# Isoprotrace®

10 µg Gozetotide (PSMA-11)

kit voor radiofarmaceutisch preparaat

# Educatief zelfstudiemateriaal voor voorschrijvers over de risico's van gozetotide.

Dit materiaal beschrijft aanbevelingen om belangrijke risico’s van gozetotide te beperken of te voorkomen.

Het materiaal is beoordeeld door het College ter Beoordeling van Geneesmiddelen (CBG).

Aanvullende informatie betreffende Gozetotide is beschikbaar in de Samenvatting van productkenmerken (SmPC) en bijsluiter op www.geneesmiddeleninformatiebank.nl

Version 0.3
September 2024

## Meld bijwerkingen bij het Nederlands Bijwerkingencentrum Lareb

Het is belangrijk om na toelating van het geneesmiddel vermoedelijke bijwerkingen te melden. Op deze wijze kan de verhouding tussen voordelen en risico's van het geneesmiddel voortdurend worden gevolgd. Beroepsbeoefenaren in de gezondheidszorg wordt verzocht alle vermoedelijke bijwerkingen te melden via het Nederlands Bijwerkingencentrum Lareb; website www.lareb.nl

# Isoprotrace®

10 µg Gozetotide (PSMA-11)

Kit for radiopharmaceutical preparation

# Educational Material for HCPs

# Legal Disclosures

- Expert recommendations in accordance with the EAU-EANM-STRO-ESUR-ISUP-SIOG guidelines on PCa
- Local law, national regulations, and guidelines are not affected by the information presented; these should be taken into consideration
- The gallium ($^{68}$Ga) gozetotide image interpretation training (educational material for HCPs) has been developed as an additional resource to help you familiarize yourself with techniques for the safe and effective usage of gallium ($^{68}$Ga) gozetotide
- Responsibility of the accurate and timely acquisition, and interpretation of images using gallium ($^{68}$Ga) gozetotide PET/CT scanning rests with the nuclear medicine physician or radiologist supervising the PET/CT imaging facility
- The gallium ($^{68}$Ga) gozetotide image interpretation training is not intended as a substitute for the independent medical judgement of the physician(s) responsible for the individual patient's management, nor is it a guarantee of any specific clinical results
- The Educational Material for HCPs were prepared based on peer reviewed publications and video educational presentations from well recognized organizations with support of Dr. Haim Golan, nuclear medicine physician and medical advisor.

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# Isoprotrace® Image Interpretation Training: Purpose of the Document

Misinterpretation of PET images may lead to patient misdiagnosis. In case of false positive image interpretation, the patients may be exposed to treatment agents whose side effects may be clinically impactful and the patient may be denied a potentially relevant treatment while still expected to receive standards of care.

This online material regarding image interpretation training contains the following information:

- Biochemical background
- Patient administration and scanning protocol
- Image reading and interpretation guidelines

This training provides essential information on the risks associated with Isoprotrace® PET imaging interpretation errors.

# Isoprotrace® – Introduction
# Therapeutic indications

- *It is important to report suspected side effects after approval of the medicine.*
  *This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.*

This medicinal product is for diagnostic use only.

After radiolabeling with gallium (68Ga) chloride solution, Isoprotrace® is indicated for positron emission tomography (PET) of prostate-specific membrane antigen (PSMA)-positive lesions in men with prostate cancer in the following clinical settings:

- Primary staging of patients with high-risk prostate cancer prior to primary curative therapy.
- Suspected prostate cancer recurrence based on elevated serum prostate-specific antigen (PSA) level, after primary curative therapy.

# Contraindications for PSMA-11 PET-CT

Hypersensitivity to the active substance or to any of the excipients listed below or to any of the components of the labelled radiopharmaceutical.

- List of excipients :
  - Hydrolyzed gelatine
  - Sodium acetate anhydrous
  - Sodium chloride

# Biochemical Background: PSMA-11 Introduction

- Prostate-specific membrane antigen (PSMA) targeting has emerged as a transformative approach in the management of prostate cancer, particularly with the advent of Gozetotide (also known as PSMA-11). This agent, as a radiolabeled compound, has shown significant contribution in improving the detection and treatment planning of prostate cancer. PSMA-11 is utilized in PET imaging to enhance the visualization of prostate cancer metastases, outperforming traditional imaging methods in accuracy.([1])
- Following the proven impact of using PSMA-11 in prostate cancer a lyophilized cold kit was evolved and showed the following outcomes:
  - Cold Kit vs. Module-Based: A comparison is made between the traditional module-based synthesis and the new cold kit method, showing that the cold kit achieves a >98% radiochemical yield and >95% purity in just 5 minutes.
  - Production Efficiency: The use of the cold kit method not only reduces labeling time but also increases production efficiency by minimizing waste of the eluted Ga-68.
  - This kit presents a significant advancement in the synthesis of radiopharmaceuticals for prostate cancer imaging, offering a more efficient and faster production method. ([2])


*References*

1) *[Michael S. Hofman, ProPSMA: A Callout to the Nuclear Medicine Community to Change Practices with Prospective, High Quality Data. Journal of Nuclear Medicine May 2020, 61 (5) 676-677; DOI: https://doi.org/10.2967/jnumed.120.245647]*
2) *[Haim Golan, Moad Esa , Keren Moshkoviz , Asher Feldhaim , Baruch Hoch and Eli Shalom. Enhancing capacity and synthesis of [68Ga]68-Ga-PSMAHBED-CC with the lyophilized ready-to-use kit for nuclear pharmacy applications. Nuclear Medicine Communications 41(9):p 986-990, September 2020. | DOI: 10.1097/MNM.0000000000001232]*

# PSMA-11 - Introduction

- The use of PSMA-11 in the diagnosis of prostate cancer has seen significant advancements. Here are some of the latest updates:
- The Food and Drug Administration (FDA) approved the radioactive tracer Gallium (Ga) 68 PSMA-11 for use in PET imaging of men with prostate cancer on December 1, 2020. This tracer can be used in PET imaging for prostate cancer that is suspected of having spread to other parts of the body.
- A study published in the Journal of Nuclear Medicine in January 2024 compared the diagnostic performance of 68Ga-PSMA-11 PET/CT versus Multiparametric MRI (mpMRI) for the detection of intraprostatic radio-recurrent prostate cancer. The study found that 68Ga-PSMA-11 PET/CT has high sensitivity that is not significantly different from mpMRI. When 68Ga-PSMA-11 PET/CT and mpMRI were used together, the results conferred a greater sensitivity and negative predictive value than with mpMRI alone. ([1])
- These advancements suggest that PSMA-11 is becoming an increasingly important tool in the diagnosis and management of prostate cancer.

*Reference*

1) *[Alexander Light, Stefan Lazic, Kate Houghton, Max Bayne, Martin J. Connor, Henry Tam, Hashim U. Ahmed, Taimur T. Shah and Tara D. Barwick. Diagnostic Performance of 68Ga-PSMA-11 PET/CT Versus Multiparametric MRI for Detection of Intraprostatic Radiorecurrent Prostate Cancer. Journal of Nuclear Medicine January 2024, jnumed.123.266527; DOI: https://doi.org/10.2967/jnumed.123.266527]*

# What is PSMA inhibitor

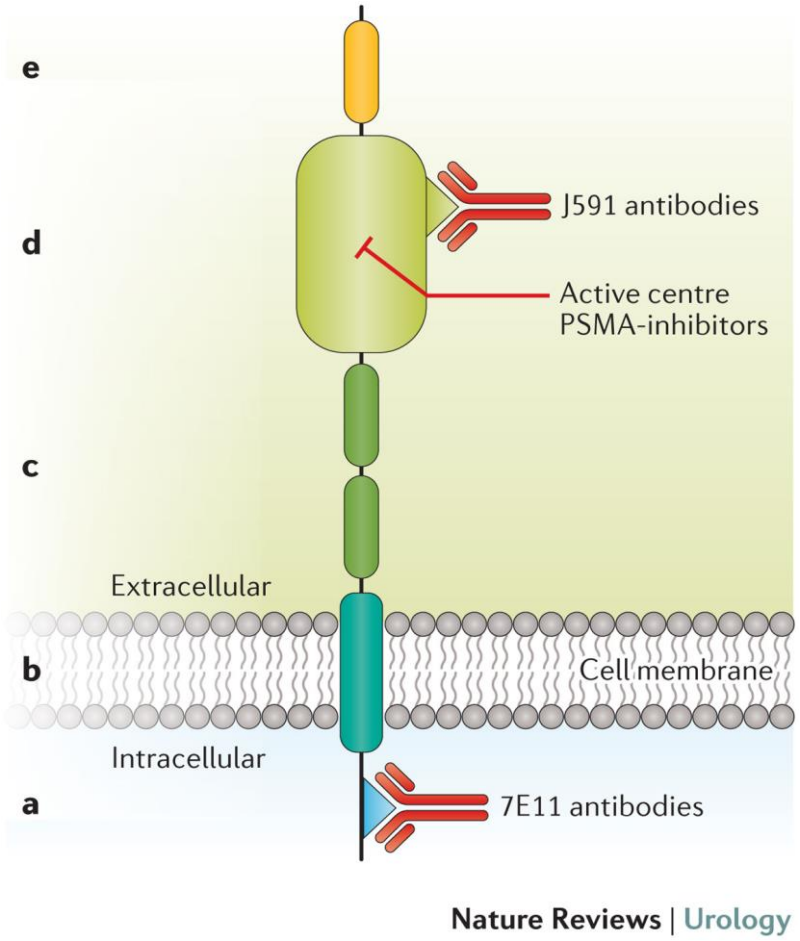


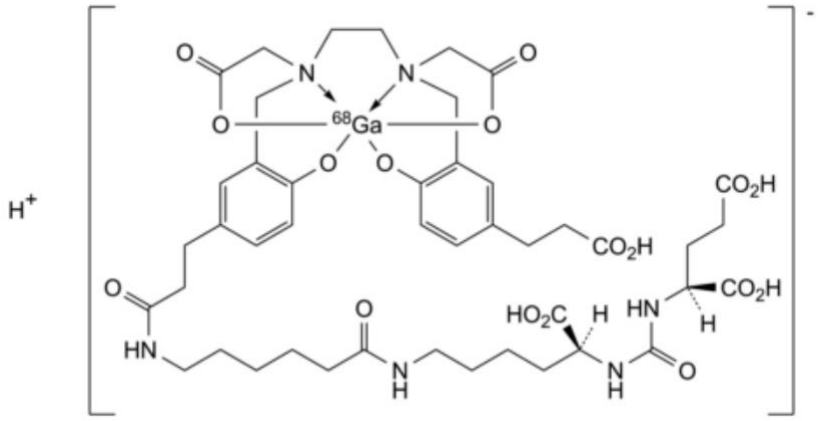

**Figure 1 -** The structure of prostate-specific membrane antigen (PSMA), its binding sites for PSMA ligands and the most frequently used antibodies

The structure of prostate-specific membrane antigen (PSMA), its binding sites for PSMA ligands and the most frequently used antibodies.

A. The short intracellular domain containing a binding site that can be targeted with antibodies.
B. The hydrophobic transmembrane region. The extracellular part of PSMA consists of section that contains two domains of unknown function and proline-rich and glycine-rich regions as linkers, that is the large catalytic domain, which contains a binding site for antibodies as well as the active substrate recognition site that is being targeting by PSMA inhibitors.

*Reference*
*Maurer, T. et al. (2016) Current use of PSMA–PET in prostate cancer management*
*Nat. Rev. Urol. doi:10.1038/nrurol.2016.26*

# What is PSMA-11



Ph. Eur. 04/2021:3044

- Gallium (68Ga) gozetotide or Gallium (68Ga) PSMA-11, is a radiopharmaceutical.
- It is made of 68Ga conjugated to a prostate-specific membrane antigen (PSMA) targeting ligand, Glu-Urea-Lys (Ahx)-HBED-CC.
- This compound is used for imaging prostate cancer by positron emission tomography (PET).
- The PSMA targeting ligand specifically directs the radiolabeled imaging agent towards the prostate cancerous lesions in men.
- Gallium (68Ga) gozetotide was approved for medical use in the United States in December 2020, and in the European Union in December 2022.
- Once administered via injection, Ga 68 PSMA-11 binds to PSMA, which is an important pharmacologic target for prostate cancer imaging because prostate cancer cells usually contain elevated levels of the PSMA antigen.

