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PET/CT Variants and Pitfalls in Prostate Cancer: What You Might See on PET and Should Never Forget

Riccardo Mei, MD,[*,†,#] Andrea Farolfi, MD,[*,#] Paolo Castellucci, MD,[*] Cristina Nanni, MD,[*] Lucia Zanoni, MD,[*] and Stefano Fanti, MD[*,†]

2-deoxy-2-[^{18}F]fluorodeoxyglucose (FDG) positron emission tomography (PET) gained an impressive role in the diagnostic management of many oncological diseases, even though its use in imaging prostate cancer (PC) is limited to selected cases, mostly advanced stage of PC and selection for prostate specific antigen membrane (PSMA) radioligand therapy (RLT). In the past years, several PET tracers have been developed for both staging and restaging PC. The three most employed PET molecules in daily practice are [^{11}C] or [^{18}F]F-Choline, [^{18}F]F-Fluciclovine (Anti-1- amino-3-[18F]Fluorocyclobutane-1-Carboxylic Acid, also known as (Anti-[^{18}F]FACBC), [^{68}Ga]Ga-PSMA and recently FDA approved the first Fluorinated PSMA-based named [^{18}F]F-DCFPyl. Each one has its own physiological and peculiarity which are worth exploring. Moreover, an increasing number of case reports and studies have reported tracers' variants, pitfalls, or even non-prostatic diseases (benign and malignant) incidentally detected. In prostate oncology, PET can be performed with several indications in different stages of disease, as highlighted in the EAU Guidelines on PC. A correct scan interpretation depends on the knowledge of both the physiological distribution of the tracers and the uptake of possible variants and pitfalls. The aim of this critical review is to provide a comprehensive knowledge of physiological distribution of these three tracers, as well as an updated overview of variants and pitfalls.
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Introduction

Prostate cancer (PC) is the most common malignancy in men.[1] Conventional imaging with computed tomography (CT), magnetic resonance imaging (MRI) and bone scintigraphy has significant limitations in the evaluation of PC. Positron emission tomography (PET) for imaging PC has been spread worldwide due to both technological improvements on PET systems (e.g. PET/MRI systems) and increased availability of several PET radiopharmaceuticals. Recent approval by international regulatory agencies of PET tracers is not far behind.[2,3] More recently, during the revision of the manuscript, FDA approved [18F]F-DCFPyL as PSMA PET tracer for PC (after [^{68}Ga]Ga-PSMA-11 approval in European Union in December 2020)[24] While FDG-PET is the pillar of molecular imaging, its utility for PC is limited to prognostication of the disease[5] and to select clinical scenarios such as in restaging advanced metastatic castration-resistant disease[6] or poorly differentiated and/or aggressive neuroendocrine histology.[7,8] As compared to MRI or even to 11C-Choline, FDG-PET demonstrated an inferior sensitivity in staging PC (31% vs 88% vs 73%, respectively).[9] Moreover, detection rate of FDG-PET is still inadequate even in a setting of biochemical recurrent PC. One explanation of these results is due to the fact that FDG uptake often overlap in some benign conditions, such as benign hypertrophy, prostatitis, or even in normal prostate. Still, some lesions may be masked by the

*Nuclear Medicine Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy.
†Department of Experimental, Diagnostic and Specialty Medicine, Alma Mater Studiorum, University of Bologna, Italy.
Corresponding Author: Riccardo Mei, Mailing Address: Nuclear Medicine Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Via Albertoni 15, 40138, Bologna, Italy. E-mail: riccardo.mei.91@gmail.com
#contributed equally

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presence of radiotracer in the urinary tract.[6] However, On the contrary, FDG-PET demonstrated a potential prognostic role, showing a direct correlation between SUVs and aggressive disease and/or treatment failure.[10] The limited-role of FDG-PET in the evaluation of PC led to developing other radiotracers for PET imaging of PC with alternative molecular mechanisms. Of those with clinical interest, only Choline (labelled with either ^{18}F and ^{11}C), Fluciclovine and PSMA ligands gained wide-ranging and extensive diffusion. This critical review aims at providing a comprehensive overview of physiological uptake and of the most frequently detected variants and pitfalls when employing PET with Choline, Fluciclovine and PSMA for PC imaging.

Choline

Radiolabeled Choline as a PET tracer, has potential clinical utility in a number of disease and cancer types even if it is mostly employed worldwide for PC imaging.[11–14] Choline is a natural molecule normally metabolized to phosphatidylcholine by the action of choline kinase. In cancer as well as some other benign processes, an abnormal modulation of cell enzymes leads to increased levels of choline precursors and also breakdown of products of membrane phospholipids.[15] Three PET tracers are most commonly used, [^{18}F]F-methylcholine (FCH), [^{18}F]F-ethylcholine and [^{11}C]C-choline.

Choline PET tracers are not PC specific nor cancer specific, as an increased choline metabolism can be detected in a variety of benign (inflammatory and infectious) and neoplastic processes.

Physiological Uptake

The uptake and phosphorylation of FCH is similar to that of [^{11}C]C-Choline and superior to that of [^{18}F]F-ethylcholine and to other choline analogues[16] (Fig. 1 A1 and A2). Fluorinated choline tracers have a long half-life (110 minutes) that allows their distribution in centers without on-site cyclotron and simplifying the daily routine. The drawback is a significant urinary excretion, limiting the exploration of several anatomical districts such ureters, bladder, urethra and, most important, the prostate fossa, where the sensitivity of this imaging procedure is impaired. On the other hand, [^{11}C]C-Choline has a shorter half-life (20 minutes), requiring an on-site cyclotron for its production and application and a fast patients management; conversely it has rapid blood clearance and low rate of radioactive urine in the urinary tract.[17] Beyond the isotope employed and the subsequent behavior on the genitourinary system, the most relevant physiological uptake of labelled choline is in the liver and pancreas. Moderate uptake is seen in the salivary glands and the spleen. Sites of variable physiological distribution are the pituitary gland, the choroid plexus, the small bowel, colon, testicles and bone marrow[18] (Fig. 1A).

