A pictorial view on false positive findings of ^{68}Ga-PSMA-11 PET/CT and their prognostic value in patients with prostate carcinoma after radical prostatectomy and undetectable PSA values

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Abstract

Objective: Recently, gallium-68-prostate-specific membrane antigen-11 (^{68}Ga-PSMA-11) positron emission tomography/computed tomography (PET/CT) has become a key imaging method in prostate carcinoma staging and biochemical progression, with varying sensitivities in different studies (from 40% to 80%). After four years of experience with ^{68}Ga-PSMA-11 PET/CT, we found that it is possible to detect lesions with increased PSMA expression in patients with undetectable prostatespecific antigen (PSA) levels after radical prostatectomy. The key questions we wanted to answer were as follows: if those lesions were malignant and could the early detection of those malignant lesions have a role in patient management? We aimed to identify and follow up PSMA-positive findings for a period of 4 years in patients with prostate cancer after radical prostatectomy and undetectable PSA values at the time of the examination. We also explored false-positive lesions in detail. **Subjects and Methods:** The study included all patients who underwent radical prostatectomy and had undetectable PSA values<0.05ng/mL and who underwent ^{68}Ga-PSMA-11 PET/CT between July 2019 and December 2019. We performed 220 studies and found 40 patients with these characteristics; these patients were included in this study. All of them were followed up until July 2023. Any finding with increased radiopharmaceutical accumulation above the background activity in the respective area was considered a false positive. Prostate-specific membrane antigen accumulation in established lesions was assessed semiquantitatively by the maximum standardized uptake value (SUVmax) and qualitatively by the four-point visual scale proposed in the E-PSMA recommendations. **Results:** We found 15/40 (37.5%) patients with PSMA-positive findings. These were predominantly bone changes without a corresponding CT abnormality or discrete cystic or osteoblastic lesions with above-background increased PSMA expression. The mean SUVmax of these nonspecific lesions was 3.02 (SD 2.86). After 3.5-4 years of follow-up, biochemical progression was found in only two of the patients. The great sensitivity of the method nowadays is a powerful engine for the development of new therapeutic options. On the other side, the lower specificity due to false positive findings, if misinterpreted, might lead to switching to a higher stage, with the planned radical treatment replaced by palliative treatment. **Conclusion:** The presence of ^{68}Ga-PSMA-11 PET/CT-positive findings in patients after radical prostatectomy and an undetectable PSA had a low predictive value for future progression. The interpretation of ^{68}Ga-PSMA-11 PET/CT should always include a complex assessment of the clinical setting-the risk group, PSA value and degree of PSMA accumulation in the lesions. In these situations, further clarification of PSMA-positive findings is appropriate before deciding to change treatment.

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Introduction

The high sensitivity of gallium-68-prostate-specific membrane antigen-11 (^{68}Ga-PSMA-11) positron emission computed tomography/computed tomography (PET/CT) for the detection of small metastatic lesions (sometimes less than 2-3mm) is the reason for the growing interest and wide application of this imaging method. It varies between 40% and 80% in different studies [1]. However, the increased sensitivity of these new imaging methods is often associated with the migration of patients to a higher stage, which does not always have a positive effect on survival (the Will Rogers phenomenon [2]). After a period of four years of experience with ^{68}Ga-PSMA-11 PET/CT, we found that it is possible to establish lesions with increased PSMA expression in patients with undetectable prostate specific antigen (PSA) values. These were predominantly bone changes, without corresponding lesions on CT images or discrete cystic or osteoblastic findings with increased PSMA expression above the background, which are difficult to interpret. The latter can be misinterpreted as metastatic, despite the undetectable PSA value after prostatectomy. The main issue with these equivocal findings was in these patients who continued hormone therapy after biochemically recurrent disease. If we consider these lesions as latent malignant lesions, can nuclear medicine physicians predict future progression, and do they require additional local treatment? A change in therapeutic approach in these upstaged pa-

tients does not always affect survival and may negatively affect quality of life related to over- or undertreatment.

Subjects and Methods

The purpose of this study was to identify and follow up PSMA-positive findings for a period of 4 years in patients after radical prostatectomy and an undetectable PSA value at the time of examination and to study their prognostic value.

The study included all patients who underwent radical prostatectomy and had undetectable PSA levels less than or equal to 0.05ng/mL scanned with ^{68}Ga-PSMA-11 PET/CT between July 2019 and December 2019. We examined 220 patients for that period of time. These criteria were met by a group of 40 patients (Table 1). The patients' indications included - patients on adjuvant treatment (n=23), seven patients with previous biochemical relapse (BCR) and 5 patients and patients with persistent PSA after treatment who reached the PSA nadir. Six of the patients were referred for an examination because of high-risk disease and one or a combination of R1 disease after prostatectomy, positive lymphovascular invasion (LV1) or positive perineural invasion (Pn1). Five of the patients had no previous treatment or high-risk disease but had nonspecific complaints, such as fatigue and bone and joint pain.

Table 1. *Patients' characteristics.*

Patients' characteristics		Number (%)
T-stage	pT2a	3 (7.5)
	pT2c	18 (45.0)
	pT3a	6 (15.0)
	pT3b	13 (32.5)
ISUP Grade	1	8 (20.0)
	2	15 (37.5)
	3	8 (20.0)
	4	5 (12.5)
	5	4 (10.0)
Adjuvant treatment	No	17 (42.5)
	Hormonetreatment	10 (25.0)
	Radiotherapy	5 (12.5)
	Radio-Hormonotherapy	8 (20.0)
BCR	Yes	7 (17.5)
	No	28 (70.0)
	PSA persistence	5 (12.5)
iPSA, mean (± SD)	14.15 (17.88)	

BCR- biochemical recurrence; PSA- prostate specific antigen

The images were reviewed again after a 4-year experience with ^{68}Ga-PSMA-11 PET/CT. The patients were between 54 and 78 years old (mean 68.4 years). The pathological T stage ranged from pT2a to pT3b, and the International Society of Urological Pathology (ISUP) score [3] ranged from 1 to 5. The initial PSA (iPSA) concentration ranged from 4.06ng/mL to 108. 40ng/mL, with a mean of 14.15ng/mL (SD 17.88). None of the patients had previously documented metastatic disease.