*Citation:* *Gallium (68Ga) gozetotide - Wikipedia*

# Isoprotrace® reconstitution and handling

- Withdrawals should be performed under aseptic conditions.
- Usual safety precautions for the handling of radioactive materials should be followed.
- The vial must not be opened before disinfecting the stopper, the solution should be withdrawn via the stopper using a single dose syringe fitted with suitable protective shielding and a disposable sterile needle or using an authorised automated application system.
- If the integrity of this vial is compromised, the product should not be used.
- Radioactive waste must be disposed of in accordance with relevant national regulations.
- After reconstitution and radiolabeling and successful quality control, gallium (68Ga) gozetotide solution for injection can be diluted with water for injections or sodium chloride 9 mg/mL (0.9%) solution for injection up to a final volume of 10 mL.

  When using IRE ELiT Galli Ad generator, dilution to a minimum volume of 4 mL is required in order to reduce osmolality.
- The patient dose should be measured by a suitable radioactivity calibration system immediately prior to patient administration. Product administration data should also be recorded.

# Isoprotrace® administration

- After reconstitution and radiolabeling, gallium (68Ga) gozetotide solution should be administered by slow intravenous injection.
- Local extravasation resulting in inadvertent radiation exposure to the patient and imaging artefacts should be avoided.
- The injection should be followed by an intravenous flush of sodium chloride 9 mg/mL (0.9%) solution for injection to ensure full delivery of the dose.
- The total radioactivity in the syringe should be verified with a dose calibrator immediately before and after administration to the patient.
- The dose calibrator must be calibrated and comply with international standards.
- Instructions regarding the dilution of the gallium (68Ga) gozetotide solution should be followed (see section 12 in the SmPC).

# Dosage and administration

The medicinal product should only be administered by trained healthcare professionals with technical expertise in using and handling nuclear medicine diagnostic agents and only in a designated nuclear medicine facility.

**Posology**

- The recommended dose of gallium (68Ga) gozetotide is 1.8-2.2 MBq/kg of body weight, with a minimum dose of 111 MBq up to a maximum dose of 259 MBq.

*Elderly population*

- No special dosage regimen for elderly patients is required.

*Pediatric population*

- There is no relevant use of gallium (68Ga) gozetotide in the paediatric population for the identification of PSMA positive lesions in prostate cancer.
- The safety and efficacy of gallium (68Ga) gozetotide in children aged 0 to 18 years have not been established.

*Hepatic impairment*

- The safety and efficacy of gallium (68Ga) gozetotide have not been studied in patients with hepatic impairment.

*Renal impairment*

- The safety and efficacy of gallium (68Ga) gozetotide have not been studied in patients with renal impairment. Careful consideration of the activity to be administered is required since an increased radiation exposure is possible in these patients.

# Imaging protocols and reporting

1. Imaging Acquisition:
    - Administer the radiopharmaceutical intravenously.
    - Image acquisition typically occurs 50-100 minutes post-injection.
    - Whole-body imaging from the skull base to the mid-thigh is recommended.
2. Interpretation:
    - Experienced nuclear medicine physicians should interpret PSMA PET/CT scans.
    - Evaluate PSMA uptake in the prostate gland, regional lymph nodes, and distant metastases.
    - SUVmax (maximum standardized uptake value) is commonly used for quantification.
3. Reporting
    - Provide a detailed report, including anatomical localization of PSMA-avid lesions.
    - Mention any equivocal findings and their clinical significance.
    - It is recommended to use the Second Version of the Prostate Cancer Molecular Imaging Standardized Evaluation Framework Including Response Evaluation for Clinical Trials (PROMISE V2) as a guideline for interpretation.

➢ *These recommendations are based on the joint EANM procedure guideline/SNMMI procedure standard for prostate cancer imaging 2.01. Clinicians and technicians can use this guidance to implement PSMA PET/CT effectively in both research and routine practice.*

# Reporting

- The description of PSMA uptake in either prostate bed, or metastases should include both qualitative and quantitative descriptions.
- Visual description compares PSMA uptake to background uptake in the blood, liver, and salivary glands on a visual scale of 0–3 (Table 1).
- Quantitative description related to SUVmax or a tumor-to-background ratio.
- Reports should include Tumor-Node-Metastasis (TNM) classification and a five-point scale, classifying individual findings, depending on the probability of disease (Table 2, slide 19).

*Citation Georgakopoulos A, Bamias A, Chatziioannou S. Current role of PSMA-PET imaging in the clinical management of prostate cancer. Therapeutic Advances in Medical Oncology. 2023;15. doi:10.1177/17588359231208960*

# Reporting – Table 1

**Table 1.** Four-point scale (visual score) of PSMA expression.[11]

| Visual score | Grade of PSMA expression |
|---|---|
| 0 | Below blood pool |
| 1 | Equal or to above the blood pool and lower than the liver |
| 2 | Equal or to above the liver and lower than the parotid gland |
| 3 | Equal or to the above parotid gland |

PSMA, prostate-specific membrane antigen.

*Citation Georgakopoulos A, Bamias A, Chatziioannou S. Current role of PSMA-PET imaging in the clinical management of prostate cancer. Therapeutic Advances in Medical Oncology. 2023;15. doi:10.1177/17588359231208960*

# Reporting – Table 2

**Table 2.** Five-point scale for interpretation of PSMA PET/CT findings.[12]

| Score | Findings |
|---|---|
| 1 | Benign lesion without PSMA uptake |
| 2 | Probably benign (faint PSMA uptake in a site atypical for PC) |
| 3 | Equivocal finding (faint PSMA uptake in a site typical for PC or intense uptake in a site atypical for PC) |
| 4 | Probably PC (intense uptake in a site typical for prostate cancer but without definitive findings on CT) |
| 5 | PC (intense uptake in a site typical for prostate cancer, with definitive findings on CT) |

PC, prostate cancer; PET/CT, positron emission tomography/computed tomography; PSMA, prostate-specific membrane antigen.

*Citation Georgakopoulos A, Bamias A, Chatziioannou S. Current role of PSMA-PET imaging in the clinical management of prostate cancer. Therapeutic Advances in Medical Oncology. 2023;15. doi:10.1177/17588359231208960*

# Normal biodistribution of PSMA (1)

Normal physiological PSMA uptake is demonstrated in:

- lacrimal glands
- parotid, and submandibular salivary glands,
- liver, spleen, bowel (especially small bowel and specifically the duodenum)
- renal activity with subsequent renal clearance through the ureters, urinary bladder, and urethra
- PSMA is also excreted through saliva and this explains possible esophageal, stomach, or laryngeal activity.
- Ga68-PSMA-11 also undergoes hepatobiliary clearance, and thus, activity may be appreciated in the bile ducts, gall bladder, and extra-hepatic ducts.
- The most intense activity is appreciated in the kidneys with subsequent urinary excretion (ureters and urinary bladder) as well as lacrimal and salivary glands.
- The high-grade uptake in small bowel, particularly the duodenum, is likely attributed to the dietary uptake of folates in this region and thus increased PSMA expression.
- Relatively low-grade activity is appreciated in the liver and spleen, and this activity should be uniform in distribution.

*Citation: Malan N and Vangu M-d-T (2022) Normal Variants, Pitfalls, and Artifacts in Ga-68 Prostate Specific Membrane Antigen (PSMA) PET/CT Imaging. Front. Nucl. Med. 2:825512.doi: 10.3389/fnume.2022.825512*

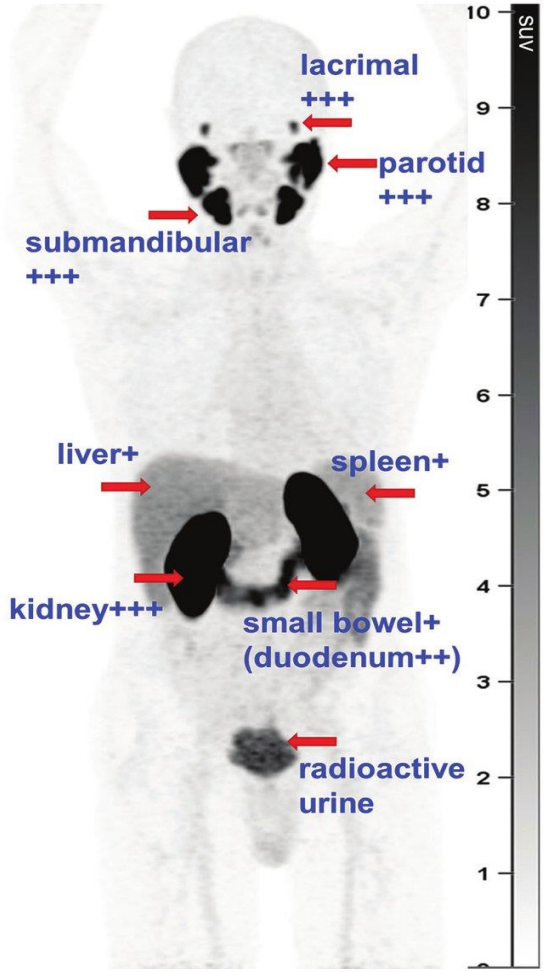
# Normal biodistribution of PSMA (2)

- Low grade physiological activity is also appreciated in:
- sympathetic ganglia (celiac, stellate, hypogastric, and presacral ganglia). This is more commonly visualized with newer PET/CT scanners with the incorporation of time-of-flight. Knowledge of the location of sympathetic ganglia is important as these may be misinterpreted as possible metastatic nodal disease.
- The stellate ganglia are typically located para-vertebral at the level of the thyroid, the coeliac ganglia are seen para-aortic at the level of the kidneys, the hypogastric ganglia are located paravertebral at the level of the iliac wings, and the sacral ganglia are in the pre-sacral area.
- Physiological activity may also be seen in the trigeminal ganglia which is located within the trigeminal (Meckel) cave.
- The pancreas may demonstrate heterogenous and variable uptake in relation to the variable number, distribution, and volume of islet cells which have been reported to express PSMA receptors.

*Citation: Malan N and Vangu M-d-T (2022) Normal Variants, Pitfalls, and Artifacts in Ga-68 Prostate Specific Membrane Antigen (PSMA) PET/CT Imaging. Front. Nucl. Med. 2:825512.doi: 10.3389/fnume.2022.825512*