Prostate Cancer

Although better performing than FDG, CT and bone scan for PC recurrence, Choline is not specifically recommended by guidelines,[19] due to its limited performance, especially for low PSA values (nodal recurrence detection rate was 40% for PSA values < 1ng/mL, 43% for a PSA-value 1-<2 ng/ml, 60% for a PSA-value 2-<3 ng/ml and 70% for a PSA-value >or= 3 ng/ml).[20] However, this tracer is routinely employed in staging and re-staging PC whenever PSMA is not available.

Benign Conditions

Choline compounds exhibit increased uptake in inflammatory, especially acute, processes, which may potentially affect tumor specificity. One possible explanation of this phenomenon, similarly to tumor cells, is the upregulation of choline kinase in macrophages, which in turn leads to an increased synthesis of macrophage-membrane phosphatidylcholine.[21,22] One other possible explanation is that increased membrane permeability secondary to phlogistic hyperemia yields passive diffusion of choline.[23]

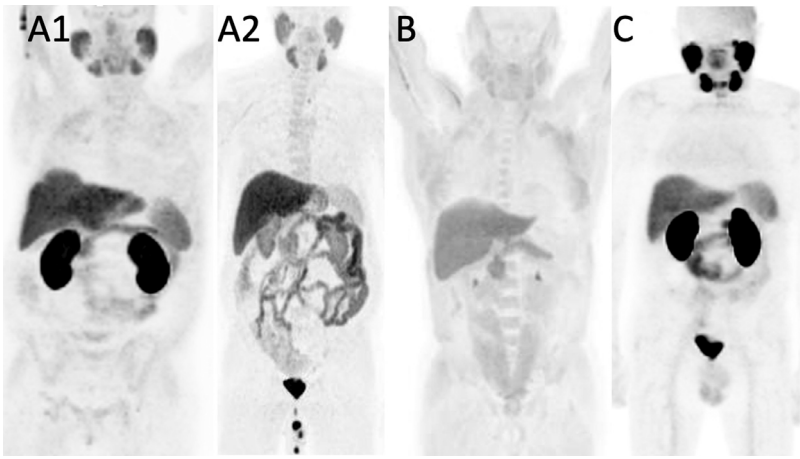

Figure 1 Maximum Intensity Projection (MIP) with [^{11}C]C-Choline(A1), ^{18}F-Choline (A2), ^{18}F-Fluciclovine (B) and [^{68}Ga]Ga-PSMA-11 (C), showing physiological distribution.

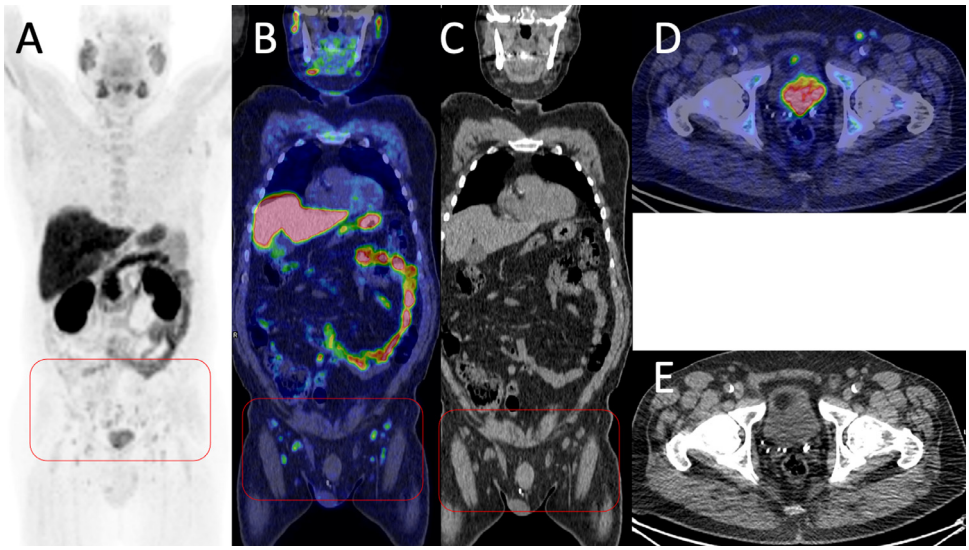

Figure 2 [^{11}C]C-CholinePET in a 63 year-old man with biochemical relapse after RP and adjuvant pelvic radiation therapy, with PSA 1.8 ng/mL. Many focal and bilateral uptakes are shown in correspondence of inguinal and external iliac bilateral lymph nodes. Symmetric and bilateral patterns are compatible with benign condition (inflammatory). Shown are MIP (A), coronal (B, C) and transaxial (D, E) fused and low-dose CT images.

The esophagus, mediastinal and inguinal lymph nodes occasionally show choline accumulation. This is probably due to the presence of inflammatory processes (Fig. 2). Sarcoidosis can be detected incidentally by using Choline PET, showing symmetrical multifocal uptake within lymph nodes in the mediastinum and within pulmonary nodules.[24,25] Diffuse thyroid uptake was observed in case of thyroiditis and hyperthyroidism.[26] Sites of recent trauma and bone fracture may also have increased choline accumulation.[26]

Paget's disease, a chronic bone disorder of unknown origin with typical increased bone turnover which results in cortical and trabeculae thickening and bone expansion, has been described as a tricky finding mimicking PC bony metastases with mild to moderate Choline activity.[27]

Choline increased uptake has been described in parathyroid adenomas,[28] which exhibit choline-kinase overexpression (similarly to inflammation processes).[29–31] Moreover, increased levels of parathormone seem to influence choline-kinase overexpression. Interestingly, FCH has demonstrated good detection accuracy in the diagnosis of parathyroid hyperplasia or multiple and/or ectopic adenomas, even in small lesions, thus acquiring importance for non-invasive preoperatively detection of the lesions in patients with mild increase of parathormone or even with normal calcemia and negative or discordant first-line tests (i.e. ultrasounds and sestamibi scan).[32] Adrenal adenomas presenting as hypodense CT nodules related to high fat content may show increased choline uptake[33] (Fig. 3).

