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Urologic Oncology: Seminars and Original Investigations 37 (2019) 611–618

UROLOGIC ONCOLOGY

Seminars article

Role of novel imaging in the management of prostate cancer

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Received 8 October 2018; received in revised form 13 March 2019; accepted 9 April 2019

Abstract

This review summarizes novel imaging in the management of prostate cancer including multiparametric MRI, PET-CT scans with different radiotracers including ^{11}C-acetate, ^{11}C-choline, ^{18}F-choline, ^{18}F sodium fluoride, prostate-specific membrane antigen, and *anti*-1-amino-3-[18F] fluorocyclobutane-1-carboxylic acid (fluciclovine).

Keywords: Prostate cancer; PET scan; Molecular imaging; MRI

Introduction

Prostate cancer is the most common noncutaneous malignancy among men in the United States. In the United States, there will be an estimated 164,690 cases and 29,430 deaths in 2018 [1]. With the development of prostate specific antigen (PSA) testing, an increasing number of prostate cancer patients are diagnosed at clinically localized stage in the past several decades. However, there is still a significant portion of men diagnosed with metastatic disease either at initial diagnosis or after completion of treatments. Recent evidence suggests that oligometastatic prostate cancer is associated with better prognosis and treatment outcomes compared to more extensive disease [2,3]. Therefore, advancement in novel imaging techniques, especially PET-CT with different radiotracers, is becoming crucial in the clinical management of prostate cancer due to their better and earlier detection of metastases compared to conventional imaging such as bone scan and computed tomography (CT) [4,5].

Biochemical failure after radical prostatectomy or radiation treatment frequently precedes the clinical manifestations of recurrent disease in the prostate bed, regional lymph nodes, or distant sites such as bones. Local salvage therapy is usually recommended in patients with regional pelvic lymph node or prostate bed recurrence, whereas systemic therapy is needed to treat distant metastases. Therefore, early and accurate detection of the site of recurrence is important for making treatment decisions.

Our review provides a summary of currently available novel imaging and their potential roles in advancing diagnosis and treatment of prostate cancer.

Novel imaging agents

Multiparametric MRI

A combination of T2 weighted imaging, diffusion weighted imaging, and dynamic contrast-enhanced imaging with or without MRI spectroscopic imaging is called multiparametric MRI (mpMRI) [6]. In addition to staging, it is used in imaging-guided biopsy, tumor characterization, active surveillance, and detection of local recurrence [7–9]. Whole-body MRI has been used for staging and evaluation of advanced disease. Some of its advantages are no additional radiation exposure and the capacity to better detect soft tissue disease. However, the cost is relatively high and availability is limited. It is also very susceptible to artifacts and has reduced ability to detect subcentimeter

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https://doi.org/10.1016/j.urolonc.2019.04.008
1078-1439/

lymph nodes [10]. Furthermore, interpretation of mpMRI images is challenging. There is also a concern that administration of gadolinium-based contrast agent is potentially harmful to human body.

Recently, several large studies have shown that mpMRI can be used to help improve detection of significant prostate cancer and reduce the number of false positive results and unnecessary biopsies in patients who were never biopsied previously. mpMRI with or without target biopsy has been shown to be noninferior compared with standard biopsy in diagnosing clinically significant prostate cancer [11–13].

PET-CT scan with different radiotracers

Position emission tomography (PET) uses a radioactive isotope attached to a ligand, which concentrates in certain areas of the body and emits positrons which are subsequently annihilated resulting in γ rays detected by the PET scanner [14]. Common radioactive isotopes include ^{18}Fluorine ($T_{1/2}$ 110 minutes), ^{11}Carbon (half-life or $T_{1/2}$ 20 minutes), ^{68}Gallium ($T_{1/2}$ 67 minutes), and ^{89}Zirconium ($T_{1/2}$ 78.4 hours). Classes of tracers include fatty acid analogs (acetate), cell membrane analogs (choline), inorganic chemical compounds (sodium fluoride), amino acid analogs (fluciclovine), and newer-generation prostate-specific membrane antigen (PSMA) ligands. The aim of PET-CT is to improve the sensitivity of detecting small nodal and bony metastasis at low PSA level, providing more accurate clinical information of the disease and potentially changing the treatment.