There were a total of 23/40 patients who received adjuvant treatment - 10 (43.5%) with hormonal therapy, 5 (21.8%) after pelvic radiotherapy (RT) or a combination of both - for 8 (34. 8%) patients. There were 7 patients after BCR (17.5%), and 5 had previous PSA persistence (12.5%). Three of the patients had both adjuvant treatment and a BCR, and three had both adjuvant treatment and persistent PSA treatment. Biochemical relapse patients - 2/7 were treated with salvage RT, 2/7 with hormonal therapy and 3/7 with combined salvage RT + hormonal treatment. All 5 patients with persistent PSA after prostatectomy were treated with a combination of salvage radiotherapy (RT) and hormone therapy, which included a combination of a luteinizing hormone-releasing hormone (LHRH) agonist and an anti-androgen (*leuprolide acetate* and *bicalutamide*). For twenty-eight of the patients (70.0%), the PSA nadirs reached undetectable values after prostatectomy (PSA <0.04ng/mL), without elevation, including at the time of the ^{68}Ga-PSMA-11 PET/CT scan. All patients were followed up until July 2023, at 42 to 48 months (mean, 44.68 [±SD 1.421]). Follow-up included a review of documentation and PSA values and a review of additional imaging studies from the hospital database (CT/MRT) and ^{68}Ga-PSMA-11 PET/CT.

Any finding of increased accumulation above the background activity of the corresponding area was considered PSMA-positive. Patients with PSMA-positive findings were characterized as false positives (FP) and analyzed in detail using corresponding CT (in all patients) and/or magnetic resonance imaging (MRI) studies (in 4 of them). The intensity of PSMA accumulation was assessed semi-quantitatively by the maximum standardized uptake value (SUVmax) and qualitatively by the four-level visual scale proposed by the European Association of Nuclear Medicine (EANM) (visual score) [4]. If more than one finding was present, the one with the highest activity was included. Findings were categorized according to the likelihood of the presence of metastases according to a 5-point confidence scale for the interpretation of PSMA-positive findings [5].

^{68}Ga-PSMA-11 PET/CT study protocol

Gallium-68-PSMA-11 PET/CT imaging was performed according to the EANM joint procedure guideline/SNMMI procedure standard for prostate cancer imaging 2.0. The examination was performed on a Philips Gemini TF PET/CT system equipped with 16 CT slices. A PET/CT scan was performed 50min after ^{68}Ga-PSMA-11 administration. A whole-body scan was taken from the vertex of the skull to the mid-thigh. We performed a low-dose CT. Depending on the weight of the patients, a dose of 200-300MBq was administered via a catheter placed in the antecubital vein.

Ethical considerations

All of the patients included in the study signed an informed

consent that the results of their imaging studies would be used in scientific projects in compliance with the terms of confidentiality. This retrospective study was conducted according to the principles of the 1964 Declaration of Helsinki.

Statistics

The statistical analysis was performed using IBM® SPSS® Statistics, v.19.0.0. We processed qualitative patient data using descriptive statistics. Quantitative data are presented as means, ranges and standard deviations. Four-year progression-free survival was estimated using Kaplan-Meier analysis. The tables were made with Microsoft Office 2019 Professional Plus.

Results

We found 15/40 (37.5%) patients with PSMA-positive lesions. There were 34 FP findings, including 20 bone lesions, and 14 soft tissue findings in seven patients, including 2 hemangiomas (in the spleen (Figure 1A) and liver (Figure 1B)), 9 enlarged lymph nodes with subtle activity (Figure 1C), 2 in the sacral ganglia (Figure 1D) and one in the pleural thickening (Figure 1E). Only bone lesions were found in 8 patients, and 3 patients had bone lesions and lesions at another site of false-positive finding- hemangioma or suspicious lymph nodes.

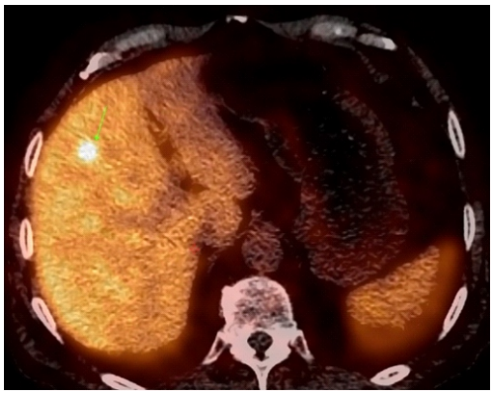

Figure 1. Gallium-68-PSMA-11 non-bone PSMA-positive lesions: **1A** ^{68}Ga-PSMA-11 transverse fused image showing a PSMA-positive liver hemangioma (arrow).

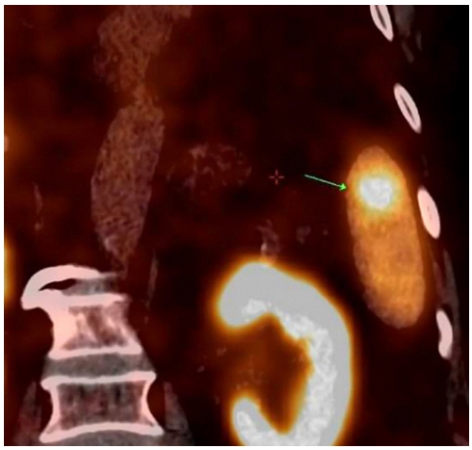

Figure 1B. Gallium-PSMA-11 PET/CT, coronal fused image, showing a PSMA-positive spleenhemangioma (arrow).

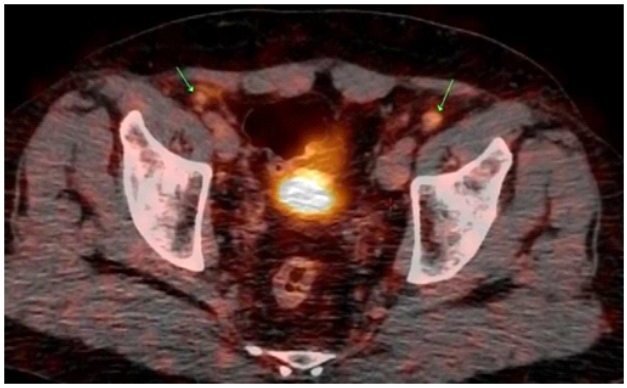

Figure 1C. Gallium-68-PSMA-11 PET/CT transverse fused image showing bilateral PSMA-positive reactive external iliac lymph nodes (arrows).