Malignant Conditions

Although Choline tracers show normal liver uptake, readers should be aware in evaluating patients with PC, while the presence of metabolic hepatic lesions might be correlated either with PC metastases[34] or with occult hepatocellular carcinoma.[35] Meningiomas show Choline uptake with a favorable tumor-to-background ratio due to the relatively very low uptake in brain parenchyma.[36] A study by Vicente *et al.* demonstrated a direct correlation among FCH uptake, tumor grade and patient prognosis.[37] A clinical application through the identification of tumor relapse from radiation induced necrosis in gliomas is suggested.[38] Several malignancies show Choline uptake, e.g. lymphoma, thymoma, esophageal carcinoma and lymph node metastases.[39–43] A careful assessment of these findings thorough clinical correlation is needed to avoid misinterpretation with inflammatory disease or PC metastases. Abnormal and focal uptake can be found in the colon, resulting in both colic adenomatosis and colon cancer.[26]

Readers should be aware of incidental increased Choline uptake in the bladder, which might unveil malignant

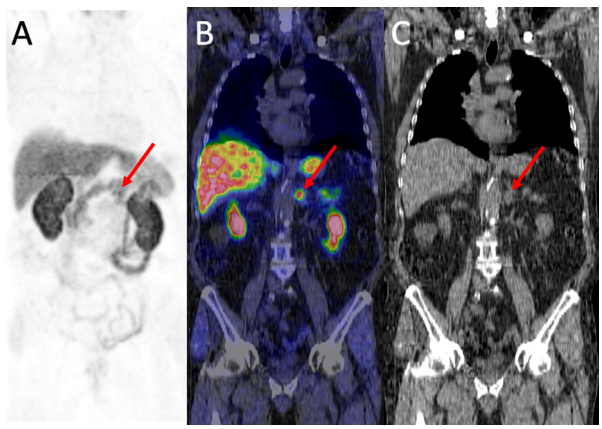

Figure 3 [^{11}C]C-Choline MIP (A), axial PET/CT (B) and low-dose CT (C) of an adrenal adenoma, appearing as a left adrenal mass (arrows), with same density of normal parenchyma and with severe tracer uptake.

lesions.[44] Taking the advantage of ^{11}C-labeled choline rapid blood clearance and high tumor-to-background ratio in the urinary tract, this tracer has been reported to be useful diagnostic tool for primary staging of bladder cancer.[45]

Another possible incidental pitfall are lytic bone lesions with increased Choline uptake, which are mostly correlated with multiple myeloma rather than PC metastases.[26,46,47] Even if Choline PET is not used in clinical practice for the management of patients with multiple myeloma, it appears to be more sensitive than FDG PET/CT for the detection of bony myelomatous lesions.[48,49]

FACBC Fluciclovine

FDA-approved and commercially available [^{18}F]F-Fluciclovine (anti-1-amino-3-^{18}F-flu-(anti-1-amino-3-^{18}F-flu-orocyclobutane-1-carboxylic acid; also known as FACBC) is a synthetic amino acid analog PET tracer, whose transmembrane transport is mediated by alanine-serine-cysteine transporter (ASCT) and L-type amino acid transporter (LAT), which are highly expressed in aggressive tumors.[50,51] Fluciclovine PET is authorized for use in the European Union[52] and is mostly employed in re-staging patients with recurrent PC, while it has a limited role in local staging PC, due to a significant overlap of uptake between malignant and benign prostate lesions.[53]

Physiological Uptake

Amino acids and amino acid transporters are globally represented in the body, thus explaining how Fluciclovine is physiologically distributed in various organs (Fig. 1B). The most relevant physiological uptake of labelled Fluciclovine is in pancreas and liver; less intense uptake is observed in salivary and pituitary gland. Gastric, bowel and colonic activity is usually variable mild to moderate. Bone marrow shows a heterogeneous pattern uptake, thus resulting in a complex background for the evaluation of bone metastases. Skeletal muscles have initial mild activity, increasing and even surpassing that of marrow with time. Mild to moderate uptake is also seen in the spleen and renal parenchyma, sometimes increased in the proximal collecting system. Adrenals as well are mildly visualized and sometimes physiological asymmetric uptake is seen. Bladder activity is usually absent or inferior to the blood pool; sometimes, increased uptake is observed, which may affect the sensitivity in the prostate fossa in primary PC local staging. a delayed pelvic acquisition in prone position or after bladder emptying may improve the reading. Other sites of physiological uptake are the myocardium (similar to muscle), salivary glands, Waldeyer's ring, thyroid, breast, scalp, brain and pituitary. Lung uptake is normally absent or less than blood pool.[54–56]

Prostate Cancer

Fluciclovine has been approved in May 2016 by the U.S. Food and Drug Administration (FDA) in May of 2016 for imaging of suspected prostate cancer recurrence following primary treatment.[57] It has also been authorized in European Union for PC recurrence.[52] In a multicentric study evaluating nearly 600 patients with PC recurrence, Fluciclovine detection rate was about 68% (38% in the prostate/bed, 33% in pelvich lymph node regions, 26% in extra-pelvic regions) and more than 40% for PSA values < 1ng/mL. Overall PPV was 62% (72% and 92% for prostate/bed and extraprostatic disease, respectively).[58] In comparison with [^{11}C]C-Choline, a single-center study demonstrated slightly superiority of Fluciclovine in recurrent PC (Choline vs Fluciclovine sensitivity was 32% and 37%, specificity was 40% and 67%, PPV was 90% and 97%, NPV was 3% and 4%, and accuracy was 32% and 38%, respectively.).[59] In evaluating primary PC, Fluciclovine has a limited role due to a significant overlap of uptake between malignant and benign prostate lesions.[60]