The most commonly available ^{18}F-FDG PET-CT is of limited use in the diagnosis and staging of prostate cancer due to the relatively low accumulation of fluorodeoxyglucose (FDG) in the prostate cancer cells. In addition, its urine excretion causes a significant bladder artifact which interferes with its capacity to evaluate prostate and pelvic lymph nodes. Thus, several novel radiotracers have been designed to overcome some of these challenges, as detailed below (see Table 1 for summary of these radiotracers).

^{11}C-Acetate PET-CT

Primary disease and staging

Cancer cells require more cell membrane lipids. Acetate is the only carbon source for fatty acid and cholesterol synthesis. Fatty acid synthase and its overexpression are associated with high Gleason scores, suggesting more aggressive prostate cancer [15]. However, Kato et al [16] demonstrated that ^{11}C-acetate PET-CT cannot distinguish between benign prostatic hyperplasia and prostate cancer while Mena et al [17] showed that ^{11}C-acetate uptake in tumor was higher than that in normal prostate tissue. Currently published studies show a sensitivity ranging from 38 to 100% and specificity ranging from 29 to 96% of detecting disease in patients with primary prostate cancer and lymph node involvement.

Recurrent disease

A systemic review performed by Mohsen et al on the application of ^{11}C-Acetate PET imaging for prostate cancer included 23 studies. The sensitivity and specificity for primary tumor evaluation were 75.1% and 75.8%, respectively. The sensitivity and specificity for detection of recurrences were 64% and 93%, respectively [18]. Due to its low sensitivities and specificities, ^{11}C-acetate PET-CT is unlikely to be very helpful for diagnosis, staging, or detection of recurrent disease in prostate cancer patients.

^{11}C-choline and ^{18}F-choline PET-CT

Prostate cancer cells overexpress choline kinase and use choline to synthesize phosphatidylcholine, a major component of cell membranes. There is physiologic uptake in the salivary glands, liver, adrenal glands, gastrointestinal, and urinary tracts. It is difficult to distinguish cancer cell uptake from benign prostate hyperplasia. There are 2 major choline radiotracers: ^{11}C-choline and ^{18}F-choline. ^{18}F-choline is favored due to longer half-life (about 110 minutes)

Table 1
A summary of PET-CT scans with different radiotracers

Modality	Mechanism	Advantage	Disadvantage	Indication
^{11}C-Acetate	cell membrane lipid synthesis	no extra radiation exposure, better for soft tissue	low sensitivities and specificities	Image-guided biopsy
^{11}C-choline/^{18}F-choline	cell membrane synthesis	excellent for PSA >1	low detection rate for PSA <1	initial staging or biochemical recurrence
^{18}F Sodium fluoride	taken up by bone cells	excellent for bone metastases	not helpful for detecting for locoregional disease	detection of bone metastases
PSMA	trans-membrane receptor overexpressed in prostate cancer cells	excellent for most PC with PSMA expression including castrate-resistant PC (CRPC)	limited utility for PSMA negative PC, such as those with neuroendocrine differentiation	biochemical recurrence or nodal/distant micro-metastases
FACBC	fluorinated synthetic amino acid	Excellent for PSA >1, slight advantage over choline [40]	low detection for PSA <1	biochemical recurrence or nodal/distant micro-metastases

compared with ^{11}C-choline (half-life 20 minutes) [14]. Short half-life of ^{11}C also requires on-site or nearby cyclotron. ^{11}C-choline PET-CT is Food and Drug Administration (FDA) approved for detecting recurrent prostate cancer but not ^{18}F-choline.

Primary disease and staging

Currently, ^{18}F-choline has a very limited role in assessing the primary disease. However, it is potentially useful in detecting lymph node metastasis. Simone et al used a new ^{18}F-choline PET/CT imaging acquisition protocol with an early dynamic phase (1–8 minutes), a conventional whole body (10–20 minutes) and a late phase (30–40 minutes). A total of 146 patients with PSA levels between 0.2 and 1 ng/ml with negative conventional imaging who did not receive salvage treatment were prospectively enrolled into the study. Sensitivity, specificity, PPV, negative predictive value (NPV), and accuracy were 78.9, 76.9, 97.2, 26.3, and 78.7%, respectively [19]. Kitajima et al compared ^{11}C-choline PET-CT with pelvic mpMRI for detection of recurrent prostate carcinoma in 115 patients who underwent prostatectomy. mpMRI with endorectal coil is superior for the detection of local recurrence while ^{11}C-choline PET-CT is superior for pelvic lymph node metastasis. Both were excellent for pelvic bone metastasis. The sensitivity, specificity, and accuracy of mpMRI for diagnosing local recurrence were 88.5% (54/61), 84.6% (22/26), and 87.4% (76/87). The sensitivity, specificity, and accuracy of ^{11}C-choline PET-CT for detecting lymph node or bone metastases were 92.3% (72/78), 100% (18/18), and 93.8% (90/96), respectively [20].