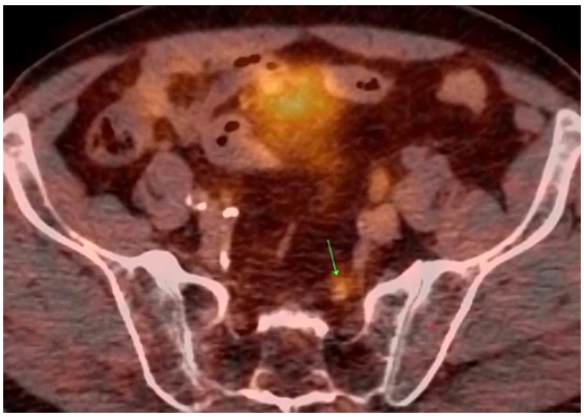

Figure 1D. Gallium-68-PSMA-11 PET/CT transverse fused image of a patient with a PSMA-positive left sacral ganglia (arrow).

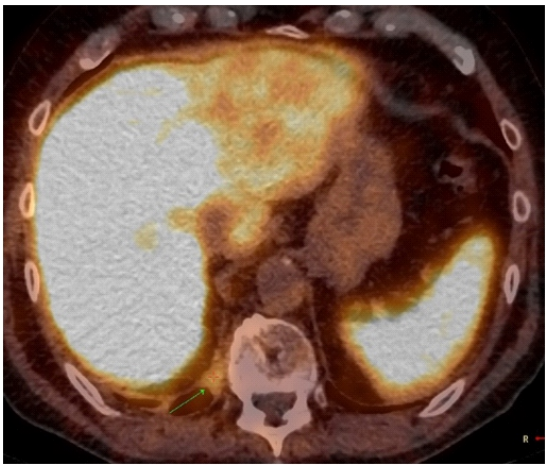

Figure 1E. Gallium-68-PSMA-11 PET/CT transverse fused image of a patient with PSMA-positive inflammatory pleural thickening (arrow).

Eight of the bone lesions (8/20) were discrete osteosclerotic, 6 had an osteosclerotic rim, 4 had focal PSMA-expressing lesions with no corresponding lesion on CT, and 2 had eminent osteosclerotic lesions. Sixteen of the lesions were confirmed to be benign by CT/MRI as bone cysts-6 (those with an osteosclerotic rim), two osteodegenerative (discrete osteosclerotic), five healing fractures/traumatic (lesions in symmetrical ribs-4 osteosclerotic and 1 with no corresponding lesion), two bone islands (2 eminent osteosclerotic), and one disc herniation (with no corresponding lesion).

Four of the bone lesions remained unclear - one without a corresponding bone lesion and 3 with discrete osteosclerosis - not confirmed as typical metastatic lesions on CT/MRT. Two of the lesions were found in one patient who had a biochemical recurrence one year before the study. He was treated with pelvic radiotherapy and hormone treatment and had undetectable PSA values six months before the first ^{68}Ga-PSMA-11 PET/CT. The lesions found were a discrete osteosclerotic lesion in the left iliac bone and a focal area of high PSMA expression in the 7th rib on the right without a corresponding bone lesion (Figure 2A) After this 4-year follow-up study, there was no change in the lesions, and no increase in PSA was detected. (Figure 2B) This patient raised concerns about whether these lesions were PSMA-positive latent metastases. This could not be excluded, but nevertheless, he had a stable disease for a follow-up period of four years.

The second patient, who had a discrete osteosclerotic lesion in the 5th rib on the left, received adjuvant radiotherapy and hormone therapy because of R1 resection but achieved the PSA nadir and had no biochemical recurrence, suggesting no metastatic disease (Figure 3).

The third patient had discrete PSMA positive osteosclerotic lesions in the right iliac bone (Figure 4). He had adjuvant treatment for R1 prostatectomy with radiotherapy and hormone therapy and no documented BCR and metastatic disease. There was no PSA elevation in the course of the study.

As a result of the follow-up, after 42-48 months, an increase in PSA was found in 2 patients, which determined an86.7% 4-year progression free survival (Figure 5). Although biochemical recurrence occurred in two of the patients (13.3%), none of the recurrences were related to the suspected lesions. In the first patient, despite the 4 observed PSMA positive bone cysts, one bone island and an inguinal LN, a local recurrence was found after 31months of follow-up (Figure 6).

The second patient with biochemical progression in the course of the follow up had a focal PSMA-positive bone lesion in L1 without a corresponding lesion on CT (Figure 7). Magnetic resonance imaging revealed a foraminal disc herni-