Benign Conditions

Fluciclovine uptake, being involved in amino acids transport, which is upregulated by many oncological and non-oncological processes, has been largely demonstrated in many infections, inflammatory and other benign diseases. In fact, ASCT and L amino-acid transport systems, which are targeted by Fluciclovine, are overexpressed in activated T or B cells, thus explaining the uptake in inflammation processes, even lower compared to that seen with [^{18}F]F-FDG because of less uptake ratios to activate macrophages and granulocytes.[61] Moreover, Fluciclovine seems to show higher uptake in chronic inflammation rather than in acute processes, as demonstrated in a pre-clinical study[62] and also in humans.[63] Inflammation findings with high Fluciclovine uptake include pulmonary hilar, axillary and inguinal lymph nodes (which are mostly non-specific) (Fig. 4), even though in certain cases a subtle inflammatory process has been demonstrated, such as bowel ringworm infection, inflammatory skin lesions, musculoskeletal inflammation.[54] Attention must be paid in the assessment of prostate disease, while non-malignant uptake might be observed with benign prostatic hyperplasia or in chronic (less in acute) inflammation.[63] Mild and diffuse uptake has also been observed after radiation therapy.[64]

Increased uptake of Fluciclovine in dilated superior sagittal sinus is a physiologic normal variant reported in literature and it is probably caused by tracer accumulation in the blood pool.[65] Another physiologic variant of Fluciclovine uptake has been observed in patients with pituitary adenoma, meningioma, osteoid osteoma and adrenal gland adenoma. Conversely, absent uptake was observed in simple renal cysts, as well as benign hepatic cysts and hemangiomas.[54]

Malignant Conditions

PC aside, many studies have shown optimal brain tumor detection with amino acid PET tracers, which seem more sensitive than [^{18}F]F-FDG PET or even MRI.[66] Fluciclovine in particular, demonstrated an optimal performance in staging glioma as compared to similar tracers like [^{11}C]C-Methionine, due to its lower background uptake that leads to greater

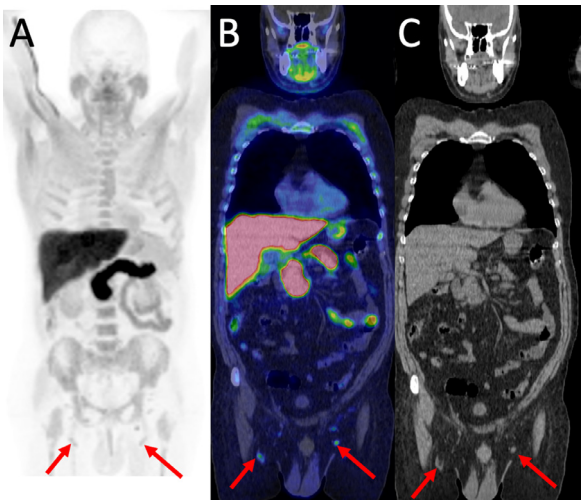

Figure 4 Primary staging ^{18}F-Fluciclovine-PET in a 65-year-old man with PC. MIP (A) and coronal images (fused, B; low-dose CT, C) show bilateral, enlarged inguinal lymph nodes with increased uptake (arrows). These findings are consistent with chronic inflammatory process (courtesy of Dr. Lucia Zanoni, principal investigator of the project "^{18}F-FACBC PET/CT for staging high risk prostate cancer" funded by "Programma di ricerca Regione- Università 2013-Area 1 "Ricerca Innovativa ", Bando "Alessandro Liberati-Giovani Ricercatori" (grant number PRUA1GR-2013-00000171).

lesion contrast and improved detection rate. Moreover, Fluciclovine can potentially distinguish between low-grade and high-grade astrocytomas, even if a small cohort of patients was considered.[67] A recent study by Michaud *et al.* demonstrated that Fluciclovine can detect recurrent and progressive gliomas, even with negative MRI, with better contrast (due to lower uptake in normal brain) as compared to standard ^{11}C-Methionine; even if not been currently demonstrated, authors also hypothesize that Fluciclovine may be superior to contrast MRI in differentiating tumor recurrence/progression from pseudo-progression findings, namely post-necrosis and/or inflammation.[68]

Fluciclovine has demonstrated, even though with a limited number of patients, optimistic results as a potential tracer for breast malignancy, showing significantly higher uptake both in invasive lobular breast cancer and invasive ductal breast cancer, as compared to benign lesions. Moreover, high Fluciclovine uptake was observed in most aggressive triple-negative breast cancer.[69] Gynecomastia in rare cases can lead to a focal area of uptake, thus making it indistinguishable from breast cancer.[70]

Fluciclovine has been reported to be a potential tracer in evaluating lung masses. A study by Amzat *et al.* explored the usefulness of Fluciclovine in characterizing pulmonary lesions and thus detecting primary lung cancer in a small cohort of 10 patients. Fluciclovine was able to differentiate between malignant and benign, i.e. inflammatory and well differentiated carcinoid lesions.[71] These results are supported by Takeuchi *et al.* who demonstrated the presence of LAT1 transporter (targeted by Fluciclovine) is highly expressed in lung carcinoma and is even associated with pathologic state and worse prognosis.[72]

A single case of incidental neuroendocrine tumour showing Fluciclovine uptake in lungs and liver (later confirmed by octreotide SPECT/CT) in a patient studied for recurrence of PC has been reported in the literature.[73] This phenomenon can be explained by the overexpression of amino acid transport LAT-1 (targeted from Fluciclovine) in some neuroendocrine tumors, such as pheochromocytoma, medullary thyroid carcinoma and lung carcinoid.[74–76]

Due to its little uptake in the kidneys (lower than FDG), Fluciclovine tracer has been studied in evaluating renal masses. Fluciclovine demonstrated significant higher uptake in papillary cell tumors, while it was not useful in visualizing clear cell renal carcinoma.[77]

Other anecdotal pitfalls of Fluciclovine have been reported in literature regarding incidental findings of colonic neoplasia, squamous cell carcinoma of the scalp, hematological disorders (Fig. 5), desmoid tumors, oropharyngeal squamous cell carcinoma and recurrent malignant melanoma in patients imaged for PC.[54,78–80]

PSMA

PSMA is a type II transmembrane glycoprotein encoded by the folate hydrolase 1 (FOLH1) gene.[81] PSMA-PET demonstrated the highest diagnostic value in imaging PC, as compared with other PET tracers. PSMA is highly expressed on the cell surface in PC cells and it correlates with tumor grade, higher PSA values and prognosis.[82]