Recurrent disease

Kwee et al examined ^{18}F-choline PET/CT in 50 patients with rising PSA levels during post-treatment follow-up. These patients received either radical prostatectomy, external beam radiation, or brachytherapy. Abnormal tumor uptake was detected in 88% patients with a PSA level >1.1 ng/ml and in only 6% patients with a PSA level <1.1 ng/ml. The conclusion was that effectiveness of ^{18}F-choline PET/CT in the detection of prostate cancer recurrence depends on the PSA level prior to imaging [21]. A meta-analysis by Kairemo et al included 47 studies from 1998 to 2013 that described choline PET-CT scans for prostate cancer. A total of 3,167 patients were evaluated regarding their findings on choline PET-CT during staging and restaging for biochemical recurrence (BCR). Choline PET-CT led to a change in the treatment decision among 381 (41%) of 938 patients, which led to complete PSA response in 101 of 404 (25%) patients. The conclusion was that ^{11}C-choline and ^{18}F-choline PET-CT are useful as the first imaging for patients with initially diagnosed prostate cancer or BCR with PSA levels ranging from 1.0 to 50 ng/ml [22]. Buchegger et al compared ^{18}F-choline with ^{11}C-acetate PET-CT for the detection of recurrent prostate cancer. Both showed excellent concordance, on both a per lesion and a per patient basis, suggesting that both tracers perform equally for recurrent prostate cancer staging [23].

^{18}F Sodium fluoride (NaF) PET-CT

Sodium fluoride is an inorganic chemical compound that dissociates into Na^+ and F^- ions. The F^- ions are then taken up by the bone cells through chemisorption process, which helps identifying regions of active bone growth. Therefore, it can only be used to detect bone metastasis and studies have shown it has better sensitivity compared with traditional bone scans. In a literature review of 11 articles with varying PSA levels, the pooled sensitivities of ^{18}F-NaF PET-CT in detecting prostate cancer bone metastases were 89 and 87% and specificities were 91 and 80% on a per lesion and per patient basis, respectively [24]. The reported sensitivities of conventional bone scans are 39 and 70% and specificities are 83 and 57% per lesion and per patient basis, respectively [25]. A meta-analysis by Luo et al evaluated the diagnostic accuracy of ^{18}F-NaF PET or PET-CT compared with conventional Tc-MDP bone scintigraphy and ^{18}F-FDG PET-CT in the detection of bone metastases, which included 20 articles containing 1,170 patients. When compared with Tc-MDP bone scintigraphy, ^{18}F-NaF PET or PET/CT showed both higher sensitivity (96% vs. 88%, $P = 0.002$) and specificity (91% vs. 80%, $P = 0.001$). When compared with ^{18}F-FDG PET-CT, ^{18}F-NaF PET, or PET/CT showed higher sensitivity (94% vs. 73%, $P = 0.003$), whereas no significant difference was observed in specificity (88% vs. 98%, $P = 0.06$) [26]. With a PSA level <20 ng/ml, the sensitivity of conventional bone scan is low. A meta-analysis of 23 articles and 8,644 patients showed that the detection rate of bone metastases was 2.3, 5.3, and 16.2% with PSA level of less than 10, 10.1 to 19.9, and at least 20, respectively [27]. Due to its higher sensitivity, ^{18}F sodium fluoride (NaF) PET-CT has a potential of increasing the detection rate of bone metastases in patients with PSA <20 ng/ml. It can be especially helpful for patients at risk for metastatic disease in whom the conventional bone scan is equivocal or negative. Currently, ^{18}F -NaF PET-CT is not reimbursed by Medicare, thus limiting its adoption.