# Normal Distribution of 68Ga-PSMA-11

Published Clinical Cases

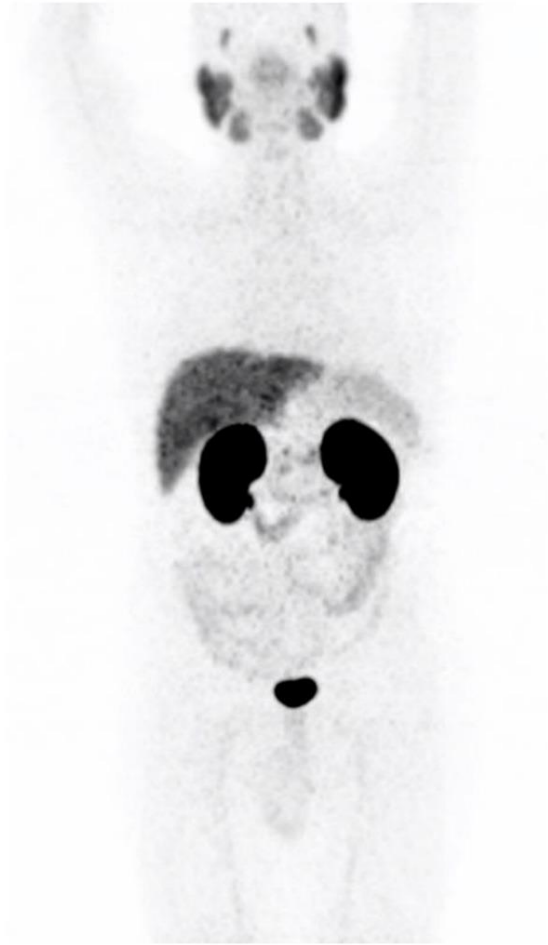



*Citation: Hofman et al. January 2018 Radiographics 38(1):200-217*

# Normal Distribution of 68Ga-PSMA-11

Published Clinical Cases

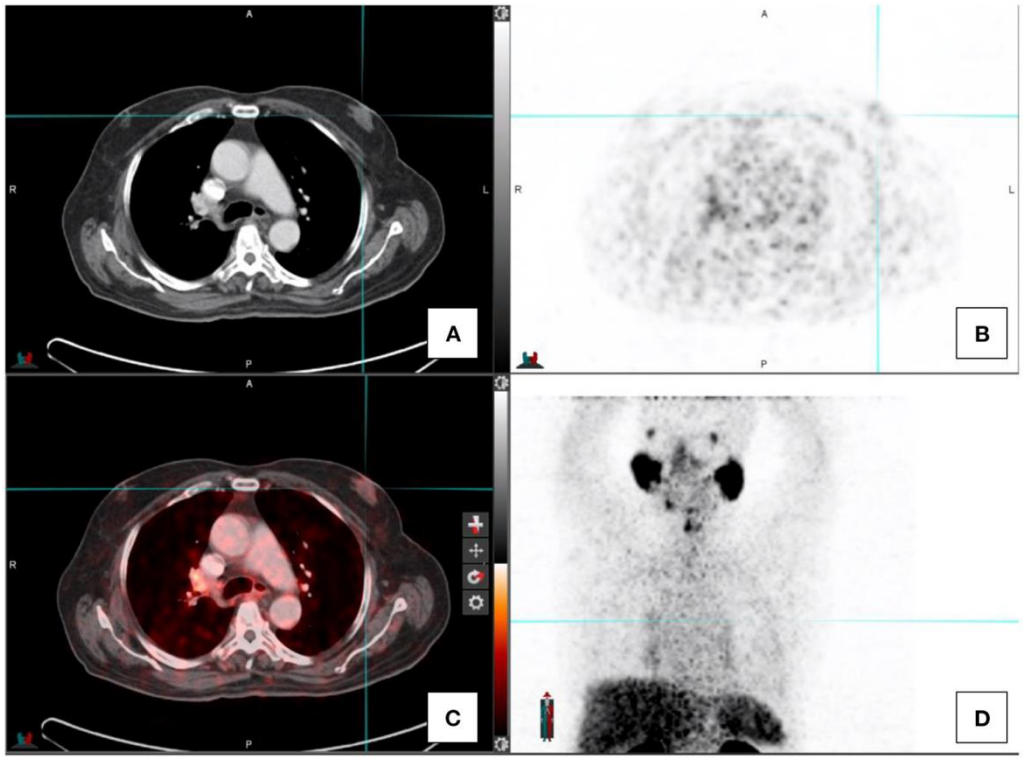
- Maximal intensity projection (MIP) image, showing the normal biodistribution of Ga68-PSMA.



*Citation: Malan N and Vangu M-d-T (2022) Normal Variants, Pitfalls, and Artifacts in Ga-68 Prostate Specific Membrane Antigen (PSMA) PET/CT Imaging. Front. Nucl. Med. 2:825512.doi:10.3389/fnume.2022.825512*

# Normal Variants - Gynecomastia

Published Clinical Cases

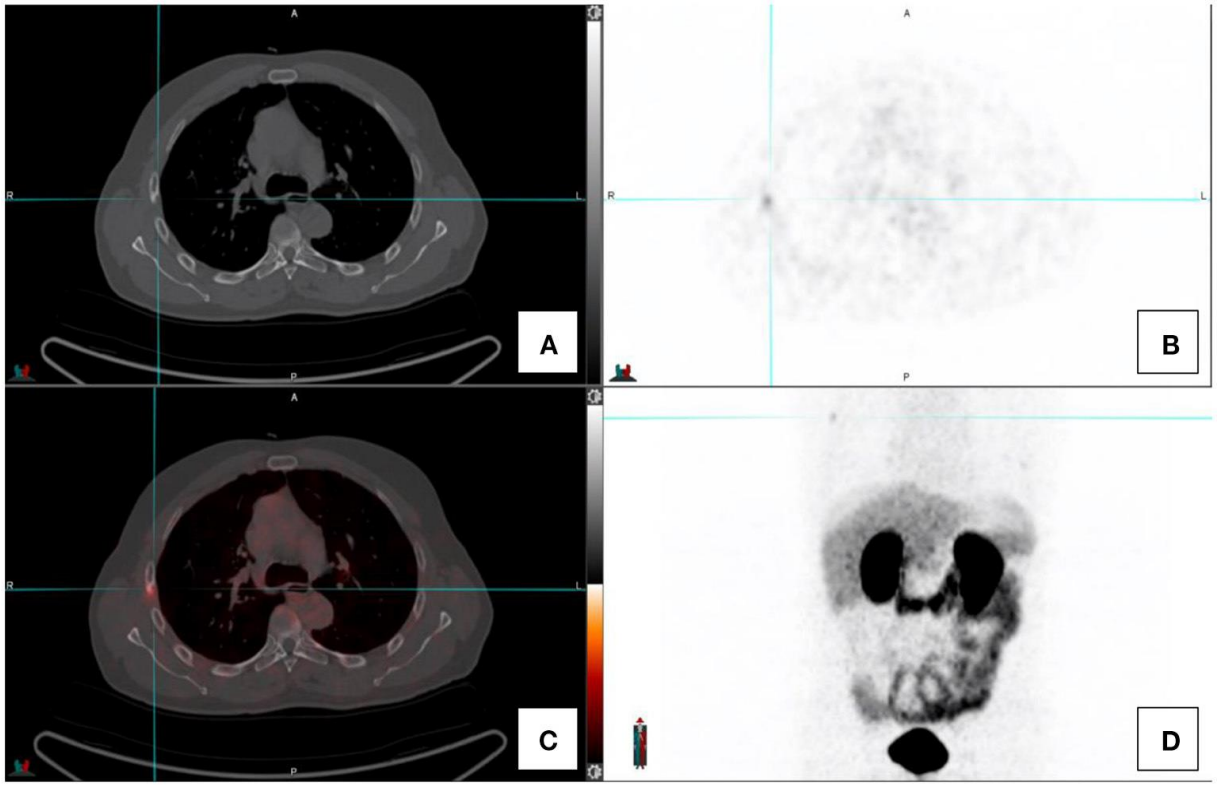



- A patient with gynecomastia with associated low-grade Ga68-PSMA activity.
- CT-image (A)
- PET image (B)
- Fused PET/CT image (C)
- Maximal intensity projection image (D).

*Citation: Malan N and Vangu M-d-T (2022) Normal Variants, Pitfalls, and Artifacts in Ga-68 Prostate Specific Membrane Antigen (PSMA) PET/CT Imaging. Front. Nucl. Med. 2:825512.doi: 10.3389/fnume.2022.825512*

# Normal Variants - Rib fracture

Published Clinical Cases

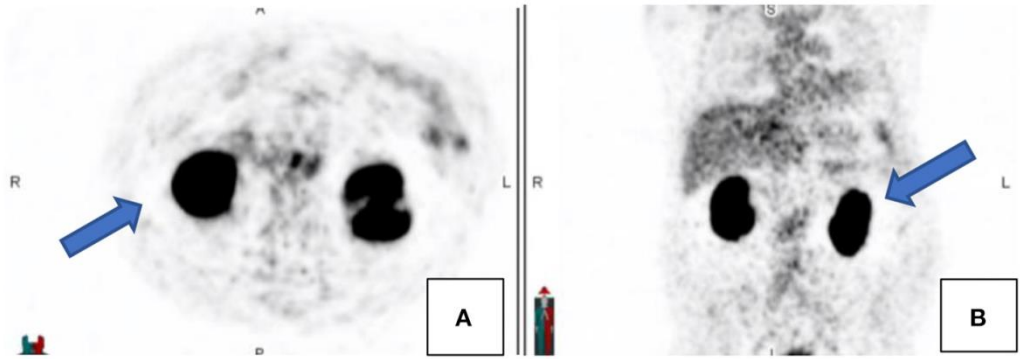



- Transaxial images in a prostate cancer patient with a right sided rib fracture.
- CT-image (A), PET image (B), fused PET/CT image (C), and the maximal intensity projection image (D).

*Citation: Malan N and Vangu M-d-T (2022) Normal Variants, Pitfalls, and Artifacts in Ga-68 Prostate Specific Membrane Antigen (PSMA) PET/CT Imaging. Front. Nucl. Med. 2:825512.doi: 10.3389/fnume.2022.825512*

# Normal Variants - Halo effect

Published Clinical Cases




- Transaxial (A) and coronal (B) PET images demonstrating the relative photopaenic areas surrounding the intense activity in the kidneys, the so-called “halo” effect, as indicated by the arrows.

*Citation:* *Malan N and Vangu M-d-T (2022) Normal Variants, Pitfalls, and Artifacts in Ga-68 Prostate Specific Membrane Antigen (PSMA) PET/CT Imaging. Front. Nucl. Med. 2:825512.doi: 10.3389/fnume.2022.825512*

# Flare Phenomenon

- Following the initiation of androgen deprivation therapy (ADT) with a gonadotropin-releasing hormone (GnRH) antagonist, a heterogenous flare response may be noted, whereby lesions may show an increase in standardized uptake value of up to 73% after 2 weeks.
- Additional lesions may also be visible following the flare response.
- Optimal period for lesion detection is 2–4 weeks after initiation of ADT.

*Citation: Malan N and Vangu M-d-T (2022) Normal Variants, Pitfalls, and Artifacts in Ga-68 Prostate Specific Membrane Antigen (PSMA) PET/CT Imaging. Front. Nucl. Med. 2:825512.doi: 10.3389/fnume.2022.825512*

# PSMA Negative Prostate Cancer

- Most prostate cancers are PSMA avid. It was reported that 10-15% of prostate cancer may exhibit low grade PSMA expression and thus may not demonstrate avid uptake but only minimal or low-grade uptake.
- It is unlikely to encounter PSMA negative nodal metastases where the primary is PSMA avid, except in heavily chemotherapy pretreated patients.
- Prostate cancer is a heterogenous disease and primary tumor and metastases do not always show concordant PSMA expression, it has been shown that increasing PSMA percentage negativity of the primary tumor on immunohistochemistry is associated with an increasing rate of PSMA negative scans as well as PSMA negative metastases.
- In cases where there is evidence of biochemical recurrence, in view of rising PSA, with a negative PSMA scan then imaging with the following radiopharmaceuticals may be considered: 18Ffluciclovine (which is internalized into prostate cancer cells by amino acid transporters LAT1-4 and ASCT1/2 which areupregulated in prostate cancer) or 11C/18F-choline (which targets increased cell membrane lipid synthesis which is increased in cancer cells).

*Citation: Malan N and Vangu M-d-T (2022) Normal Variants, Pitfalls, and Artifacts in Ga-68 Prostate Specific Membrane Antigen (PSMA) PET/CT Imaging. Front. Nucl. Med. 2:825512.doi: 10.3389/fnume.2022.825512*

# Isoprotrace® Summary of artifacts and pitfalls associated with 68Ga-PSMA-11 imaging.

- Halo artifact - intense renal activity causing photopaenia surrounding the kidneys
- Motion artifacts (respiratory and patient motion causing misregistration between PET and CT images)
- False negatives - PSMA negative prostate cancer (10-15% of prostate carcinomas)
- Iatrogenic errors (injection of wrong radiopharmaceutical)
- Flare phenomenon - Additional lesions visualized and increased Standardized Uptake Value (SUV) early after Androgen Deprivation Therapy (ADT)
- False positives - Infection/inflammation (pulmonary, prostatitis, post radiation etc.)
- Bone conditions (osteophytes, fractures, hemangiomas etc.)
- Benign neoplasms (related to vascular proliferation - e.g., thyroid, parathyroid, adrenal adenomas, etc.)
- Malignant neoplasms (tumors expressing PSMA - breast ca, lung ca, lymphoma, colorectal tumors, etc.)