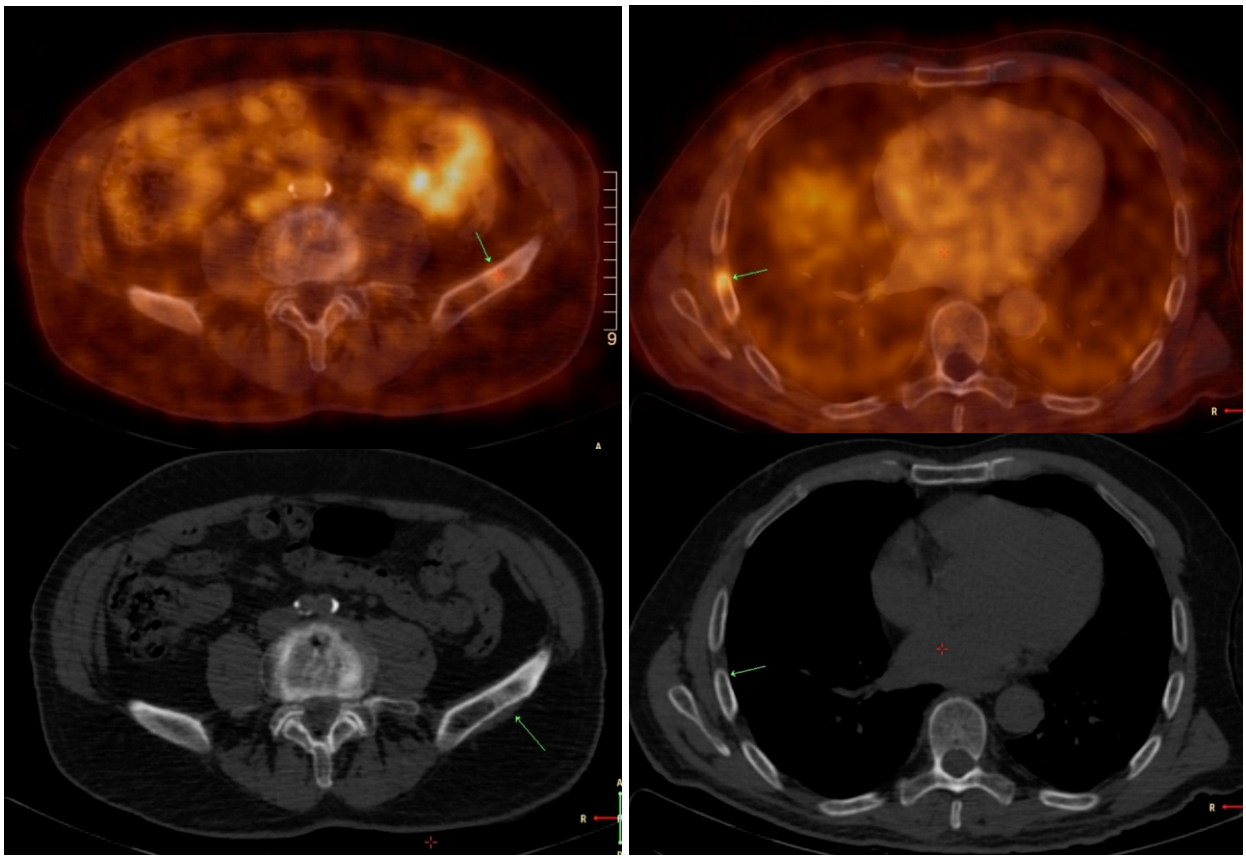

Figure 2A. Gallium-68-PSMA-11 PET/CT transverse fused images and a CT images of a patient with a PSMA positive discrete osteosclerotic lesion in left iliac bone and 7th rib on the right.

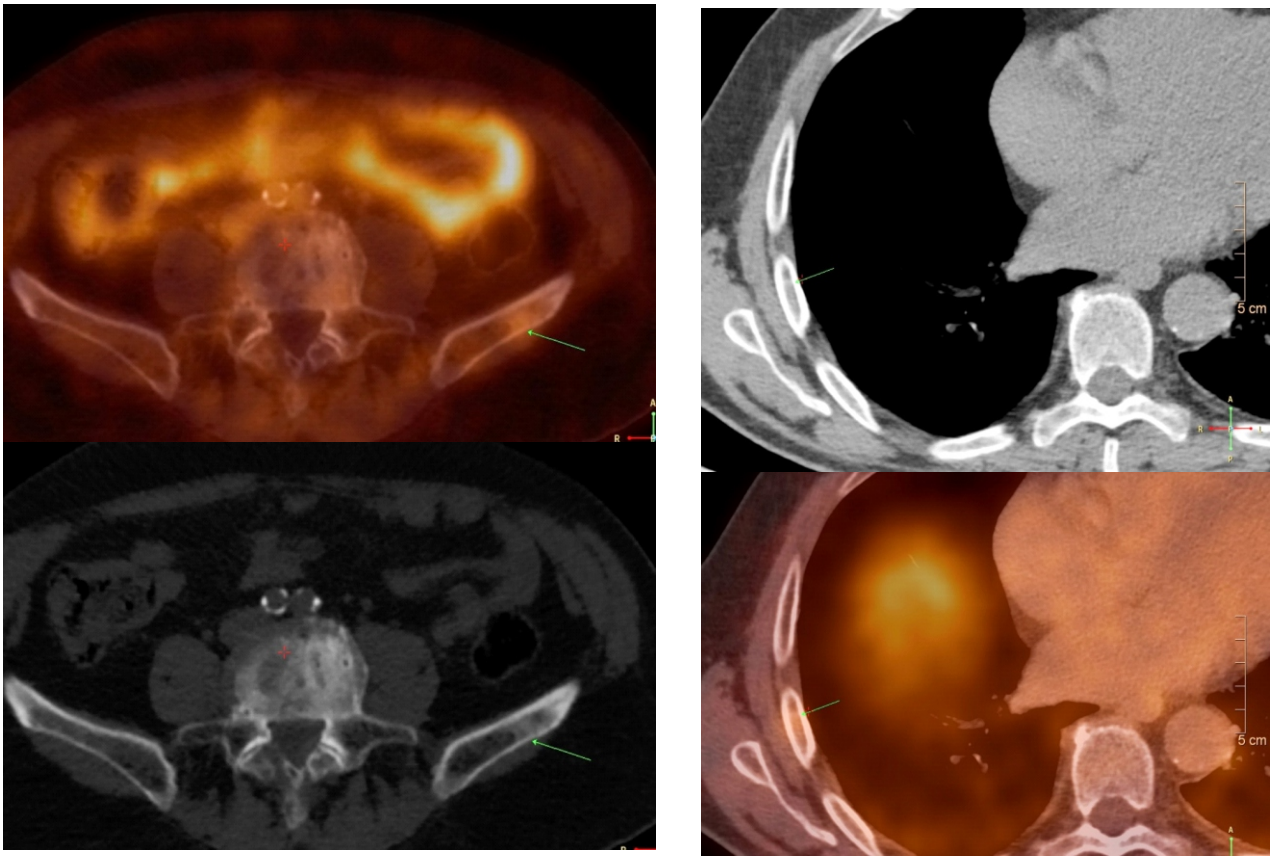

Figure 2B. Gallium-68-PSMA-11 PET/CT transverse fused images and a CT images of the same patient 43 months later with same lesions- a PSMA positive discrete osteosclerotic lesion in the left iliac bone and 7th rib on the right.