Prostate-specific membrane antigen (PSMA) PET-CT

PSMA is a transmembrane receptor that is overexpressed in most prostate cancer cells. It has an external and internal domain. The external domain contains folate hydrolase and N-acetyl-L-aspartyl-L-glutamate peptidase enzymes. The function of the internal domain is unclear [14]. Several generations of PSMA-targeted small molecules have been developed. The first generation was the antibody 111In-capromab pendetide (trade name ProstaScint; Cytogen Corporation, Princeton, NJ). It was FDA approved in the 1990s. However, it targets the internal

domain of PSMA and has low sensitivity and specificity. The most commonly studied and used tracer is the ^{68}Ga-labeled PSMAHBED-CC (68Ga-PSMA) PET tracer. Notably, PSMA is the only theranostic (combination of a diagnostic biomarker with a therapeutic agent) available currently for prostate cancer [28].

Primary disease and staging

Similarly to other PET tracers, PSMA has limited value in the detection and characterization of primary disease. However, it is useful in the staging of high-risk primary prostate cancer. Hijazi et al performed a retrospective analysis of 35 prostate cancer patients who underwent ^{68}Ga-PSMA PET/CT with either BCR after curative treatment (n = 23) or before primary treatment of high-risk prostate cancer (n = 12). They performed pelvic extended lymph node dissection associated with pathologic imaging in 17 men with nodal oligometastatic prostate cancer. Diagnostic accuracies per nodal lesion in total of 213 removed nodes were the following: sensitivity, 94%; specificity, 99%; positive predictive value (PPV), 89%, andNPV, 99.5% [29].

Recurrent disease

Perera et al performed a systematic review and meta-analysis of ^{68}Ga-PSMA PET that included 37 articles involving 4,790 patients. Per-node analysis showed high sensitivity (75%) and specificity (99%). Positivity differed significantly after BCR in the prostate bed between patients who received radical prostatectomy (22%) and those with radiotherapy (52%).Positive ^{68}Ga-PSMA PET scans for BCR patients increased with PSA levels prior to imaging. For the PSA levels 0 to 0.19, 0.2 to 0.49, 0.5 to 0.99, 1 to 1.99 and >2 ng/ml, 33%, 45%, 59%, 75%, and 95% scans, respectively, were positive . Positivity between Gleason score ≤7 and ≥8 did not differ significantly [30]. A prospective study by Van Leeuwen et al examined the detection rates of ^{68}Ga-PSMA PET-CT in patients with BCR after radical prostatectomy (RP), which included a total of 70 patients. 53 ^{68}Ga-PSMA positive lesions were detected in 38 (54%) patients. Among patients with PSA levels 0.05 to 0.09 ng/ml, 8% were definitely positive. The detection rates for the other PSA ranges were the following: PSA 0.1 to 0.19 ng/ml, 23%; PSA 0.2 to 0.29 ng/ml, 58%; PSA 0.3 to 0.49 ng/ml, 36%; and PSA 0.5 to 0.99 ng/ml, 57% [31]. Overall, ^{68}Ga-PSMA PET-CT is a promising imaging modality that can potentially improve the accuracy of detecting BCR or nodal micro-metastases, especially in well-differentiated prostate cancer.

Bombesin PET-CT

^{68}Ga-labeled DOTA-4-amino-1-carboxymethyl-piperidine-D-Phe-Gln-Trp-Ala-Val-Gly-His-Sta-Leu-NH2 (^{68}Ga-RM2, or ^{68}Ga-DOTA-bombesin, formerly also known as BAY86-7548) is a synthetic bombesin receptor antagonist that targets gastrin-releasing peptide receptors, which are overexpressed in prostate cancer with little activity in normal prostate tissue. It targets a different biologic process compared with ^{68}Ga-PSMA PET/CT. Bombesin PET-CT is still under active investigation. A pilot study by Minamimoto et al included 7 men with biochemically recurrent who underwent both ^{68}Ga-PSMA-11 PET/CT and ^{68}Ga-RM2 PET/MRI scans. ^{68}Ga-PSMA-11 had the highest physiologic uptake in the salivary glands and small bowel with hepatobiliary and renal clearance while ^{68}Ga-RM2 had the highest physiologic uptake in the pancreas, with renal clearance. There was no significant difference in the uptake outside the expected physiologic biodistribution. In 2 patients, periaortic lymph nodes were better visualized by ^{68}Ga-RM2 as it has low uptake in the small intestine which minimizes the interference. In 1 patient, abnormal uptake in a pelvic node and seminal vesicle was only seen with ^{68}Ga-PSMA [32].