The most used PSMA-tracer is gallium [^{68}Ga]Ga-PSMA-11 and its analogs [^{68}Ga]Ga-PSMA-HBED-CC, [^{68}Ga]Ga-HBED-PSMA, and [^{68}Ga]Ga-DKFZ-PSMA-11 which have the higher tumor-to-background contrast. Other radiotracers include [^{68}Ga]Ga-PSMA-I&T,[83] [^{68}Ga]Ga-THP-PSMA,[84] ^{18}F−DCFPyL,[85,86] and [^{18}F]F-PSMA-1007[88]. Both ^{68}Ga and ^{18}F PSMA are FDA approved,[2,4] while a waiver of the use of [^{68}Ga]Ga-PSMA-11 was granted by the European Union in 2019.[88] Although similar, fluorinated PSMA tracers seem highly promising as compared to ^{68}Ga-labeled tracers, due to longer half-life, higher production capacity and improved image resolution related to lower energy positron emissions and possibly improved detection rate.[89]

Despite the term PSMA seems to be related only to prostate gland, the expression of this molecule has been studied in many other normal tissues, as well as in various benign and malignant pathologies.

Physiological Distribution

The physiological distribution of [^{68}Ga]Ga-PSMA reflects its expression and excretory pathways in normal tissues (Fig. 1C). Kidneys, ureters and bladder show very high uptake because [^{68}Ga]Ga-PSMA is mainly excreted renally.[90] This result might generate difficulty in some patients in assessing abdominal and pelvic nodes beside the urinary tract or even in the prostate bed. To overcome this issue, administration of diuretics, delayed imaging or use of intravenous

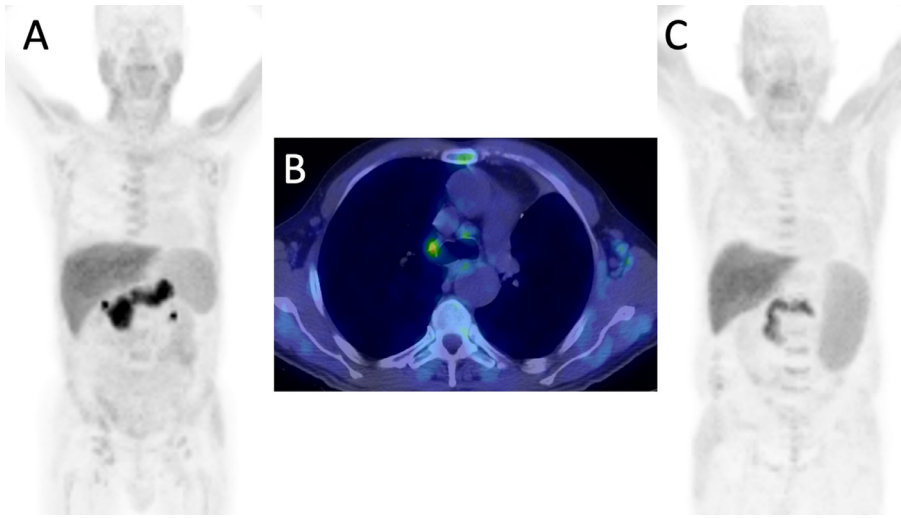

Figure 5 [^{18}F]F-Fluciclovine-PET in a 58-year-old man with biochemical relapse after radical prostatectomy and PSA 0.45 ng/mL (MIP, A). Diffuse, faint uptake in bone marrow was observed and in enlarged mediastinal lymph nodes (fused transaxial image, B). Biopsy was consistent with chronic lymphocytic leukemia. [^{18}F]F-Fluciclovine-PET in a 71 year-old man with PSA 2.0 ng/mL after radical prostatectomy and incidental finding of mild uptake in the spleen that appears enlarged (MIP, C), consistent with idiopathic myelofibrosis (courtesy of Dr Cristina Nanni, principal investigator of the project entitled "ANTI-3-^{18}F-FACBC(anti1-amino-3-^{18}F-fluorocyclobutane-1-carboxylic acid) in comparison to [^{11}C]C-CholinePET/CT in the evaluation of patients with prostate cancer radically treated and with rising PSA,"Programma di ricerca Regione- Università 2010-2012-Area 1 "Ricerca Innovativa ", Bando "Alessandro Liberati"-Giovani Ricercatori").

contrast materials can be helpful in discriminating urinary activity from pathological findings.[91]

Parotid, submandibular and lacrimal glands normally show high uptake, probably due to both expression and non-specific excretion of [^{68}Ga]Ga-PSMA.[92] Due to its salivary excretion, [^{68}Ga]Ga-PSMA mild uptake has been observed in oropharyngeal, laryngeal and esophageal tract.[91] Another common site of physiological uptake is the first tract of small bowel (duodenum), in the liver and in the spleen. Lower uptake is commonly seen in the ganglion Schwann cells of sympathetic ganglia, namely celiac, stellate, presacral ganglia.[93] Sometimes these physiological findings might be misinterpreted with pathological lymph nodes, which potentially can be located in proximity to these structures. Bialek and colleagues compared morphologic and [^{68}Ga]Ga-PSMA-11 PET/MRI uptake of celiac ganglia (CG) in 120 patients. Interestingly, although in the vast majority of patients PSMA uptake in CG was above the cutoff usually considered for PC lymph nodes metastases (i.e. SUVmax above or equal to 2), the main features for appropriate detection of CG were morphology and location, which are worthy to be learned. Normally, non-suspected CGs are thin (i.e. short-axis diameter less than 10 mm) and linear-shaped. By contrast, typical mistaking CGs appear thicker (i.e. short-axis diameter more or equal to 10mm) nodular, oval and longitudinal (i.e. longitudinal nodular, longitudinal thick or longitudinal with oval parts) shape. CGs location seemed to be the main feature in discriminating CG: they usually lie between D12 and L2, most of right GC are located below and caudal to the right adrenal gland, whereas left CG usually lies in proximity of the left adrenal gland.[94] Fluorinated PSMA have similar distribution to Gallium radiolabeled tracers, having the advantage of lack of renal excretion and low urinary activity (if we consider rh-PSMA and PSMA-1007), thus increasing the accuracy for lesions near the urinary tract.[95]