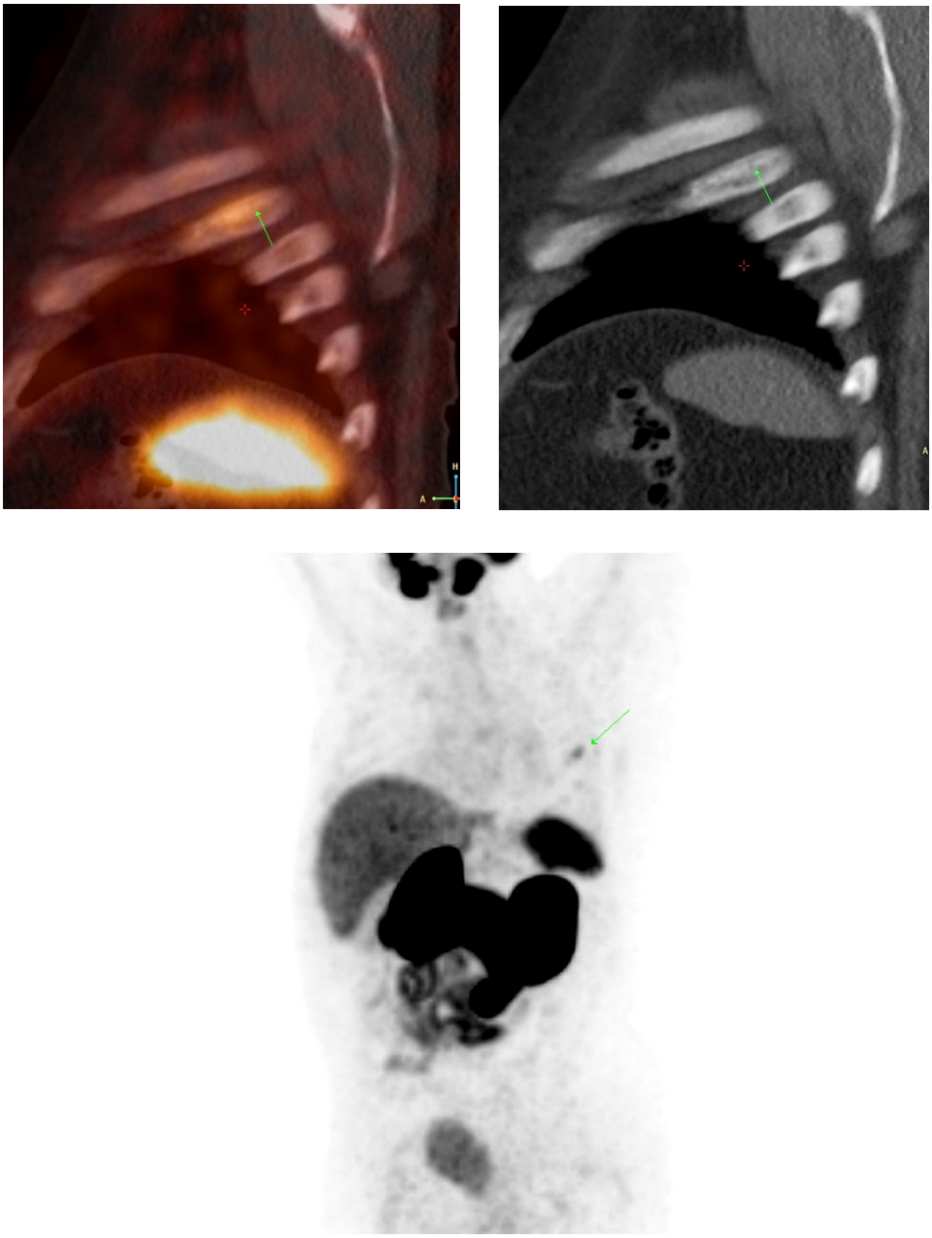

Figure 3A. Gallium-68-PSMA-11 PET/CT sagittal fused, CT image and MIP of a patient with a PSMA positive discrete osteosclerotic lesion in the 5th rib on the left.

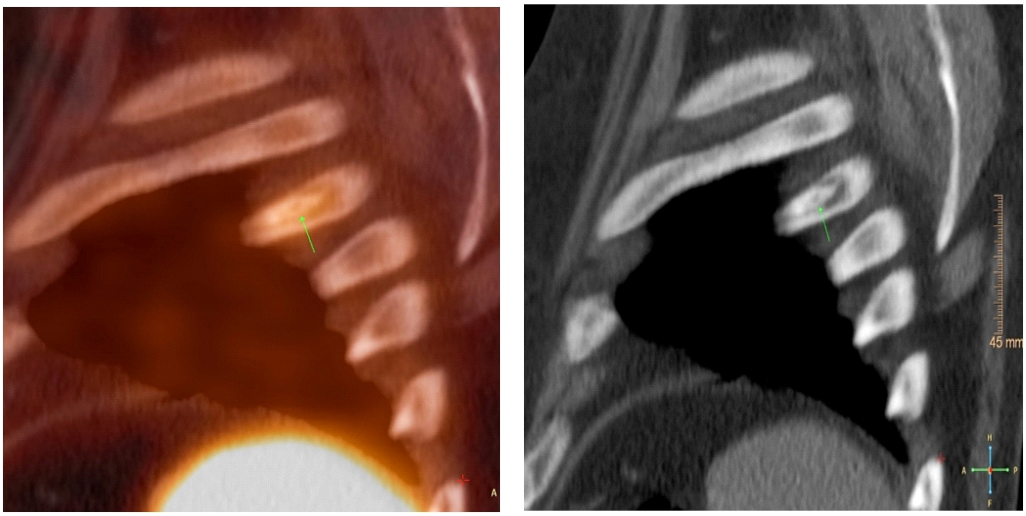

Figure 3B. Gallium-68-PSMA-11 PET/CT sagittal fused and a CT image of the same patient 32 months later with the same PSMA positive findig-discrete osteosclerotic lesion in the 5th rib on the left.

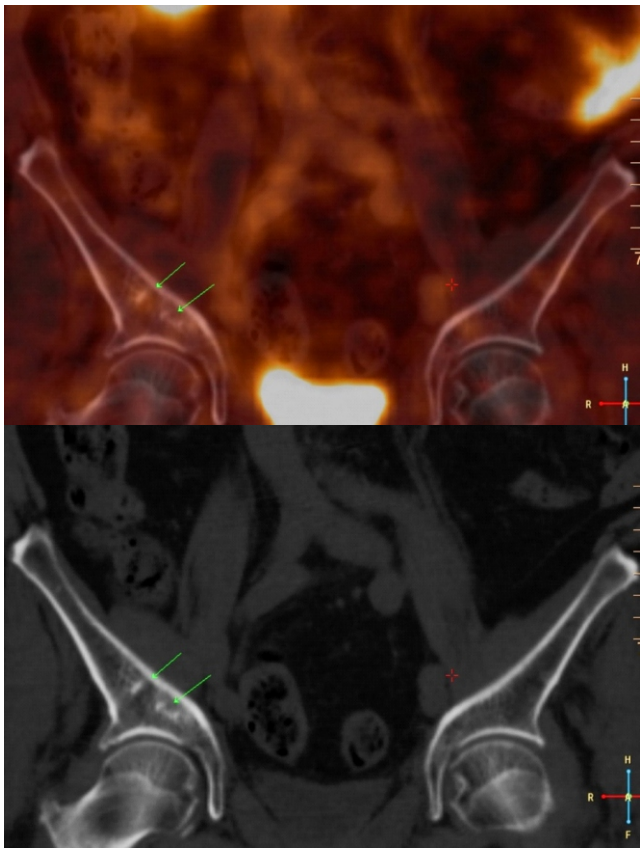

Figure 4. Gallium-68-PSMA-11 PET/CT coronal fused and CT image of a patient with PSMA positive discrete osteosclerotic lesions in the right iliac bone.