Fluorinated bombesin PET-CT ^{18}F-BAY 86-4367 and ^{64}Cu labeled GRPR antagonist, ^{64}Cu-CB-TE2A-AR-06 have also been investigated in preclinical work and small-size human studies with some promising results [38].

Anti-1-amino-3-[18F] fluorocyclobutane-1-carboxylic acid (FACBC or fluciclovine) PET-CT

Amino acid transport is up-regulated in prostate and other cancer cells. Fluciclovine is a fluorinated synthetic amino acid PET radiotracer transported primarily by the amino acid transporters ASCT2 and LAT1 [33]. Fluciclovine has relatively low urinary excretion, and advantage with pelvic imaging. Due to the kinetics of the radiotracer, PET imaging is performed shortly after injection of fluciclovine in the PET scanner, which is also helpful for more rapid patient throughput, compared to other PET radiotracers which require 60 minutes or more uptake time. Fluciclovine was approved by the United States FDA in May 2016 for imaging of suspected prostate cancer recurrence based on elevated PSA level after previous treatments.

Recurrent disease

A prospective clinical trial by Akin-Akintayo et al explored the impact of fluciclovine PET-CT on the decision making of radiation treatment (whether to offer radiotherapy and the size of radiation fields) in patients with recurrent prostate cancer after prostatectomy. Eighty-seven patients with detectable PSA levels were recruited. Forty-four of 87 patients were randomized to undergo fluciclovine PET-CT but 2 patients dropped out. Thirty-four (81.0%) of 42 had positive results on fluciclovine scan. Overall radiotherapy decision was changed in 17 (40.5%) of 42. Radiotherapy field decision was changed in 15 (35.7%) of 42. Eleven (73.3%) of 15 had fields changed from prostate bed only to both prostate bed and pelvis, while 4 (26.7%) of 15 had fields changed from both prostate bed and pelvis to

prostate bed only. Disease detection rates generally improved as PSA level increased: 72.0%, 83.3%, and 100% at PSA levels <1, 1 to <2, and ≥2 ng/ml, respectively. Another prospective study by Akin-Akintayo et al investigated the disease detection rate, diagnostic performance and interobserver agreement of fluciclovine PET-CT and mpMR in recurrent prostate cancer. Twenty-four patients with biochemical failure after nonprostatectomy definitive therapy, underwent fluciclovine PET-CT and mpMR with interpretation by imaging readers blinded to patient history, PSA, and other imaging results. The disease detection rate for fluciclovine PET-CT in nonprostatectomy patients with biochemical failure was 94.7% vs. 31.6 to 36.8% for mpMR [34]. A prospective study was conducted by Schuster et al to compare fluciclovine PET-CT with ProstaScint (111Incapromab pendetide) single photon emission computerized tomography-computerized tomography in the detection of recurrent prostate carcinoma [35]. Among the 91 of 93 patients with enough evidence for a consensus on the presence or absence of prostate/bed disease, fluciclovine scan had 90.2% sensitivity, 40.0% specificity, 73.6% accuracy, 75.3% PPV and 66.7% NPV compared to 111In-capromab pendetide with 67.2%, 56.7%, 63.7%, 75.9%, and 45.9%, respectively. Among the 70 out of 93 patients with a consensus on the presence or absence of extraprostatic disease, fluciclovine PET-CT had 55.0% sensitivity, 96.7% specificity, 72.9% accuracy, 95.7% PPV and 61.7% NPV compared to 10.0%, 86.7%, 42.9%, 50.0% and 41.9% for ^{111}In-capromabpendetide, respectively.