In evaluating PC, a small percentage of PSMA-PET shows absent or faint uptake, reflecting low PSMA expression. Neuroendocrine differentiated PCs do not express PSMA and are associated with aggressive behavior and worse prognosis[96,97] (Fig. 6). Usually, expression of PSMA at metastasis reflects PSMA avidity in the primary tumor. However, recent histochemistry analysis demonstrated both intratumor and interpatient heterogeneity between primary tumor and metastases.[98] False-negative findings of absent PSMA uptake might be also seen in patients with advanced castration-resistant metastatic disease, where multiple-lines or chemotherapy inhibit PSMA expression. Interestingly androgen-deprivation therapy (ADT) may influence PSMA expression, as reported by many studies, although results are heterogeneous or even contradictory. In general, short-term ADT seems to increase PSMA expression in some patients, while long-term ADT might exhibit the opposite effect.[87]

Summarizing, once acknowledged the sites of physiological uptake of PSMA and any factor that may influence PSMA expression (well differentiated neuroendocrine histotype, ADT, chemotherapy) any focal and intense uptake has to be considered pathological finding PC-related.

However, PSMA is overexpressed in many other tumors, showing lower or even non-focal intensity as compared to PC lesions.

Prostate Cancer

In primary staging PC, PSMA demonstrated higher detection rate for pelvic lymph nodes and distant metastasis as compared to standard imaging (sensibility 85% [74–96] vs 38%

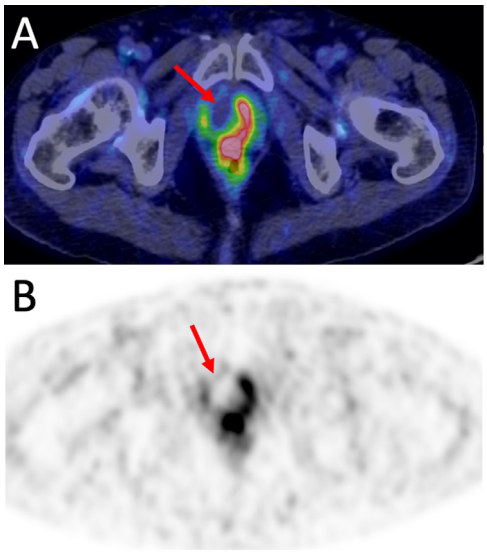

Figure 6 Staging [^{68}Ga]Ga-PSMA-11 in a 72 year-old, RP and pelvic lymph node dissection GS 4+3, showing homogeneous prostate gland uptake (fused and PET transaxial images, A and B), with exception to a circumscribed area of absent uptake in the right lobe (arrows). Patient underwent radical prostatectomy and this finding was related to PC with neuroendocrine differentiation. Despite the fact that neuroendocrine differentiation is not so common, the reader should be aware of this potential missing interpretation of a negative finding in primary staging of PC.

[24–52] vs) and specificity (98% [95–100] vs 91% [85–97]), with subsequent clinical management changes.[99] Moreover, PSMA showed higher detection rate in restaging PC patients, in particular with low PSA values (91.7% for PSA levels ≥ 2 ng/mL, 82.1% for PSA levels 1–1.99 ng/mL, 62.8% for PSA levels 0.5–0.99 ng/mL, 58.7% for PSA levels 0.2–0.49 ng/mL, and 63.6% (7/11) for PSA levels ≤ 0.2 ng/mL).[100,101] Recent EAU Guidelines (2020) recommend PSMA PET/CT for men with a persistent PSA > 0.2 ng/mL and suitable for treatments.[19] Patients with multi-metastatic castration-resistant PC (mCRPC) may also benefit from radioligand therapy with ^{177}Lu-PSMA.[102] A head-to-head comparison between [^{68}Ga]Ga-PSMA and Fluciclovine in recurrent PC showed a superior detection rate of the rformer tracer, being able to disease in 50% more patients and additional lymph node metastasis in 20% of the patients.[103]

Benign Conditions

PSMA uptake is frequently observed in both acute and chronic processes (Fig. 7). Granulomatous diseases and sarcoidosis in particular, which is a chronic multi-system granulomatous inflammatory disease, have been reported in the literature to show increased PSMA uptake. However, the precise molecular mechanism of PSMA uptake in granulomatous disease is still on debate.[93]

As mentioned before, PSMA uptake is frequently seen in ganglia; moreover, some benign tumors of neurogenic origin may show PSMA activity. These include meningioma, schwannomas and peripheral nerve sheath tumor. Rarely meningioma may become host for metastasis of a secondary non prostate tumor (more often lung and breast cancer), as reported by few cases in the literature.[104] As a general statement, any increased PSMA uptake in meningiomas is worth to be further characterized with imaging or even histopathology.[105]

Any osteoblastic activity may show low and/or moderate PSMA uptake. These conditions include osteoarthritis, fractures, fibrous dysplasia, degenerative changes. Paget's disease may also resemble bone metastasis. In case of uncertainty, conventional imaging techniques (bone scintigraphy, CT, MRI) are required to discriminate benign bone lesions from PC metastase.[91] Rauscher *et al.* compared [^{18}F]F-PSMA-1007 PET and [^{68}Ga]Ga-PSMA-11 PET in two large series of patients showing respectively 369 and 178 PSMA-ligand-positive lesions. [^{18}F]F-PSMA-1007 PET revealed five times