*Citation: Malan N and Vangu M-d-T (2022) Normal Variants, Pitfalls, and Artifacts in Ga-68 Prostate Specific Membrane Antigen (PSMA) PET/CT Imaging. Front. Nucl. Med. 2:825512.doi: 10.3389/fnume.2022.825512*

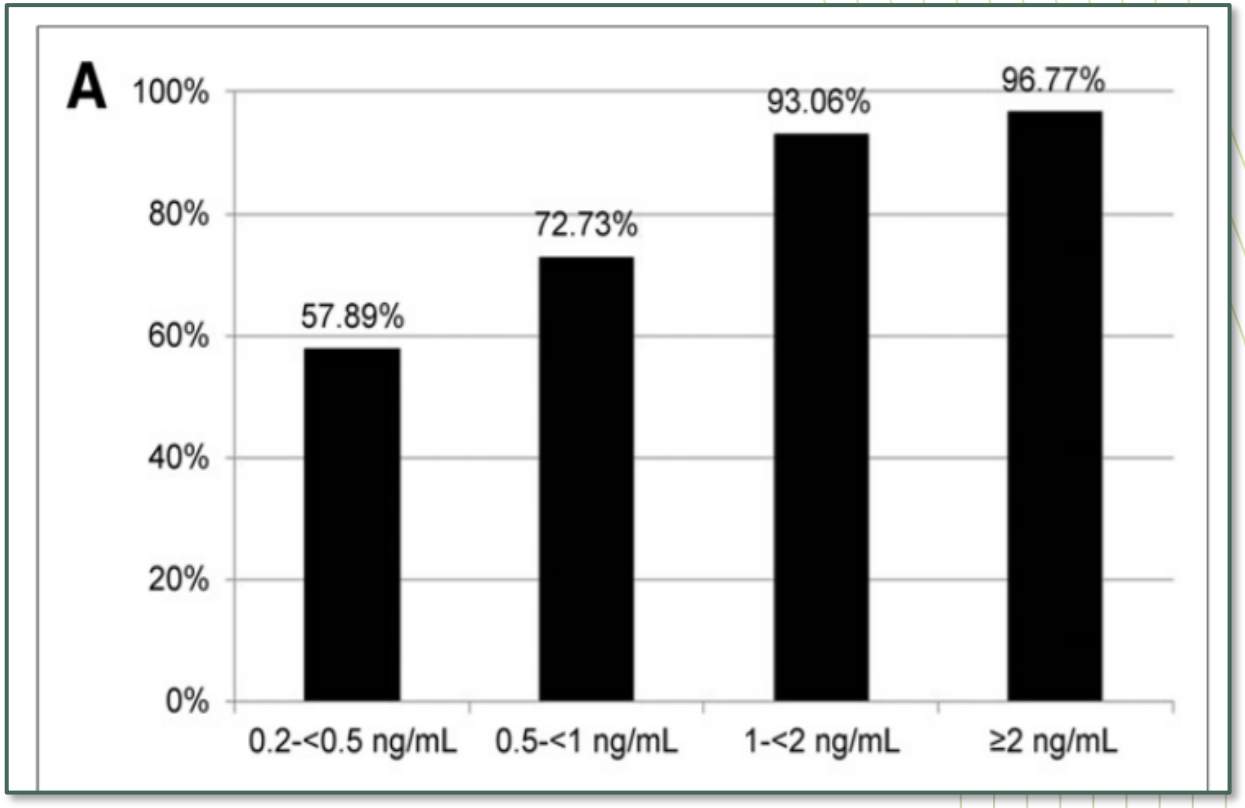
# Educational Video

- *It is recommended to watch this video in order to understand how experts read PSMA scans.*

# 68-Ga-PSMA PET-CT Detection Rate in Biochemical Recurrence by PSA values

**Evaluation of Hybrid $^{68}$Ga-PSMA Ligand PET/CT in 248 Patients with Biochemical Recurrence After Radical Prostatectomy**

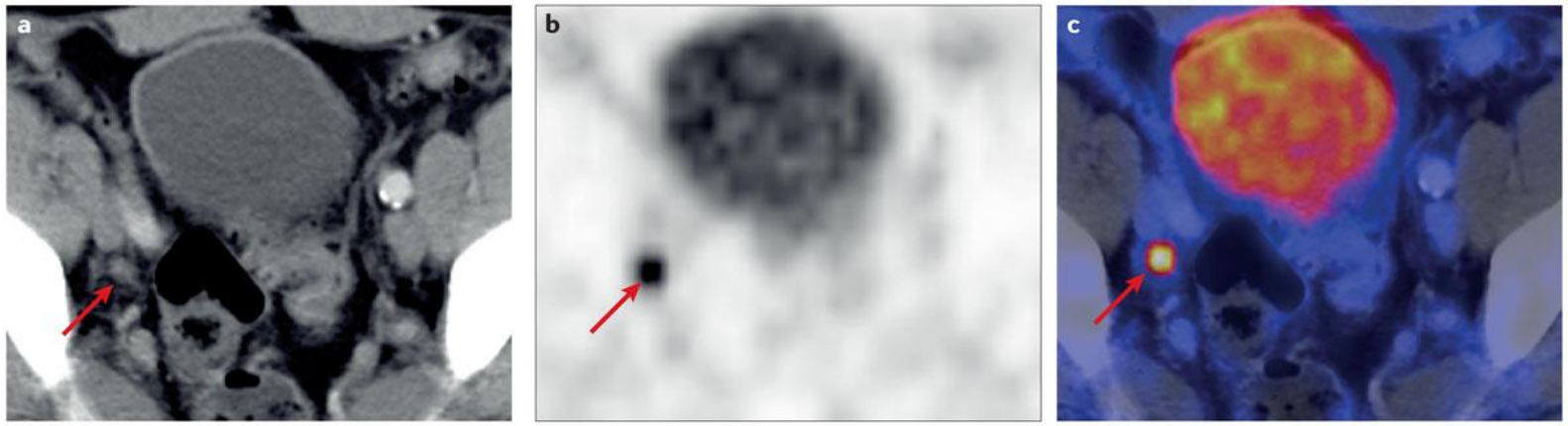
Matthias Eiber*[1,2], Tobias Maurer*[3], Michael Souvatzoglou[1], Ambros J. Beer[1,4], Alexander Ruffani[1], Bernhard Haller[5], Frank-Philipp Graner[1], Hubert Kübler[3], Uwe Haberhorn[6], Michael Eisenhut[6], Hans-Jürgen Wester[7], Jürgen E. Gschwend[3], and Markus Schwaiger[1]




*Eiber et al. J Nucl Med 2015; 56:668–674*

# Published Clinical Cases

$^{68}$Ga-PSMA–PET–CT of a 52-year-old patient with primary prostate cancer (serum PSA value of 19 ng/ml and Gleason score 7 at biopsy)




Nature Reviews | Urology

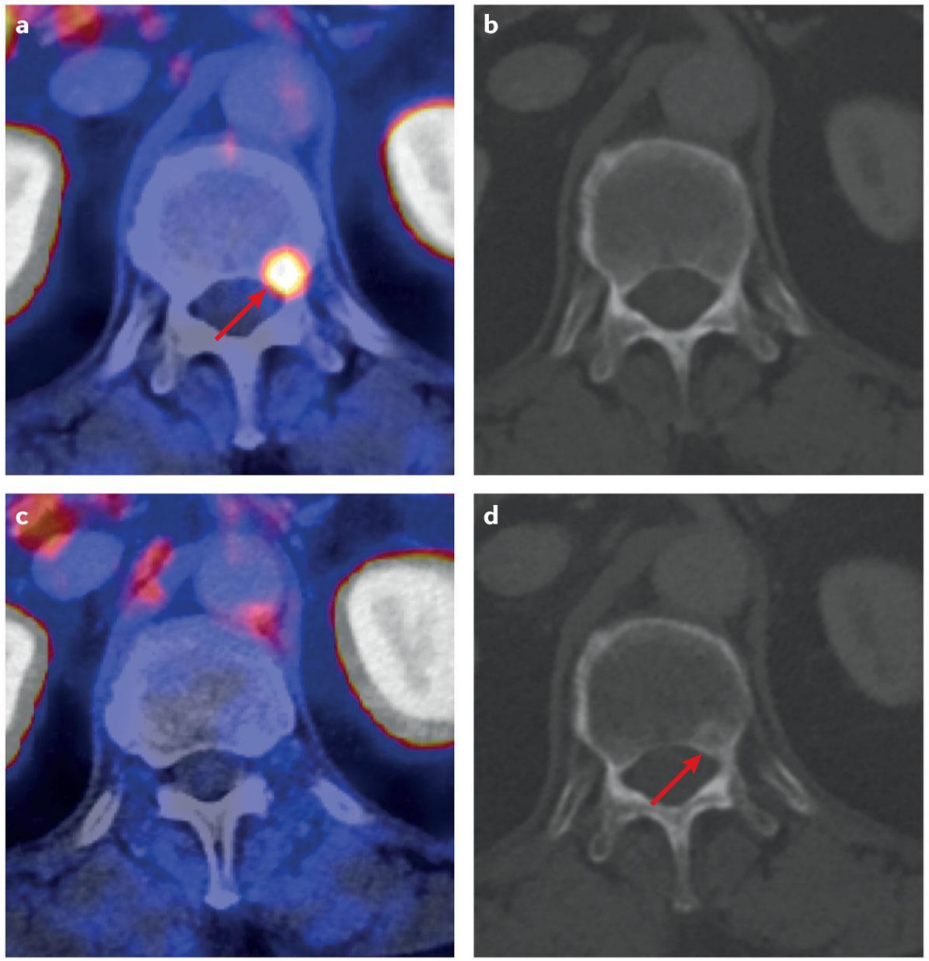
68Ga-PSMA–PET–CT of a 52-year-old patient with primary prostate cancer (serum PSA value of 19 ng/ml and Gleason score 7 at biopsy).

- **a** | Contrast enhanced CT s68Ga-PSMA–PET–CT of a 52-year-old hows a small lymph node (6 mm) adjacent to the right internal iliac artery.
- **b** | PET and **c** | fused PET–CT images demonstrate intense prostate-specific membrane antigen (PSMA) expression in this lymph node.
- Radical prostatectomy and lymphadenectomy revealed a lymph node metastasis in the corresponding template field.

*Maurer, T. et al. (2016) Current use of PSMA–PET in prostate cancer management*
*Nat. Rev. Urol. doi:10.1038/nrurol.2016.26*

# Published Clinical Cases

68Ga-PSMA–PET–CT of a 73-year-old patient with recurrent prostate cancer after radical prostatectomy (initial Gleason score 9) and local salvage radiotherapy

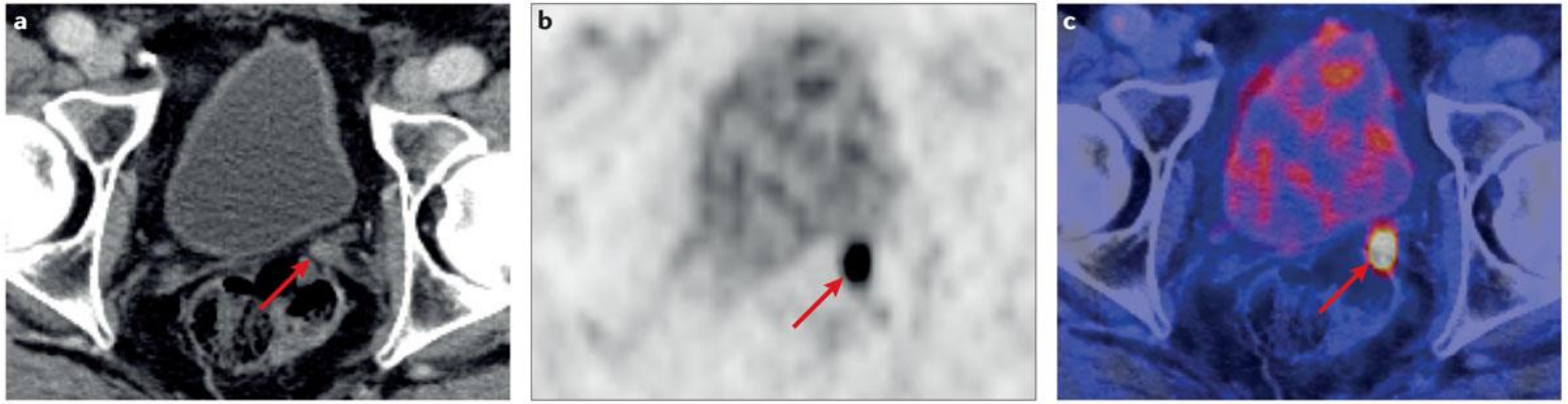



- $^{68}$Ga-PSMA–PET–CT of a 73-year-old patient with recurrent prostate cancer after radical prostatectomy (initial Gleason score 9) and local salvage radiotherapy.
- Upper images are from a staging $^{68}$Ga-PSMA-PET–CT examination at a serum PSA value of 3.6 ng/ml and the lower images are from a restaging examination six months later at a serum PSA value of 1.8 ng/ml.
- **a** | Fused PET–CT demonstrates an intense uptake in the thoracic spine suspicious for a bone metastasis.
- **b** | The corresponding CT reveals no morphological correlation.
- **c** | Fused PET–CT images, 6 months later, shows no substantial uptake of $^{68}$Ga-PSMA in the lesion after external radiotherapy.
- **d** | CT shows a new sclerosis indicating post-therapeutic changes. PSMA, prostate-specific membrane antigen.