Jani et al showed that incorporating information from FACBC PET-CT could lead to significant differences in the defined target volumes, with higher radiation doses to the penile bulb but no significant differences in rectal or bladder dose or in acute genitourinary or gastrointestinal toxicity,

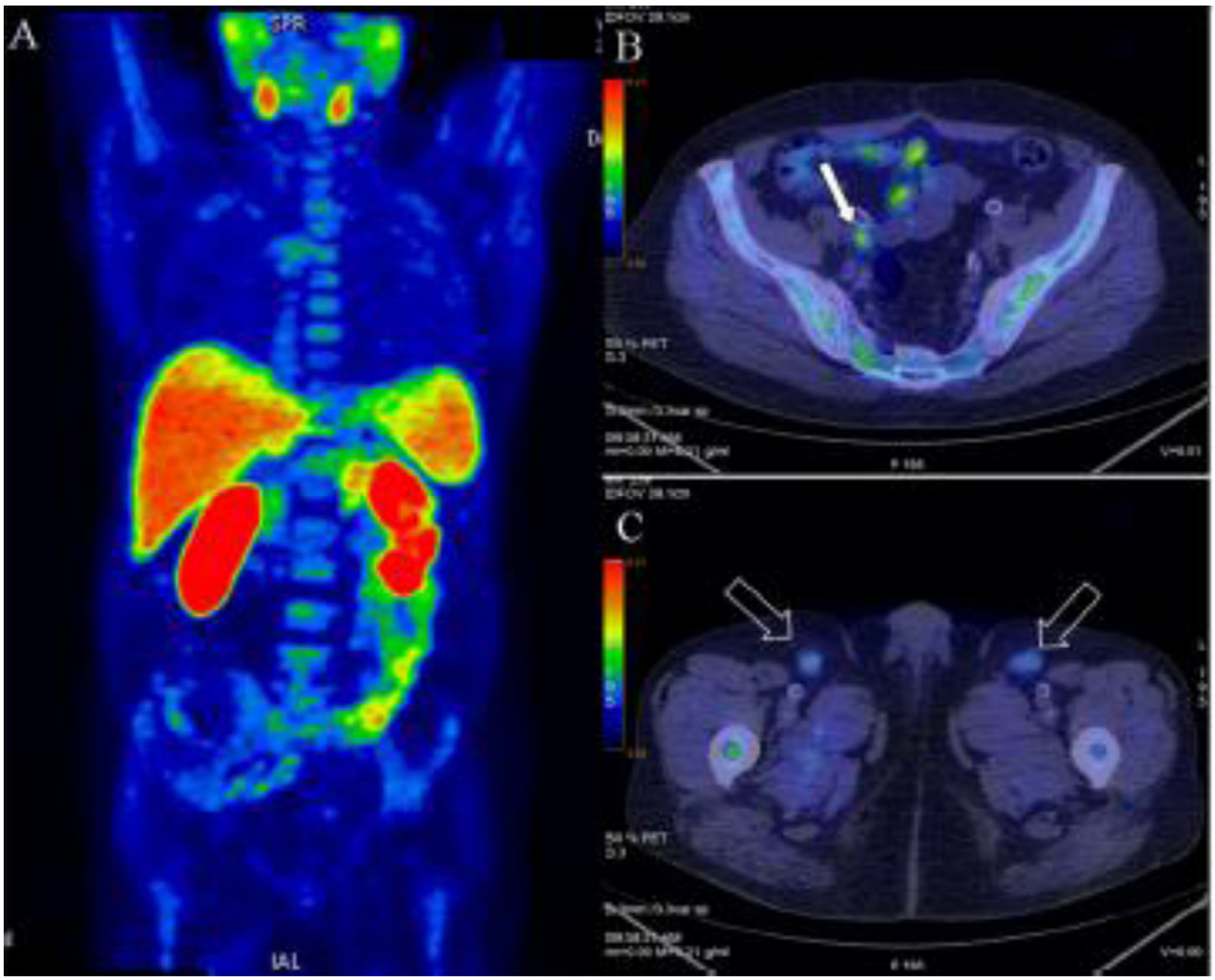

Fig. 1. 11C-choline-PET in a patient after radical prostatectomy and adjuvant ADT. PSA subsequently increased to 2.3 ng/ml. (A) Maximum intensity projection (MIP) image. (B) Axial PET-CT showing increased focal uptake in small right iliac lymph node consistent with relapse (arrow). (C) Axial PET-CT showing increased uptake in bilateral inguinal nodes consistent with inflammation (arrows). From Schuster DM et al [38].