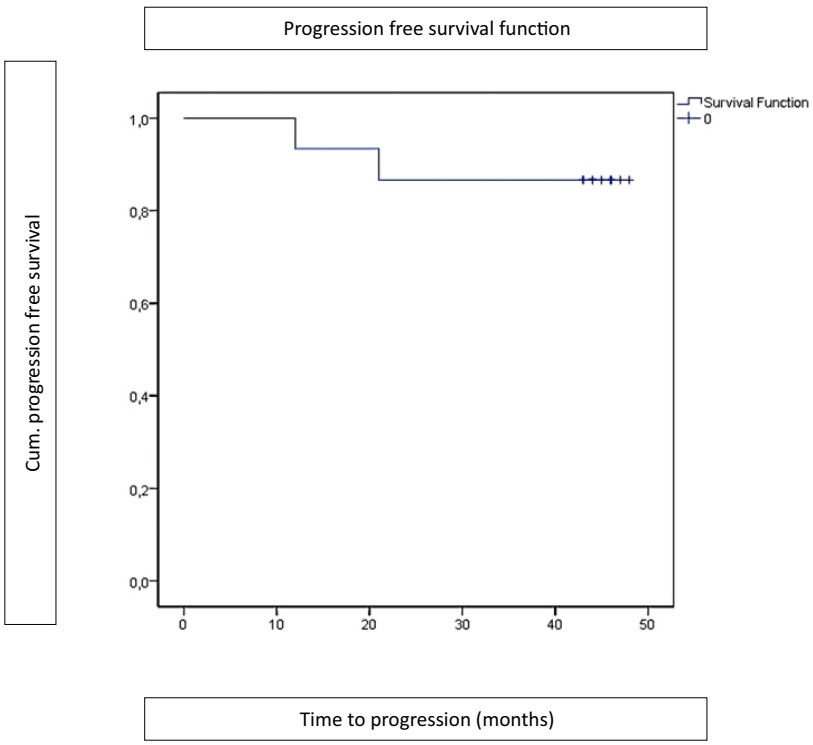

Figure 5. Kaplan-Meier progression-free survival function of the patients with PSMA positive findings after radical prostatectomy and undetectable PSA values in ^{68}Ga-PSMA-11 PET/CTperformed between July 2019 and December 2019.