*Maurer, T. et al. (2016) Current use of PSMA–PET in prostate cancer management Nat. Rev. Urol. doi:10.1038/nrurol.2016.26*

# Published Clinical Cases

$^{68}$Ga-PSMA–PET–CT of a 74-year-old patient with recurrent prostate cancer (initial Gleason score 7) after radical prostatectomy and local salvage radiotherapy with rising serum PSA value (1.76 ng/ml at the time of assessment)



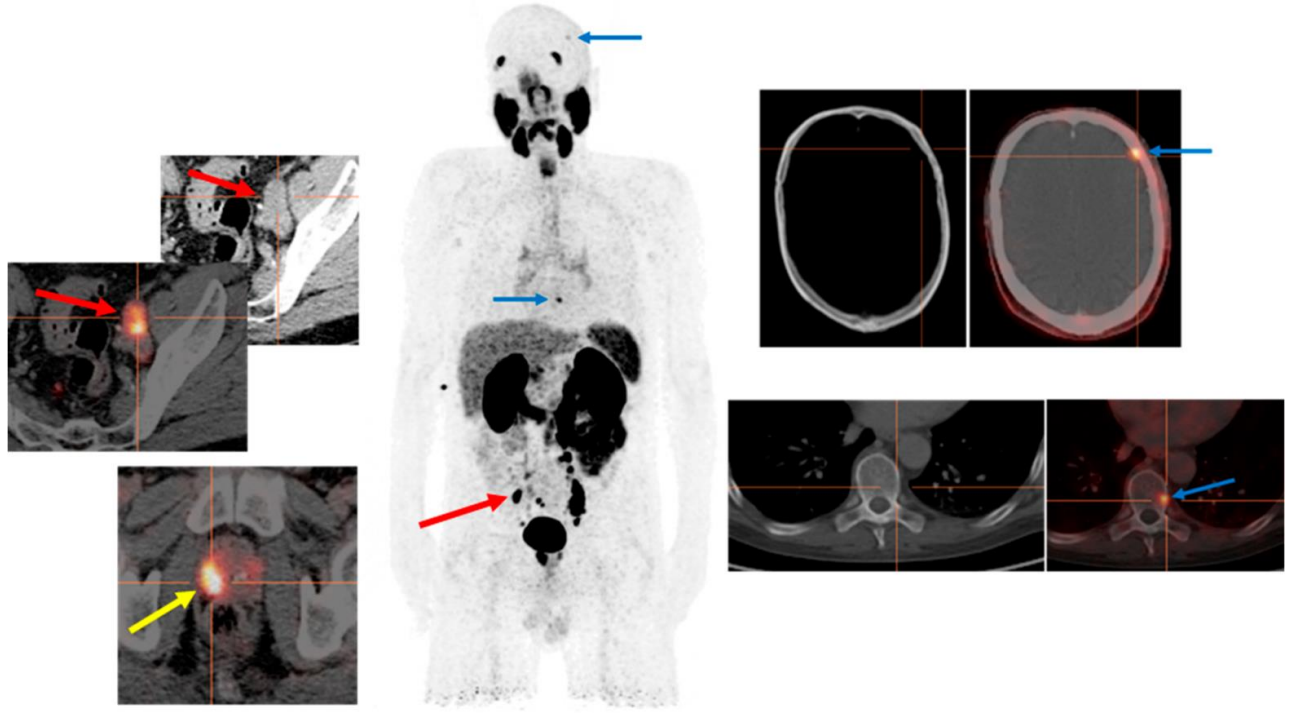

Nature Reviews | Urology

- $^{68}$Ga-PSMA–PET–CT of a 74-year-old patient with recurrent prostate cancer (initial Gleason score 7) after radical prostatectomy and local salvage radiotherapy with rising serum PSA value (1.76 ng/ml at the time of assessment).
- **a** | Contrast-enhanced CT shows a mass in the area of the former left seminal vesicle having residual tissue, reactive fibrosis or recurrent disease.
- **b** | PET and **c** | fused PET–CT images demonstrate intense $^{68}$Ga-PSMA-11 uptake, indicative of a locally recurrent tumour.
- Salvage PSMA-radioguided surgery revealed soft-tissue poorly differentiated adenocarcinoma of the prostate (Gleason score 7) including a seminal vesicle with a cribriform carcinoma.

*Maurer, T. et al. (2016) Current use of PSMA–PET in prostate cancer management*
*Nat. Rev. Urol. doi:10.1038/nrurol.2016.26*

# Primary Staging

Published Clinical Cases

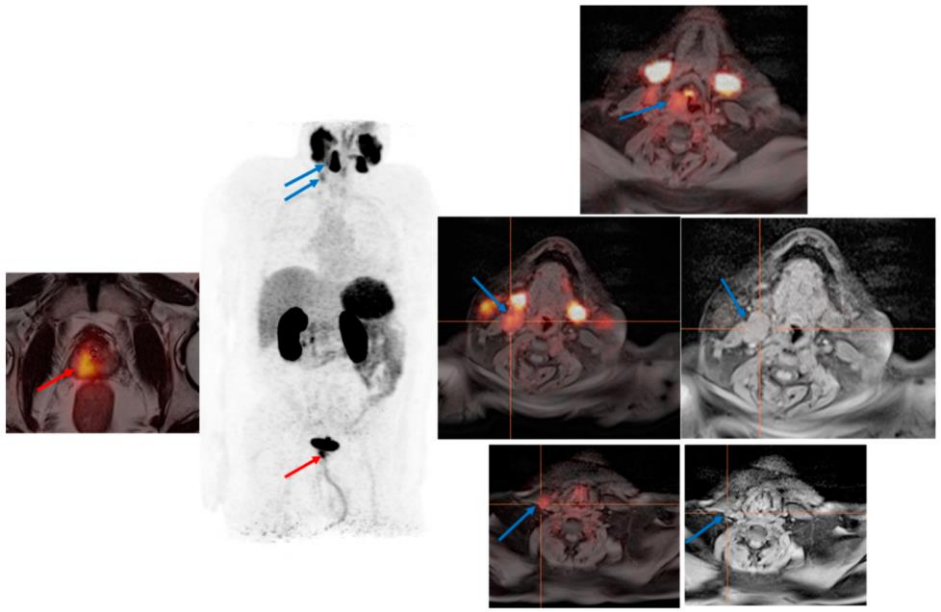


- PSMA-11 PET-CT Images for primary staging of a 56-year-old man, newly diagnosed with PCa: Gleason score (5 + 5) and a PSA value of 45.96 ng/mL showing two PSMA-avid bone lesions.
- frontoparietal in the left side of the skull and the ninth thoracic vertebra (blue arrows) in addition to the primary tumor in the right lobe of the prostate (yellow arrow) and bilateral iliac lymph node metastases (red arrows). Both these bone lesions were not visible on CT examination separately performed for the patient.

*Citation: Rasul, S.; Haug, A.R. Clinical Applications of PSMA PET Examination in Patients with Prostate Cancer. Cancers 2022, 14, 3768. https://doi.org/10.3390/cancers14153768*

Published Clinical Cases

# Primary Staging with incidental detection of squamous cell carcinoma of the larynx

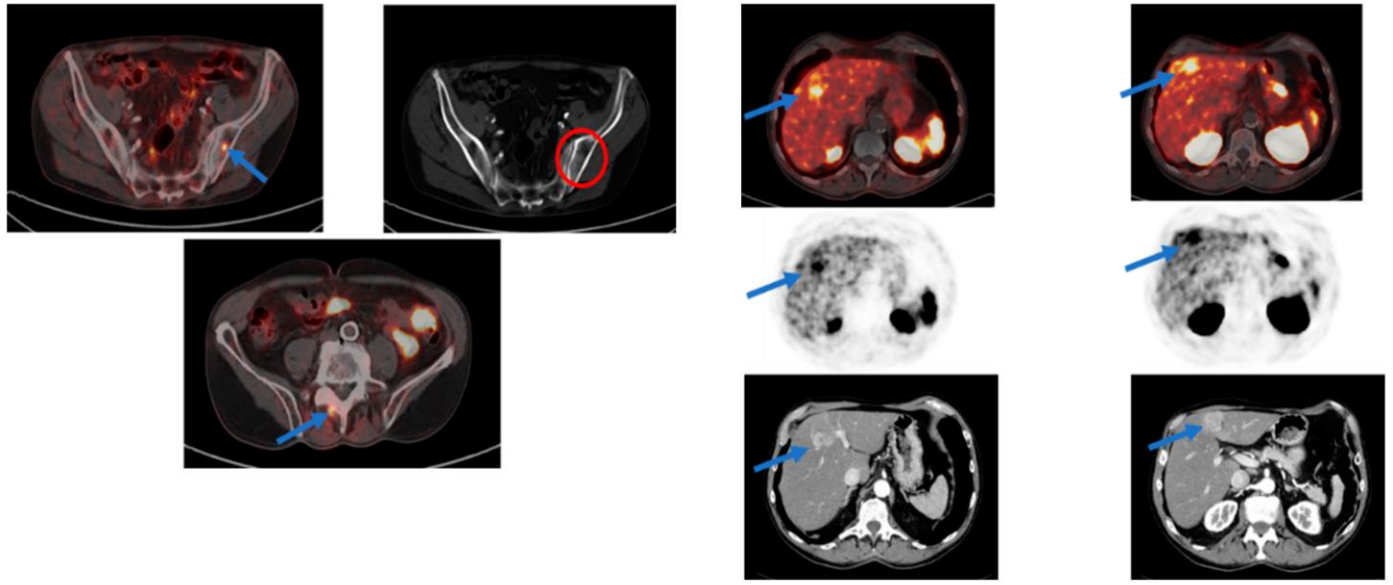


- PSMA-11 PET examination for primary staging of a high-risk prostate cancer.
- Primary staging of a 60 year old patient with a newly diagnosed high-risk prostate cancer (PSA value: 30.9 ng/mL).
- revealed the primary tumor in the right lobe of the prostate with a clear PSMA-expression (red arrow).
- and an incidental detection of a suspicious lesion with marked PSMA expression in the right piriform sinus (area of the right vocal cord) with multiple suspicious lymph nodes in the right neck region (blue arrows).
- The final histological examination of this neck lesion confirmed squamous cell carcinoma of the larynx.