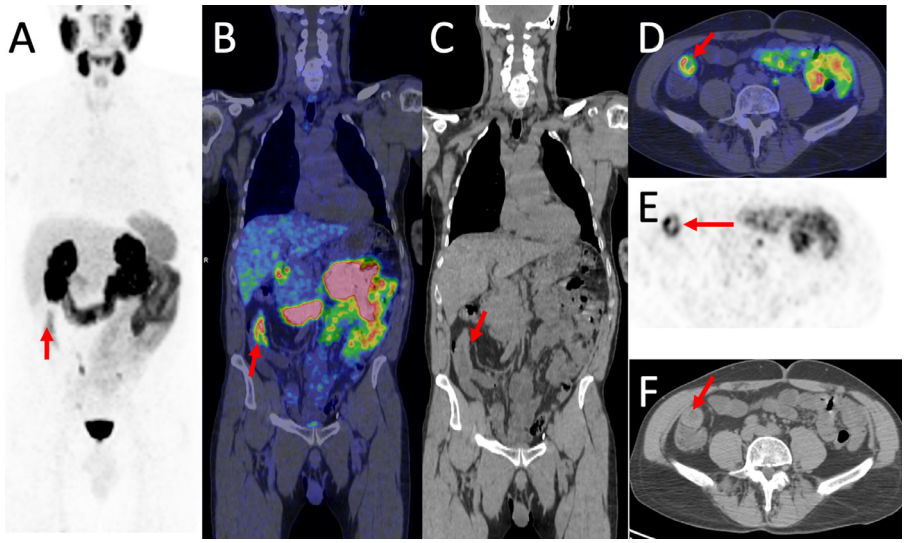

Figure 7 [^{68}Ga]Ga-PSMA-11 performed in a patient with active Crohn disease. Diffuse and moderate intestinal uptake was observed (MIP, A), especially in terminal ileum, which is typically involved, in correspondence of bowel wall thickening (coronal and transaxial fused and low-dose CT images, B, C, D, F; PET transaxial image, E).

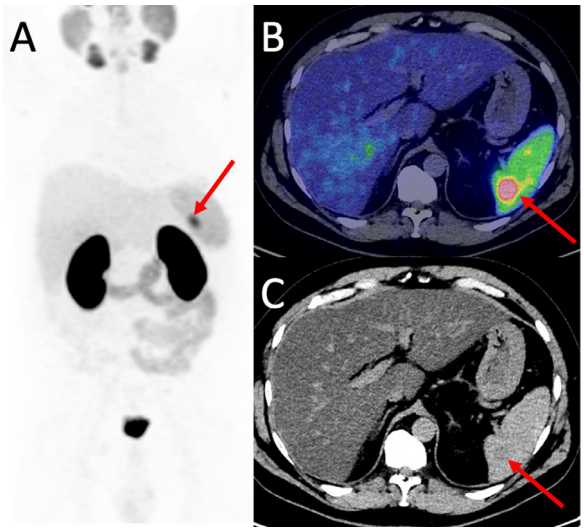

Figure 8 [^{68}Ga]Ga-PSMA-11 (MIP, A; fused and low-CT transaxial images, B and C) showing intense and focal uptake in the superior splenic pole, in correspondence of a centimetric hypodense area (arrows). This was a case of splenic angioma confirmed with ultrasonography.

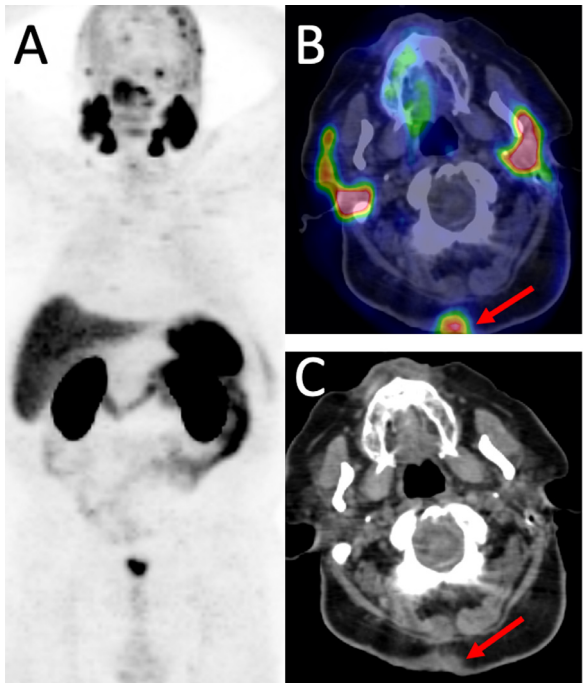

Figure 9 [^{68}Ga]Ga-PSMA-11 in a 72-year-old man with von Recklinghausen disease (i.e. type 1 neurofibromatosis) and biochemical relapse after radical prostatectomy and radiation therapy. Multiple, avid subcutaneous fibromas are observed in the scalp (MIP, fused and low-dose CT images, A,B,C). Otherwise, PET was negative for any PC metastases.

more benign lesions than did [^{68}Ga]Ga-PSMA-11 PET, especially in the bones.[106]

Hemangiomas usually show increased PSMA uptake, due to the high number of endothelial cells and vascular density; these incidental findings were observed in the liver, vertebrae, spleen (Fig. 8) and abdominal skin.[107–109]

A conspicuous number of other cases of non-prostatic increased PSMA uptake in soft tissues has been reported. These findings included desmoid tumor, fasciitis nodularis, intramuscular myxoma, acrochordon, dermatofibroma and pseudoangiomatous stromal hyperplasia.[110–114] Although rare, patients with von Recklinghausen disease might exhibit increased PSMA uptake in cutaneous fibromas[115] (Fig. 9).