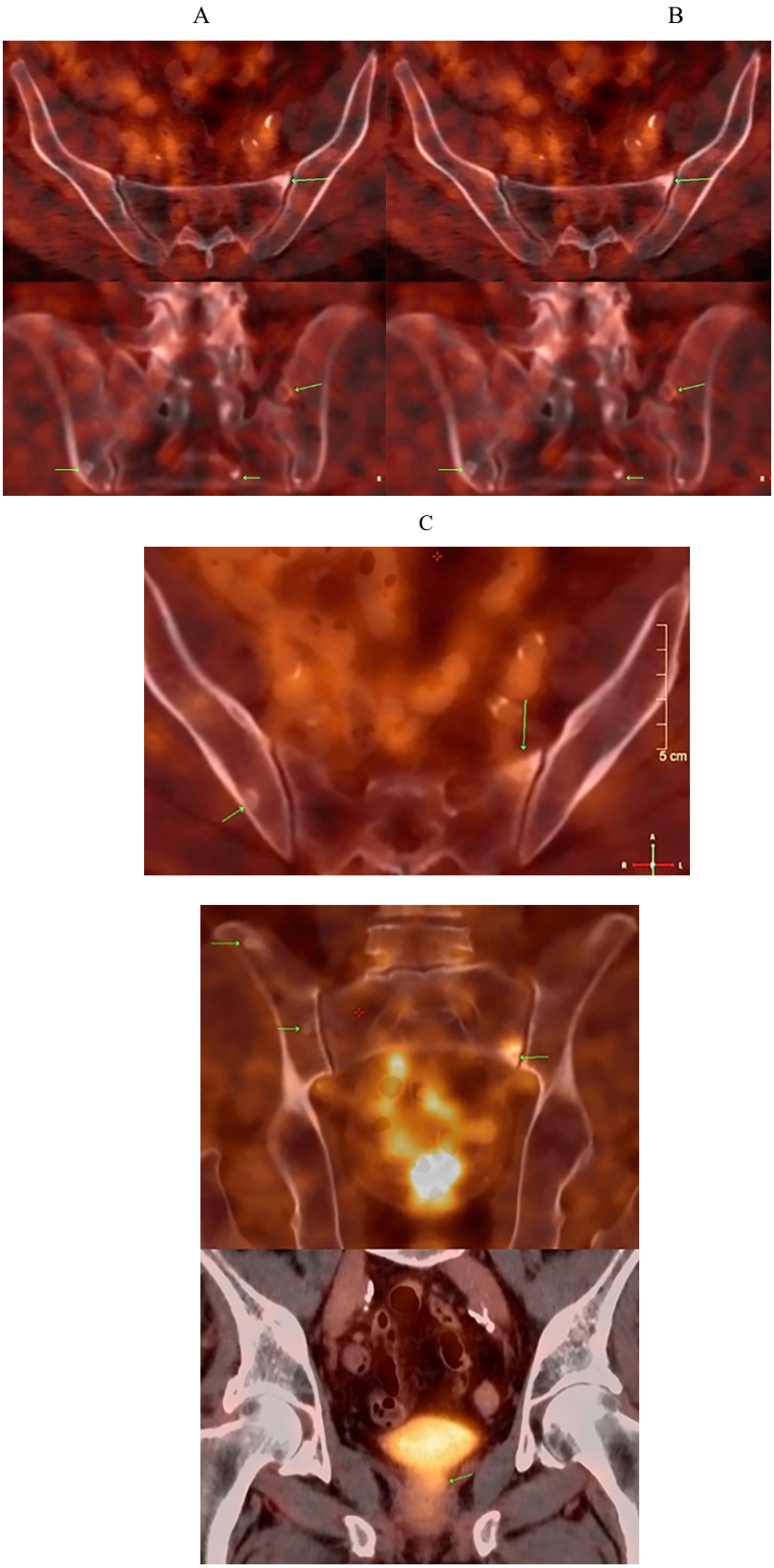

Figure 6. Gallium-68-PSMA-11 PET/CT fused images (A and C- transverse view, B, D and E- coronal view) of a prostate cancer patient, pT3bN0M0, GS 4+4=8, iPSA- 11.6. In 2015, a prostatectomy and pelvic lymph dissection were performed. First ^{68}Ga-PSMA-11 PET/CT - November 2019. (A) A PSMA-positive osteoblastic structure in the sacrum (arrow) and (B) 4 pelvic bone cysts (arrows). His PSA level slightly increased in July 2020 - 0.075ng/mL PSA, PSAdt- 12 months. The second ^{68}Ga-PSMA-11 PET/CT in June 2021 was interpreted as stable disease (C) with the same pelvic bone cysts (left arrow) and an osteosclerotic structure in the sacrum (right arrow). Third ^{68}Ga-PSMA-11 PET/CT one year later (in June 2022): PSA- 0.192- revealed the same bone lesions in the pelvis (left arrows) and sacrum (right arrow) (D) but also a focal zone in the prostate bed (E), with an arrow showing an area of slightly greater PSMA accumulation, which was suspected for local recurrence. The latter was also interpreted as suspect on magnetic resonance tomography (MRT) images.

ation. Eleven months after ^{68}Ga-PSMA-11 PET/CT, the patient was admitted for another ^{68}Ga-PSMA-11 PET/CT study with a mildly elevated PSA level of 0.141ng/mL. Gallium-68-PSMA-11 PET/CT showed the same focal PSMA-positive lesion as that in the baseline study. Ten months later, hormonal therapy was started because of a progressive increase in the PSA concentration of up to 0.200ng/mL. A third ^{68}Ga-PSMA-11 PET/CT study was performed 3 months after hormonal therapy, and the PSA level was undetectable, revealing the same lesion in L1.

When quantifying the lesions, the resulting mean SUVmax of all false-positive lesions was 3.02 (range 1.0 to 12.8, median 2.1, SD 2.86). The highest SUVmax values were found for the hemangiomas (12.8- liver, 3.7- spleen) and for one of the bone lesions, proven by MRT as foraminal disc herniation, for which the corresponding CT image SUVmax was 3.4. According to the visual score (V-score PSMA) proposed for the interpretation of images by EANM, hemangiomas in the liver were categorized with a score of 2, with activity exceeding that of the liver but lower than that of the salivary glands. According to the confidence scale proposed by the EANM, lesions in this population fall into category 3 - borderline findings - a high-activity lesion, with an atypical location for a metastatic lesion from prostate carcinoma. The bone lesion was otherwise in a location typical for prostate cancer (Figure 7) without any CT lesion, opposing a higher category score of 4. The visual grade in most of the patients (n=12) was a score of 1, with activity lower than that of the liver, and the osteophyte in the sacrum and a rib bone island had discrete activity close to the background score of 0.

Discussion

The introduction of ^{68}Ga-PSMA-11 PET/CT had a significant impact on the treatment of prostate cancer patients. The role of methodology in BCR is most prominent. It can also be used in the staging of intermediate- and high-risk patients and has been found to influence treatment decisions in up to half of patients [6, 7]. However, its role in evaluating the effect of treatment still remains unclear, although a consensus article was published in 2020 [8].

After the initial enthusiasm regarding the great sensitivity and specificity of ^{68}Ga-PSMA-11 PET/CT, which allows visualization of subclinical metastatic lesions, it was found that neither PSMA expression was prostate-specific nor the ligand itself [9]. The method is highly sensitive, but its specificity decreases due to the presence of false positive findings, which may be observed physiologically or due to various benign and malignant diseases. Prostate-specific membrane antigenligands have been found in lesions with increased osteoblastic activity, such as osteoarthritis, osteophytes, healing fractures, after radiation therapy, Paget's disease, and fibrous dysplasia. Corresponding anatomical bone changes visible on CT are frequently absent. Nonspecific accumulation of PSMA was also observed due to increased expression in the endothelial cells of the neovasculature, as well as increased

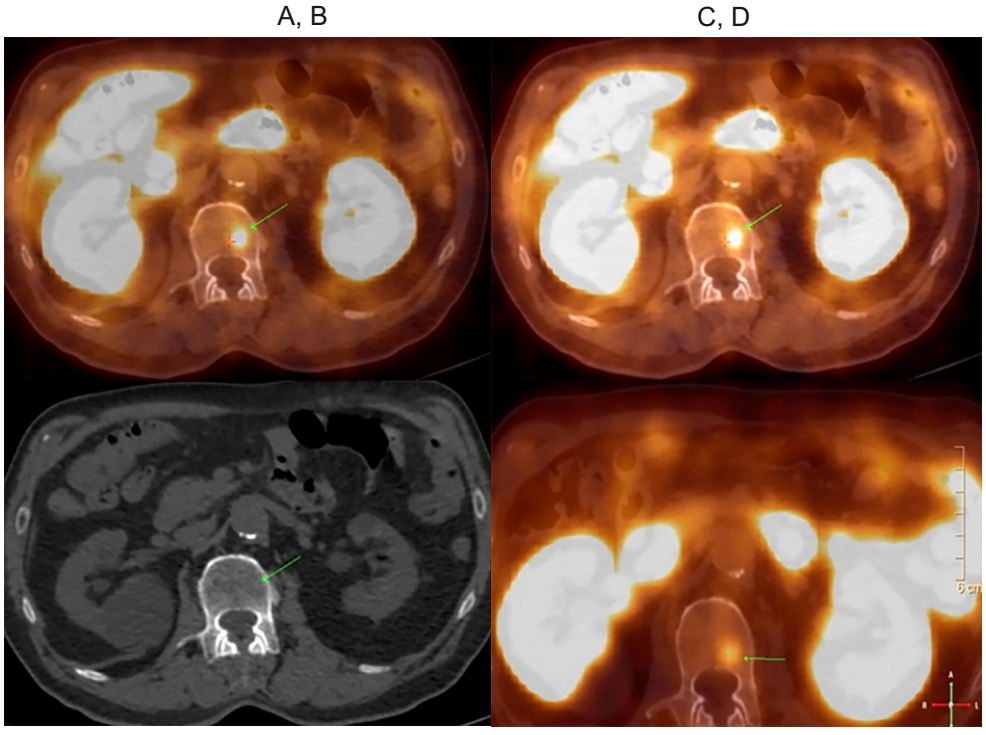

Figure 7. Gallium-68-PSMA-11 PET/CT transverse fused images (A, C and D) and a CT image (B) demonstrating a prostate cancer patient after radical prostatectomy and pelvic lymph dissection in 2018; pT2 pN0 cM0, GS 3+4=7, and iPSA - 18.87ng/mL. The first ^{68}Ga-PSMA-11 PET/CT was performed in October 2019 (A and B). (A) A focal PSMA-positive lesion was found at L1 (arrow) without a corresponding CT lesion (B) (arrow). An increase in the PSA concentration was detected in September 2020 - 0.141ng/mL. A second ^{68}Ga-PSMA-11 PET/CT (C) revealed the same focal vertebral lesion (arrow). Hormonal treatment started in August 2021. In October 2021, a third ^{68}Ga-PSMA-11 PET/CT was performed (D), and the PSA level was undetectable. D)shows the same focal lesion on the third ^{68}Ga-PSMA-11 PET/CT (arrow). The patient was confirmed to have foraminal disc herniation via MRT.

vascular permeability to inflammatory cells and macrophages expressing folate receptors [10].