*Citation: Rasul, S.; Haug, A.R. Clinical Applications of PSMA PET Examination in Patients with Prostate Cancer. Cancers 2022, 14, 3768. https://doi.org/10.3390/cancers14153768*

# Primary PSMA-11 PET in Biochemical Recurrence PCa

## Published Clinical Cases

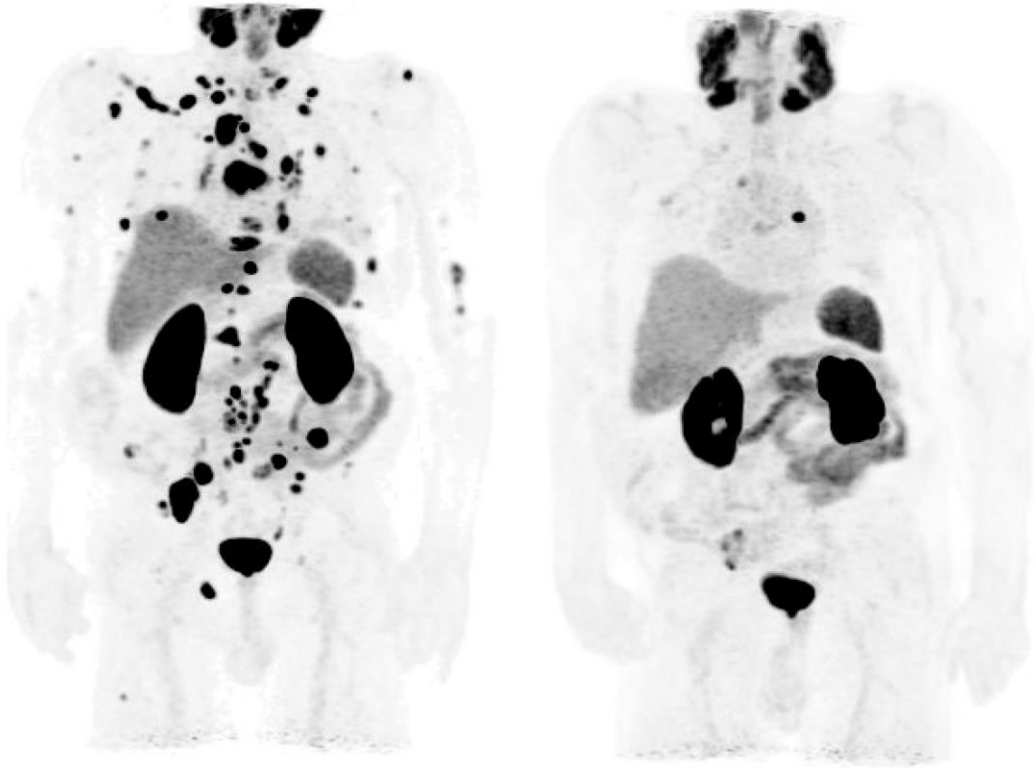



- PSMA PET examination for biochemical recurrence of prostate cancer. [$^{68}$Ga]Ga-PSMA-11 PET-CT of a 74 year old patient with biochemical recurrence of prostate cancer revealed (**A**) PSMA-positive bone lesions in the left iliac bone with corresponding bone changes on the CT scan (red circle) and the vertebral arch of the fourth lumbar spine. (**B**) Additional PSMA-avid and contrast-enhanced intrahepatic lesions in liver segments IVa and IVb. Histological examination of these hepatic lesions demonstrated hepatocellular carcinoma.

*Citation: Rasul, S.; Haug, A.R. Clinical Applications of PSMA PET Examination in Patients with Prostate Cancer. Cancers 2022, 14, 3768. https://doi.org/10.3390/cancers14153768*

# Primary PSMA-11 PET in Biochemical Recurrence PCa

Published Clinical Cases

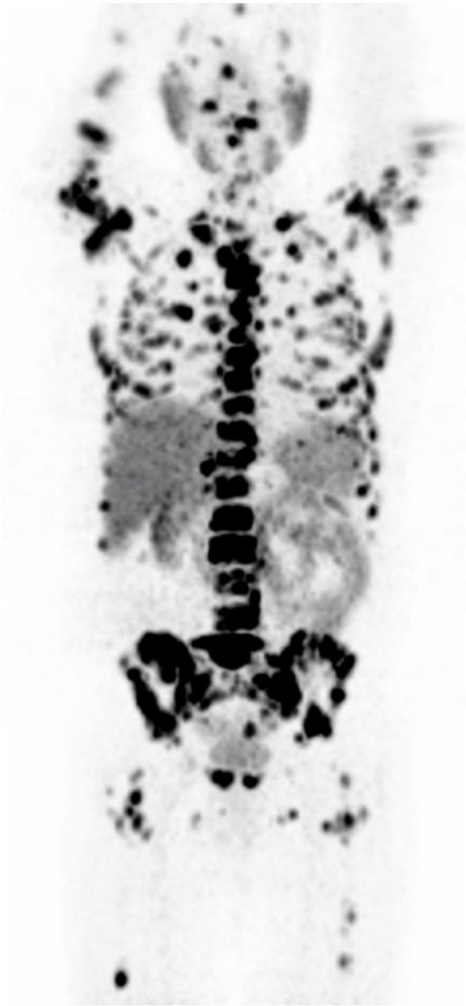


- PSMA-11 PET examination of a patient with metastatic castration-resistant prostate cancer and a PSA level of 65.74 ng/mL. Before PSMA-RLT (**left**), showing multiple bone and lymph node metastasis with highly increased PSMA-expression.

*Citation: Rasul, S.; Haug, A.R. Clinical Applications of PSMA PET Examination in Patients with Prostate Cancer. Cancers 2022, 14, 3768. https://doi.org/10.3390/cancers14153768*

# PSMA-11 – Metastatic Disease

Published Clinical Cases

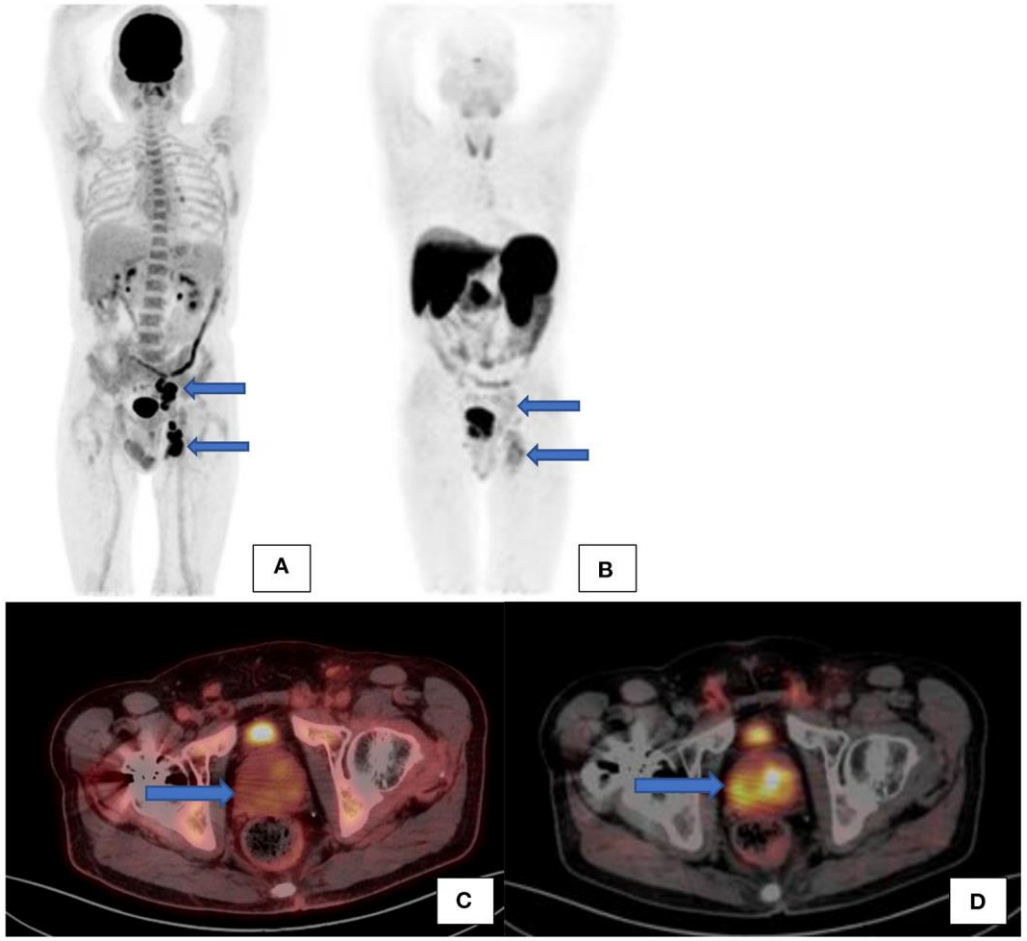


- Maximal intensity projection (MIP) image showing widespread osteoblastic metastases in a castrate resistant prostate carcinoma patient.

*Citation: Malan N and Vangu M-d-T (2022) Normal Variants, Pitfalls, and Artifacts in Ga-68 Prostate Specific Membrane Antigen (PSMA) PET/CT Imaging. Front. Nucl. Med. 2:825512.doi: 10.3389/fnume.2022.825512*

# Prostate Cancer – Metastases Discordance

Published Clinical Cases

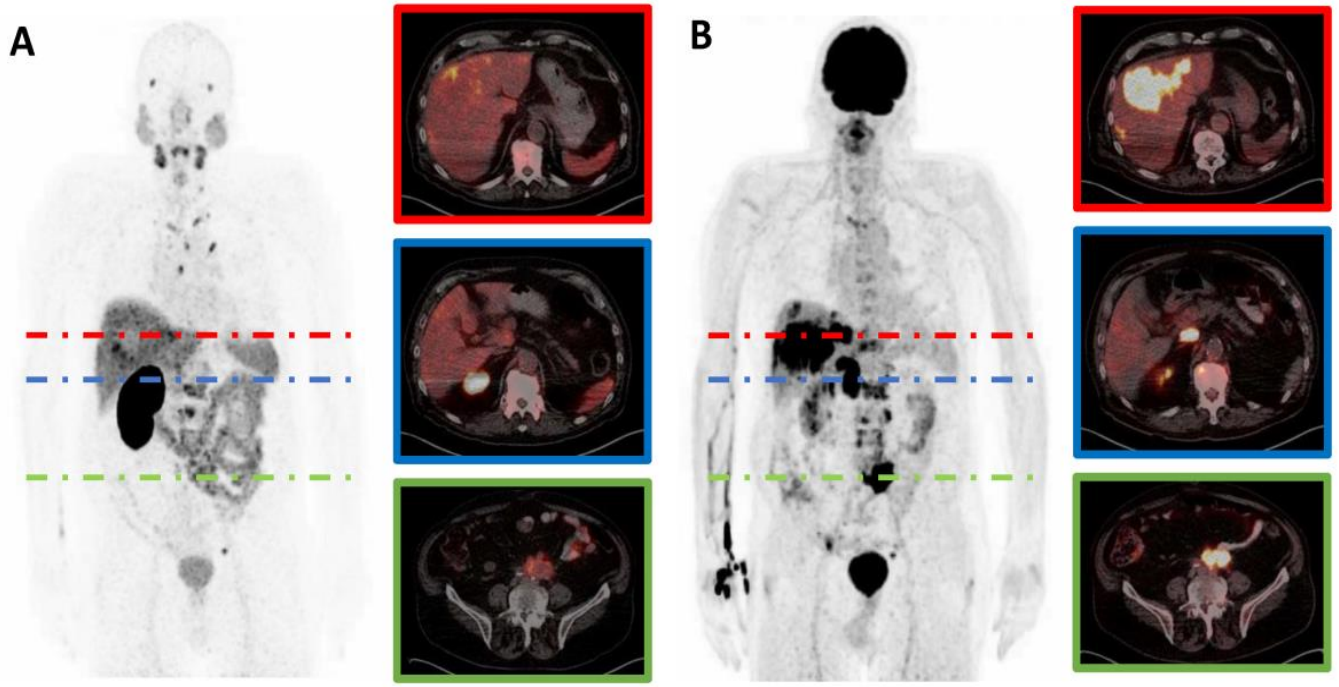



- A patient with confirmed prostate carcinoma underwent a Ga68-PSMA scan (see the maximal intensity projection image (B) and transaxial fused PET/CT image (D) showing avid uptake in the prostate gland and low-grade uptake in the left internal iliac and inguinal nodes.
- F18-FDG scan [(A)–maximal intensity projection images and (C)– transaxial fused PET/CT image] was also performed on the same patient showing low grade uptake in the prostate gland but avid uptake in the same left internal iliac and inguinal nodes.
- Consistent with “DISCORDANT FDG vs PSMA uptake”.