Malignant Conditions

Many other malignant tumors exhibit increased PSMA uptake, more possibly related to tumor neo-angiogenesis (Fig. 10 and 11). Renal cell carcinoma (RCC), which is characterized by high PSMA expression on the endothelial cell membrane, is one of the first incidental findings reported in the literature,[116] so that recent studies propose this tracer for the diagnostic work-up of RCC especially those with clear

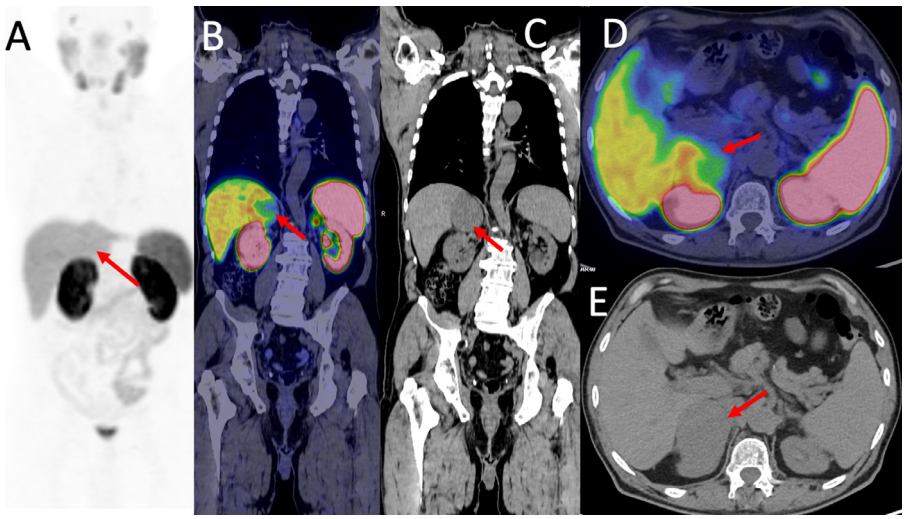

Figure 10 [^{68}Ga]Ga-PSMA-11 (MIP, A) with incidental finding of mild, patchy uptake in a large right adrenal mass (arrows in coronal and transaxial fused and low-dose CT images, B, C, D, E) subsequently confirmed to be adrenal carcinoma by histopathology.

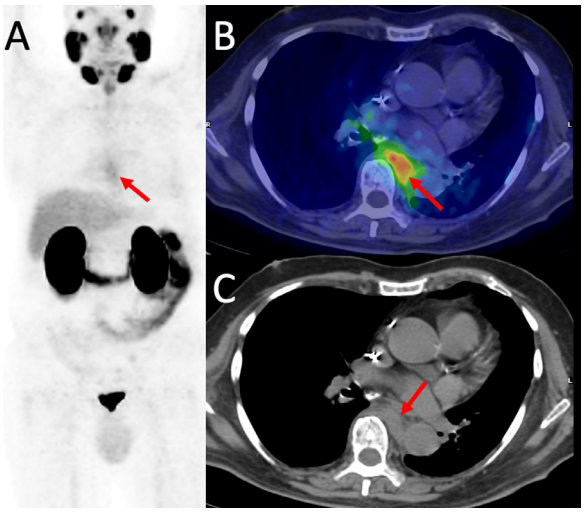

Figure 11 [^{68}Ga]Ga-PSMA-11 showing mild and diffuse uptake in mediastinum (arrow in MIP, A). An incidental avid mass was detected in the posterior mediastinum, adjacent to esophagus (arrows in fused and low-dose CT images, B and C). Biopsy was compatible with non-Hodgkin B lymphoma.

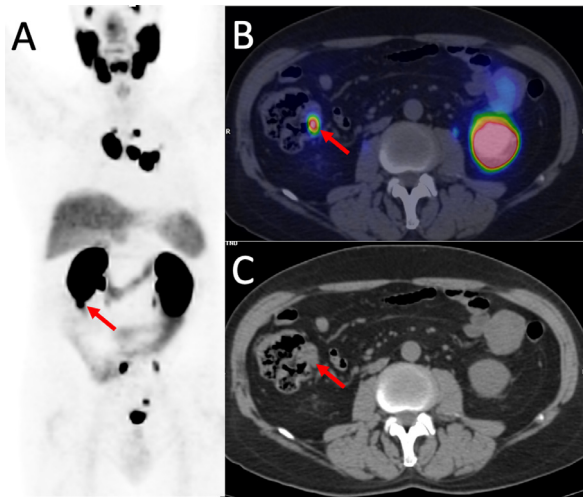

Figure 12 [^{68}Ga]Ga-PSMA-11 MIP (A), fused and low-dose images (B and C) showing intensely avid PSMA uptake in a case of colon adenocarcinoma (mass in internal bowel wall, arrows) and with mediastinal metastasis from PC.

cell histotype, with promising results.[117] Hepatocellular carcinoma (HCC), which is the third most frequent cause of cancer-related death worldwide, has demonstrated significant PSMA expression at immunohistochemistry on its neovasculature, thus making it feasible for PSMA-PET evaluation.[100] In a recent study by Hirmas *et al.* forty patients with imaging consistent with HCC were evaluated with additional PSMA-PET. [^{68}Ga]Ga-PSMA-11 PET demonstrated higher accuracy than CT in the detection of HCC metastases and was associated with management change in about half of the patients.[118]

Several benign and malignant pancreatic lesions show PSMA uptake, spacing from papillary mucinous neoplasm,[119] to serous cystadenoma[120] and neuroendocrine tumor.[121]

Many other incidental findings of malignancies with high PSMA expression are reported in the literature, leading to a growing number of studies aimed to explore the potential role of PSMA-PET in these tumors. A recent review by Sheikhbahaei and colleagues reported several studies of PSMA in adenocarcinoma of urinary bladder, glioblastoma, breast carcinoma, gastric and colorectal cancer (Fig. 12), malignant epithelioid hemangioendothelioma of the liver, adenoid cystic carcinoma of the salivary gland, thymic carcinoma,[122] multiple myeloma, papillary thyroid carcinomas and sarcomatous transformation of fibrous dysplasia.[110]

Despite the promising results, larger, prospective trials are needed to validate the potential role of PSMA-PET in the evaluation of non-prostatic malignancies.

Conclusion

The widespread use of the presented tracers for PC requires an awareness about potential pitfalls reported in the literature and to acquire familiarity with normal distribution and possible variants. Although mainly employed in PC, Choline Fluciclovine and PSMA PET tracers are able to detect many other pathologies. Deep knowledge of tracers' behavior is mandatory as well as the full patient history and those characteristics suggesting a higher risk for metastatic disease on PET images, e.g. PSA kinetics and pathological staging, in order to provide the best diagnostic information for the patient. The conspicuous amount of incidental reporting and the growing number of studies aimed to explore the potential role of these radiotracers in different pathologies, suggest their potential role in the diagnosis of other malignancies.

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