The National Comprehensive Cancer Network (NCCN) recommends histologic or radiographic confirmation of involvement detected by positron emission tomography (PET) whenever feasible due to the presence of false positives. To reduce the false-positive rate, physicians should consider the intensity of PSMA uptake and correlative CT findings when interpreting scans. [11] Several reporting systems have been proposed but have not been validated or widely used. [12, 13].

In clinical practice, any PSMA-positive lesion detected in the staging of intermediate- or high-risk prostate cancer patients is considered suspicious for metastatic disease, except for those proven benign by other imaging methods or histology. Histological validation of such findings is often impossible. In many studies, the origin of these lesions has remained unclear [1].

In the present study, we considered PSMA-positive lesions from a different perspective, assuming that all PSMA-positive lesions in patients with undetectable PSA after radical prostatectomy were false positive. Some of our patients had ongoing adjuvant treatment or successful salvage and hormonal therapy after local recurrence or BCR and undetectable PSA values. None of them had documented metastatic disease. We identified 11 patients with 20 false-positive bone lesions. The most common false-positive lesions were found in the ribs (n=9 in five patients) and in the iliac bones (n=8) in 5 patients. Chen et al. reported that 98.4% of solitary PSMA-positive lesions in the ribs were benign [14]. An explanation for these bony focal lesions, termed by some authors "nonspecific" or "non-PSMA-related", is still lacking. Potentially, the etiology of these lesions is likely related to bone remodeling. When using digital PET/CT systems, these findings are seen even more frequently, up to 70%, than when using analog systems, up to 40% [9]. Wondergem et al. (2021) performed histopathological examination of equivocal bone lesions on fluorine-18 (^{18}F)-PSMA-1007 in three patients. None of these lesions proved to be malignant. Histopathology revealed benign etiologies: non-specific necrosis, non-specific lytic bone lesions with reactive changes, and normal bone tissue. [15] Furthermore, false-positive lesions are detected more often using ^{18}F-PSMA-1007 PET/CT than with ^{18}F-2-(3-{1-carboxy-5-[(6-[^{18}F]fluoro-pyridine-3-carbonyl)-amino]-pentyl}-ureido)-pentanedioic acid (DCFPyL) [15, 16].

Arnfield et al. (2021) suggested that lesions with an SUVmax<7.2 were more likely to be benign [17]. In the present study, the mean SUVmax for false positives was 3.02, with a median of 2.1. The highest activity was observed in hemangiomas (12.8 in the liver and 3.7 in the spleen), and the activity was significantly lower in the bone lesions, in which the activity ranged from 1.0 to 3.4. According to the confidence scale of the EANM, which determines the risk of metastatic disease, most of the lesions have a score of 3, which indicates that they are equivocal lesions.

In a prospective randomized multicenter study (proPSMA study) published in 2020 and conducted on 302 patients prior to radical surgery or radiation therapy, ^{68}Ga-PSMA-11 PET/CT detected 37.0% more lesions and led to a change in therapeutic approach in 23.0% of patients compared to the combination of CT and bone scintigraphy (WBS) [1]. As a result, these patients have been switched to a higher stage, with the planned radical treatment replaced by palliative treatment. This raises the following questions: if these lesions are truly metastatic and would this switch in patient management result in a better patient outcome? There are randomized controlled trials proving the role of the combination of adjuvant hormone therapy and radical radiation therapy in terms of survival in patients with high-risk prostate cancer [18]. The migration of patients with a single small PSMA-positive lesion to the metastatic group would result in a switch to less radical palliative treatment methods and a corresponding reduction in the chance of cure. In this vein, patients with equivocal lesions detected by ^{68}Ga-PSMA-11 PET/CT may be denied life-prolonging prostate cancer treatment. On the other hand, ^{68}Ga-PSMA-11 PET/CT data may lead to currently redundant toxic chemotherapy. To date, the benefit of changing treatment after staging with ^{68}Ga-PSMA-11 PET/CT to improve patient survival compared with that after staging with conventional imaging modalities has not been established. However, the biological and clinical significance of small PSMA-positive distant metastases has not been determined. In this regard, the EAU-EANM-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer also lack data from randomized controlled trials (RCT) evaluating the management and outcome of patients with (and without) metastases detected by more sensitive imaging before evidence-based decisions can be made on how to treat those patients [19].

An interesting issue is the persistent PSMA expression in equivocal lesions, especially in bones, in patients with undetectable PSA values on hormonal therapy. The main question is whether those patients require additional regional treatment for those lesions. According to our study, these lesions have low prognostic value for future progression, and none of those patients had progressive bone metastatic disease during the four years of follow-up.

Extensive workup of imaging findings that may otherwise be benign or indolent (i.e., overdetection) can lead to significant patient anxiety, additional and unnecessary imaging, and invasive procedures that carry their own risks for adverse outcomes.

Additionally, two important issues are raised in this study. First, baseline ^{68}Ga-PSMA-11 PET/CT might be needed for all patients, regardless of the ISUP score, to account for false-positive lesions in each patient in case of future progression. Second, we should remember that in the case of treatment with lutetium-177-PSMA, the absorbed dose will be greater because of false PSMA-positive lesions accumulating the radiopharmaceutical.

In conclusion, ^{68}Ga-PSMA-11 PET/CT-positive findings in radically treated patients with undetectable PSA levels have low prognostic value for future progression. These findings confirm the importance of elevated PSA levels as a major marker of progression, and further workup is needed to avoid overdiagnosis of progressive disease. The interpretation of ^{68}Ga-PSMA-11 should always include the clinical setting, patient risk group, PSA value and degree of accumulation in the lesions.

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