*Citation: Malan N and Vangu M-d-T (2022) Normal Variants, Pitfalls, and Artifacts in Ga-68 Prostate Specific Membrane Antigen (PSMA) PET/CT Imaging. Front. Nucl. Med. 2:825512.doi: 10.3389/fnume.2022.825512*

# Prostate Cancer – Metastases Discordance

Published Clinical Cases

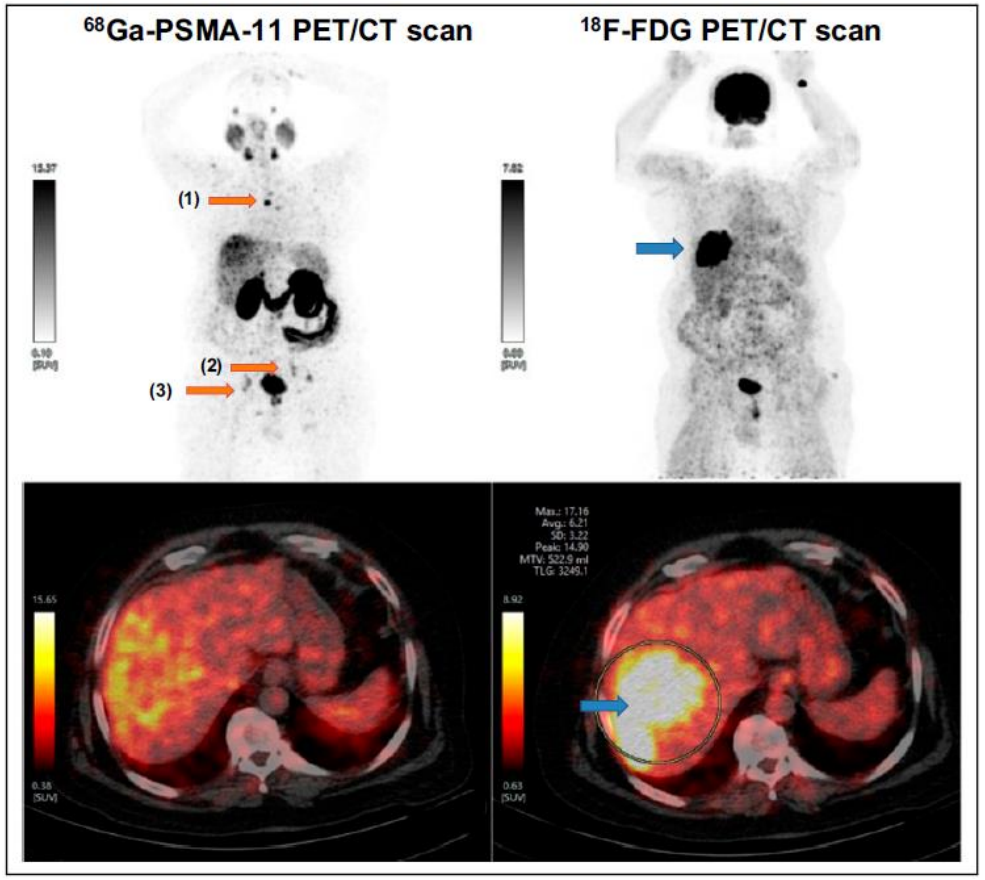



- [$^{68}$Ga]Ga-PSMA-11 (**A**) and [$^{18}$F]FDG (**B**) PET/CT images of a representative mCRPC patient with hepatic (red) and lymphonodular (blue and green) discordant uptake lesions.
- Note: mCRPC, metastatic castration-resistant prostate cancer with “DISCORDANT FDG vs PSMA uptake”.
- Important for patients selection for **[$^{177}$Lu]Lu-PSMA-617 RLT.**

*Citation: Khreish, F.; Ribbat, K.; Bartholomä, M.; Maus, S.; Stemler, T.;Hierlmeier, I.; Linxweiler, J.;Schreckenberger, M.; Ezziddin, S.;Rosar, F. Value of Combined PET Imaging with [18F]FDG and [68Ga]Ga-PSMA-11 in mCRPC Patients with Worsening Disease during [177Lu]Lu-PSMA-617 RLT. Cancers 2021, 13, 4134. https://doi.org/10.3390/cancers13164134*

# Prostate Cancer – Discordance with second primary

Published Clinical Cases

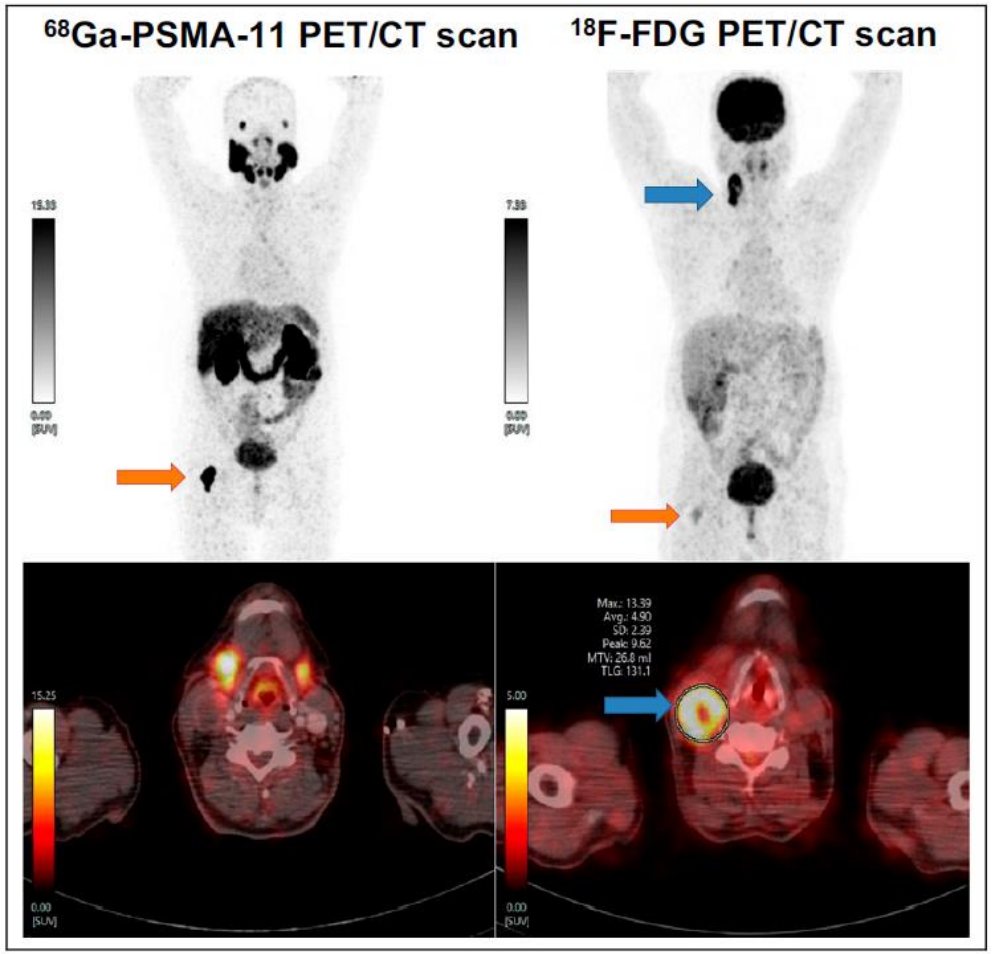



- Whole-body 68Ga-PSMA-11 PET/CT and 18F-FDG PET/CT scans showing 68Ga-PSMA-11 expression (orange arrows) in sclerotic skeletal lesions in body of D4 vertebra (lesion 1), in left internal iliac lymph nodes (lesion 2), and bilaterally in pelvic bones (lesion 3).
- None of these showed any 18F-FDG uptake.
- Hypodense lesion in segment VII/VIII of liver. showed 18F-FDG uptake (blue arrow) but did not show any significant 68Ga-PSMA-11 expression.
- ultrasonography-guided biopsy of the liver segments was advised and revealed **combined hepatocellular carcinoma and cholangiocarcinoma.**

*Citation: Ashwini Chalikandy, Subhash Yadav, and Sandip Basu.Differentiation of Discordant Lesions on Dual-Tracer PET/CT (68Ga-PSMA-11 and 18F-FDG) in Prostate Carcinoma: Diagnosis of Second Primary Malignancies. J Nucl Med Technol 2023; 51:339–342 DOI: 10.2967/jnmt.123.265779*

# Prostate Cancer – Discordance with second primary

Published Clinical Cases

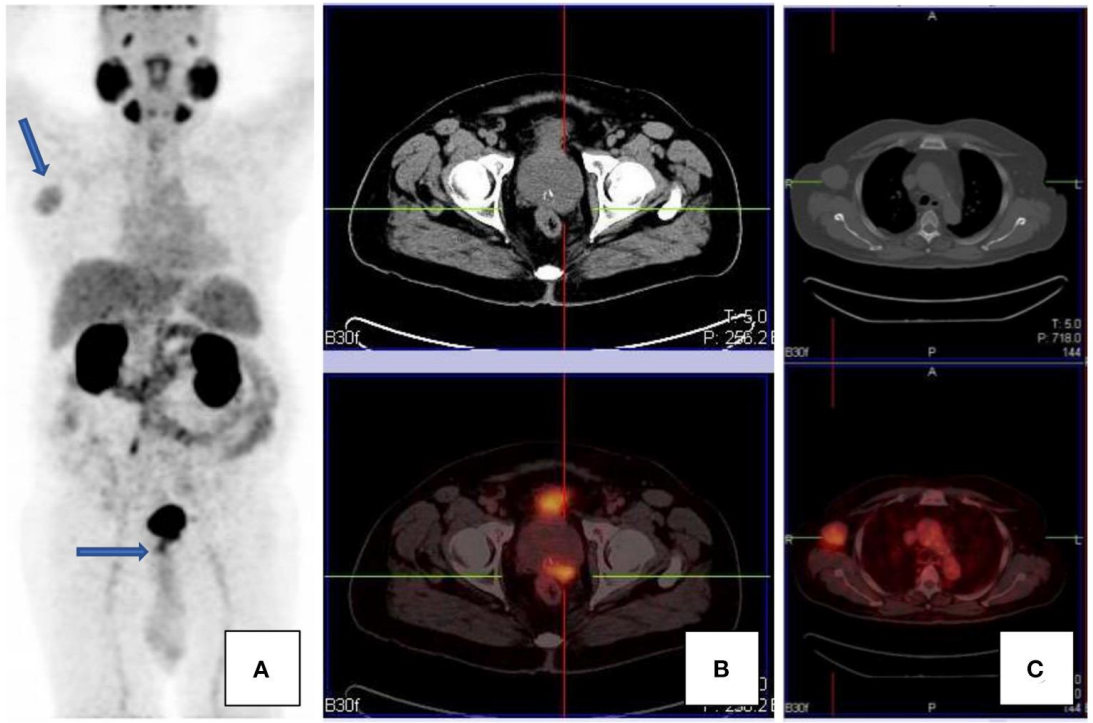



- Whole-body 68Ga-PSMA-11PET/CT and 18F-FDG PET/CT images showing 68Ga-PSMA-11 expression (orange arrows) in sclerotic lesion involving right neck of femur, and low-grade 18F-FDG uptake, consistent with diagnosis of prostate carcinoma with skeletal metastasis.
- Right cervical III/IC lymph node shows 18F-FDG uptake (blue arrows) but not 68Ga-PSMA-11 expression.
- Ultrasonography-guided biopsy of the right cervical lymph node showed **poorly differentiated metastatic squamous cell carcinoma.**

*Citation: Ashwini Chalikandy, Subhash Yadav, and Sandip Basu.Differentiation of Discordant Lesions on Dual-Tracer PET/CT (68Ga-PSMA-11 and 18F-FDG) in Prostate Carcinoma: Diagnosis of Second Primary Malignancies. J Nucl Med Technol 2023; 51:339–342 DOI: 10.2967/jnmt.123.265779*

# Non-Prostate Cancer Hodgkin's Lymphoma

Published Clinical Cases




- A patient with confirmed prostate carcinoma, with focal uptake in the prostate gland.
- Maximal intensity projection images are shown in (A).
- Transaxial CT and fused PET/CT images, (B).
- An avid right axillary nodal mass transaxial CT and fused PET/CT images, (C).
- The axillary mass was an unlikely site of metastases, given the paucity of other metastases. The mass was excised and histology confirmed Hodgkin’s lymphoma.

