastatic disease in the spine with sclerotic changes. One lesion in the upper spine showed additional intense uptake. The other sclerotic lesions in the middle spine had only very low uptake (arrows), which is due to previous external beam radiation therapy from Th9-L2. CT = computed tomography; PET = positron emission tomography; PSMA-RADS = Prostate-specific Membrane Antigen Reporting and Data System.

sify single or multiple disease sites scheduled for local external beam radiation therapy as having responded. Further applications include assessment of therapeutic effectiveness of PSMA-RLT, once it becomes incorporated

earlier in the treatment algorithm of PC, for example, for neoadjuvant treatment or after onset of abiraterone-, enzalutamide-, or taxane-based chemotherapy [36]. In this regard, the (quantified) changes in uptake (increase or

Table 1 – Overview of different PSMA-RADS scores (version 2.0)

PSMA-RADS 1 (benign)	Benign lesion characterized by biopsy or pathognomonic finding on anatomic imaging and with focal radiotracer uptake (Fig. 1 and 2)
PSMA-RADS 2 (likely benign)	Equivocal (focal, but low level such as blood pool) uptake in soft-tissue site atypical of PC involvement (eg, axillary or hilar lymph nodes); equivocal uptake in bone lesion atypical of PC involvement (eg, uptake fused to bone lesion and strongly suspected of being degenerative or another benign etiology; Fig. 3) Upon follow-up, stable lesions without treatment are likely benign and could then be scored with PSMA-RADS 1 or 2
PSMA-RADS 3 (equivocal)	
PSMA-RADS 3A	Equivocal uptake in soft-tissue site typical of PC involvement (eg, pelvic or retroperitoneal lymph nodes; Fig. 4). If targetable, biopsy may help confirm diagnosis. Alternatively, follow-up imaging (either anatomic or PSMA-targeted PET/CT) showing progression can establish diagnosis. We recommend initial follow-up period of 3–6 mo In oligometastatic patients (>5 metastases), it is at the reader's discretion to reclassify this lesion to PSMA-RADS 4 [a]
PSMA-RADS 3B	Equivocal uptake in bone lesion not definitive but also typical of PC on anatomic imaging (ie, pure marrow-based lesion with little if any surrounding bony reaction, lytic or infiltrative lesion, or classic osteoblastic lesion; Fig. 5). Na[18]F-PET/CT or bone biopsy may be considered. Alternatively, follow-up imaging (either anatomic or PSMA-targeted PET/CT) with evidence of progression may confirm diagnosis In oligometastatic patients (>5 metastases), it is at the reader's discretion to reclassify this lesion to PSMA-RADS 4 [a]
PSMA-RADS 3C	Intense uptake in site highly atypical of all but advanced stages of PC, which requires further workup (Fig. 6). Biopsy to confirm diagnosis histologically is often preferred, although organ-specific follow-up imaging may be considered (eg, liver-protocol MRI to evaluate possible primary hepatocellular carcinoma)

Table 1 (*continued*)

PSMA-RADS 3D	Any lesion on CT that requires further workup but does not show any tracer uptake (Fig. 7) Biopsy to confirm diagnosis is often preferred, although organ-specific follow-up imaging may be applicable.
PSMA-RADS 4 **(PC highly likely)**	Intense uptake in site typical of PC but lacking definitive findings on conventional imaging (Fig. 8) [b]
PSMA-RADS 5 **(PC almost certainly present)**	Intense uptake in site typical of PC and having corresponding findings on conventional imaging (Fig. 9) [b], although obtaining tissue for genomic analysis or other purposes may be useful
PSMA-RADS 5T **(treated PC metastasis)**	Previously identified metastases after treatment (eg, irradiated sclerotic bone lesions) with or without uptake (Fig. 10)
Overall RADS score	Defined by the highest PSMA-RADS score of any of the individual target lesions

CT = computed tomography; PC = prostate cancer; PET = positron emission tomography; PSMA-RADS = Prostate-specific Membrane Antigen Reporting and Data System; RADS = reporting and data system.
All updated aspects relative to version 1.0 are highlighted in red.
[a] Lesion-based classification may be omitted in patients with large scale metastases.
[b] Given the high specificity of PSMA expression in prostate cancer cells [39] and high accurate detection rates for selected radiotracers [40,41], it is unlikely that biopsy confirmation will be needed.

decrease) can be compared, for example, between a lesion that was initially classified as PSMA-RADS 5 on baseline and 5T on follow-up. Such an approach may then allow improved risk stratification of patients prone to treatment failure or prediction of prognosis during long-term monitoring.

Moreover, relative to conventional imaging, PSMA-PET/CT has already demonstrated an improved stage migration (according to Prostate Cancer Clinical Trials Working Group 3 [PCWG3]). As such, this image modality could be used to identify PCWG3 trial patient cohorts, but also for endpoint assessments, for example, by investigating baseline or follow-up PSMA-PET/CT findings in castration-resistant PC for outcome prediction. In this regard, previous studies assessing up/downstaging on molecular imaging have not applied structured reporting systems for scan interpretation [37]. Thus, one may speculate on an even higher stage migration rate if PSMA-RADS 2.0 is incorporated, suggesting that this framework could serve as a gatekeeper for trial entries or PET-based endpoint assessments (eg, by comparing PSMA-RADS 4/5 with 5T lesions upon restaging).

Peer Review Summary

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