*Citation: Malan N and Vangu M-d-T (2022) Normal Variants, Pitfalls, and Artifacts in Ga-68 Prostate Specific Membrane Antigen (PSMA) PET/CT Imaging. Front. Nucl. Med. 2:825512.doi: 10.3389/fnume.2022.825512*

# Isoprotrace®

## Self-assessment test

Self-assessment test on Isoprotrace® educational material

1. **What is the primary purpose of Isoprotrace® (Gozetotide) as a radiopharmaceutical?**

   a) To treat prostate cancer.

   b) To prevent prostate cancer from spreading.

   c) To diagnose and stage prostate cancer.

   d) To reduce side effects of prostate cancer treatment.

Self-assessment test on Isoprotrace® educational material

1. **What is the primary purpose of Isoprotrace® (Gozetotide) as a radiopharmaceutical?**

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   d) To reduce side effects of prostate cancer treatment.

c) To diagnose and stage prostate cancer.
Isoprotrace® is a diagnostic tool used to identify and characterize prostate cancer lesions.

Self-assessment test on Isoprotrace® educational material

**2. What is PSMA, and why is it a crucial target in prostate cancer imaging?**

a) PSMA is a protein found in healthy cells, and its presence indicates the spread of prostate cancer.

b) PSMA is a protein found only in prostate cancer cells, making it a specific marker for diagnosis.

c) PSMA is a protein found in both healthy and cancer cells, but its levels are significantly higher in prostate cancer cells.

d) PSMA is a protein that inhibits the growth of prostate cancer cells.

Self-assessment test on Isoprotrace® educational material

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d) PSMA is a protein that inhibits the growth of prostate cancer cells.

c) PSMA is a protein found in both healthy and cancer cells, but its levels are significantly higher in prostate cancer cells. This makes PSMA a valuable target for imaging, as the higher levels in cancer cells allow for better visualization.

Self-assessment test on Isoprotrace® educational material

**3. What are the primary clinical settings where Isoprotrace® is indicated for use?**

a) To monitor the effectiveness of prostate cancer treatment.

b) To diagnose prostate cancer in men with a low PSA level.

c) To diagnose prostate cancer in men with a family history of the disease.

d) To diagnose and stage high-risk prostate cancer and to detect suspected recurrence.

Self-assessment test on Isoprotrace® educational material

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d) To diagnose and stage high-risk prostate cancer and to detect suspected recurrence.

d) To diagnose and stage high-risk prostate cancer and to detect suspected recurrence. Isoprotrace® is used to diagnose and stage high-risk prostate cancer, as well as to monitor for recurrence following treatment.

Self-assessment test on Isoprotrace® educational material

**4. What is the recommended dose of Isoprotrace® for a patient?**

a) 1.8-2.2 MBq/kg of body weight with a minimum dose of 111 MBq and a maximum of 259 MBq.

b) 1-2 MBq/kg of body weight with a minimum dose of 100 MBq and a maximum of 200 MBq.

c) 0.5-1 MBq/kg of body weight with a minimum dose of 50 MBq and a maximum of 150 MBq.

d) The dose varies depending on the individual patient's needs and is determined by a healthcare professional.

Self-assessment test on Isoprotrace® educational material

**4. What is the recommended dose of Isoprotrace® for a patient?**

a) 1.8-2.2 MBq/kg of body weight with a minimum dose of 111 MBq and a maximum of 259 MBq.

b) 1-2 MBq/kg of body weight with a minimum dose of 100 MBq and a maximum of 200 MBq.

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a) 1.8-2.2 MBq/kg of body weight with a minimum dose of 111 MBq and a maximum of 259 MBq. The recommended dose is based on body weight, with specific minimum and maximum limits.

Self-assessment test on Isoprotrace® educational material

**5. What is the typical time frame for image acquisition after Isoprotrace® administration?**

a) 10-20 minutes.

b) 30-40 minutes.

c) 50-100 minutes.

d) 120-150 minutes.

Self-assessment test on Isoprotrace® educational material

**5. What is the typical time frame for image acquisition after Isoprotrace® administration?**

a) 10-20 minutes.

b) 30-40 minutes.

c) 50-100 minutes.

d) 120-150 minutes.

c) 50-100 minutes. Image acquisition typically takes place 50-100 minutes after Isoprotrace® administration, allowing for adequate time for the tracer to accumulate in target tissues.

Self-assessment test on Isoprotrace® educational material

**6. What is SUVmax, and how is it used in PSMA PET/CT imaging?**

a) SUVmax is a measure of blood flow to the prostate gland.

b) SUVmax is a measure of the size of prostate cancer lesions.

c) SUVmax is a measure of the metabolic activity of prostate cancer cells.

d) SUVmax is a measure of the amount of Isoprotrace® taken up by the prostate gland.

Self-assessment test on Isoprotrace® educational material

**6. What is SUVmax, and how is it used in PSMA PET/CT imaging?**

a) SUVmax is a measure of blood flow to the prostate gland.

b) SUVmax is a measure of the size of prostate cancer lesions.

c) SUVmax is a measure of the metabolic activity of prostate cancer cells.

d) SUVmax is a measure of the amount of Isoprotrace® taken up by the prostate gland.

c) SUVmax is a measure of the tracer avidity of prostate cancer cells. SUVmax (Standardized Uptake Value maximum) reflects the amount of tracer taken up by a lesion, indicating the PSMA avidity of the cancer cells.

Self-assessment test on Isoprotrace® educational material

**7. What is the "flare phenomenon" in PSMA PET/CT imaging, and what does it indicate?**

a) It is a temporary decrease in PSMA uptake, indicating that the treatment is working.

b) It is a temporary increase in PSMA uptake, potentially indicating a response to treatment.

c) It is a consistent pattern of high PSMA uptake in specific areas, indicating a high risk of recurrence.

d) It is a rare occurrence where no PSMA uptake is observed, indicating the absence of prostate cancer.

Self-assessment test on Isoprotrace® educational material

**7. What is the "flare phenomenon" in PSMA PET/CT imaging, and what does it indicate?**

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b) It is a temporary increase in PSMA uptake, potentially indicating a response to treatment.

c) It is a consistent pattern of high PSMA uptake in specific areas, indicating a high risk of recurrence.

d) It is a rare occurrence where no PSMA uptake is observed, indicating the absence of prostate cancer.

b) It is a temporary increase in PSMA uptake, potentially indicating a response to treatment. The "flare phenomenon" is characterized by a temporary increase in PSMA uptake after starting androgen deprivation therapy, which may indicate a response to treatment.

Self-assessment test on Isoprotrace® educational material

**8. What are some of the potential pitfalls or artifacts that may affect the accuracy of PSMA PET/CT imaging?**

a) Only motion artifacts are a concern, as they can cause misregistration between PET and CT images.

b) False negatives can occur due to PSMA-negative prostate cancer, infection/inflammation, and bone conditions.

c) False positives can occur due to benign neoplasms, malignant neoplasms, and iatrogenic errors.

d) All of the above are potential pitfalls or artifacts that may affect the accuracy of PSMA PET/CT imaging.

Self-assessment test on Isoprotrace® educational material

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d) All of the above are potential pitfalls or artifacts that may affect the accuracy of PSMA PET/CT imaging.

d) All of the above are potential pitfalls or artifacts that may affect the accuracy of PSMA PET/CT imaging. These artifacts can affect the accuracy of the scan, making it essential for experienced physicians to interpret the images carefully.

Self-assessment test on Isoprotrace® educational material

**9. What is the role of the PROMISE V2 framework in PSMA PET/CT interpretation?**

a) It is a comprehensive guide for the interpretation of PSMA PET/CT scans.

b) It is a standardized method for measuring the size and location of prostate cancer lesions.

c) It is a tool for calculating the risk of prostate cancer recurrence.

d) It is a system for classifying the severity of prostate cancer based on PSMA uptake.

Self-assessment test on Isoprotrace® educational material

**9. What is the role of the PROMISE V2 framework in PSMA PET/CT interpretation?**

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d) It is a system for classifying the severity of prostate cancer based on PSMA uptake.

a) It is a comprehensive guide for the interpretation of PSMA PET/CT scans. PROMISE V2 provides a standardized framework for interpreting PSMA PET/CT scans, ensuring consistency in reporting and clinical decision-making.

Self-assessment test on Isoprotrace® educational material

**10. What are the most common physiological areas of PSMA uptake on a PET/CT scan?**

a) The brain, lungs, and bones.

b) The liver, spleen, and kidneys.

c) The heart, pancreas, and thyroid.

d) The bladder, prostate, and testicles.

Self-assessment test on Isoprotrace® educational material

**10. What are the most common physiological areas of PSMA uptake on a PET/CT scan?**

a) The brain, lungs, and bones.

b) The liver, spleen, and kidneys.

c) The heart, pancreas, and thyroid.

d) The bladder, prostate, and testicles.

b) The liver, spleen, and kidneys. These organs exhibit normal physiological PSMA uptake, which should be considered during interpretation.

Self-assessment test on Isoprotrace® educational material

**11. What is the recommended approach to reporting PSMA uptake in prostate cancer patients?**

a) Provide a qualitative description only, focusing on the presence or absence of PSMA-avid lesions.

b) Provide a quantitative description only, using SUVmax values to quantify the uptake.

c) Provide both a qualitative and quantitative description, including the visual scale and SUVmax values.

d) The reporting approach depends on the specific case and is determined by the healthcare professional.

Self-assessment test on Isoprotrace® educational material

**11. What is the recommended approach to reporting PSMA uptake in prostate cancer patients?**

a) Provide a qualitative description only, focusing on the presence or absence of PSMA-avid lesions.

b) Provide a quantitative description only, using SUVmax values to quantify the uptake.

c) Provide both a qualitative and quantitative description, including the visual scale and SUVmax values.

d) The reporting approach depends on the specific case and is determined by the healthcare professional.

c) Provide both a qualitative and quantitative description, including the visual scale and SUVmax values. A comprehensive report should include both qualitative and quantitative descriptions of PSMA uptake, ensuring accurate documentation and communication.

Self-assessment test on Isoprotrace® educational material

**12. What is the primary purpose of the educational video mentioned in the text?**

a) To explain the basic principles of PSMA PET/CT imaging.

b) To demonstrate the proper techniques for preparing and administering Isoprotrace®.

c) To provide insights into how experts interpret PSMA PET/CT scans.

d) To discuss the ethical considerations associated with PSMA PET/CT imaging.

Self-assessment test on Isoprotrace® educational material

**12. What is the primary purpose of the educational video mentioned in the text?**

a) To explain the basic principles of PSMA PET/CT imaging.

b) To demonstrate the proper techniques for preparing and administering Isoprotrace®.

c) To provide insights into how experts interpret PSMA PET/CT scans.

d) To discuss the ethical considerations associated with PSMA PET/CT imaging.

c) To provide insights into how experts interpret PSMA PET/CT scans. The educational video aims to showcase how experienced professionals read and interpret PSMA PET/CT scans, providing valuable learning opportunities.

Self-assessment test on Isoprotrace® educational material

**13. What is the primary purpose of Isoprotrace® (Gozetotide) as a radiopharmaceutical?**

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d) It highlighted the importance of using PSMA PET/CT in conjunction with other diagnostic tools. The study emphasized that PSMA PET/CT can be used effectively alongside other diagnostic tools like mpMRI to improve diagnostic accuracy and patient management.

# Thank you

## Educational material for HCP. Isoprotrace® image intepretation training

U kunt extra materiaal opvragen bij Information Service van Isotopia, te bereiken of via isoprotrace@isotopia-global.com. Het materiaal is online beschikbaar op https://isotopia-global.com/isoprotrace-NL/

Aanvullende informatie betreffende Isoprotrace is beschikbaar in de Samenvatting van productkenmerken (SmPC) en bijsluiter op www.geneesmiddeleninformatiebank.nl.