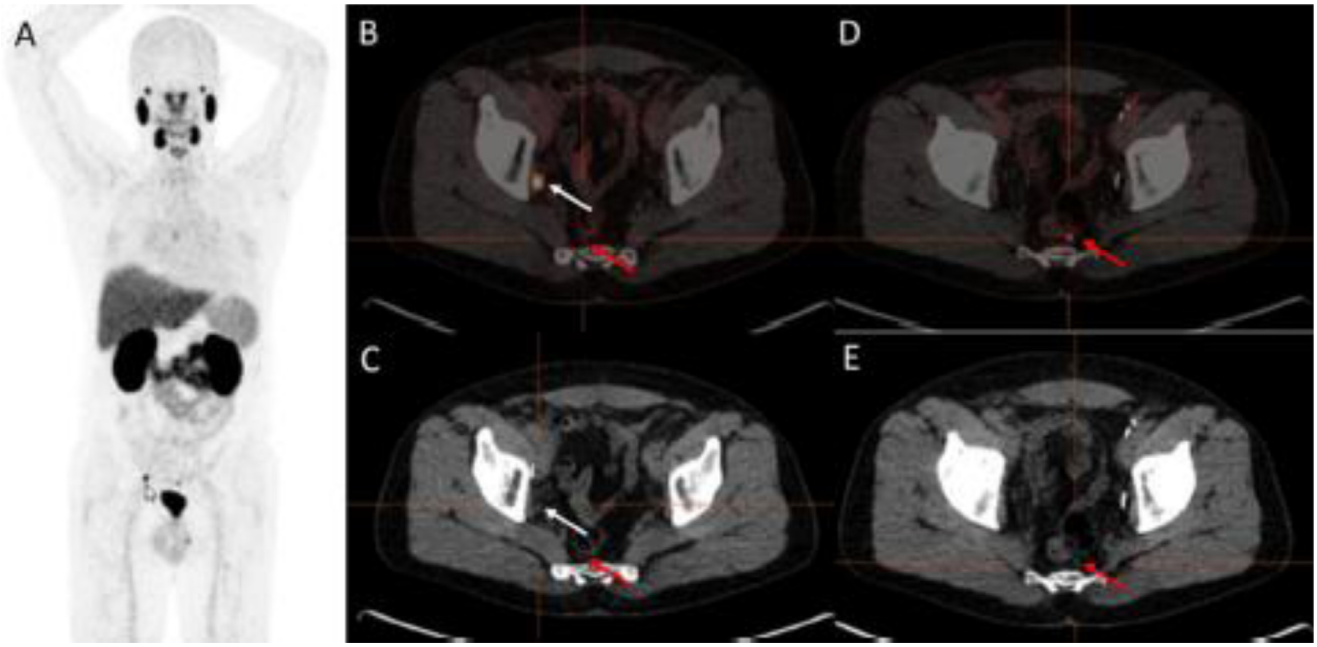

Fig. 2. A 59-year-old man with known high-risk prostate cancer (T3, Gleason 9) treated with radical prostatectomy. After 3 years, PSA was rising to 1.6. ^{68}Ga-PSMA PET/CT showed no signs of recurrence in the prostatic bed or bone metastases. However, several small lymph node node metastases were detected on PSMA PET/CT. A 5 mm lymph node metastase is seen on MIP and axial fused image (white arrow, A and B), and very small lymph node metastases (<5 mm) are seen on the axial fused PET/CT images (red arrows, B and D) and on corresponding axial CT images (red arrows, C and E). MIP, maximum intensity projection. From Bouchelouche K et al [39].

among postprostatectomy patients who underwent salvage radiotherapy [36]. Schreibmann et al demonstrated the use of FACBC scan in postprostatectomy radiation therapy planning was feasible and it led to augmentation of the target volumes in the majority (30 of 41) of the patients studied [37].

Figs. 1–4 are examples of how ^{11}C-choline, PSMA, and fluciclovine PET-CT may be utilized to detect recurrent disease or decide whether to offer radiotherapy and the size of radiation fields in prostate cancer patients [38,39].

Conclusions

There have been significant advancements in the development of novel imaging for prostate cancer, especially in radiotracer-based PET-CT. Overall, previous studies have suggested ^{18}F-choline, PSMA, and fluciclovine PET-CT have adequate diagnostic performance and detection rates which can lead to significant changes in treatment decisions and target volume delineations. Several may have the potential of replacing conventional bone scan, especially

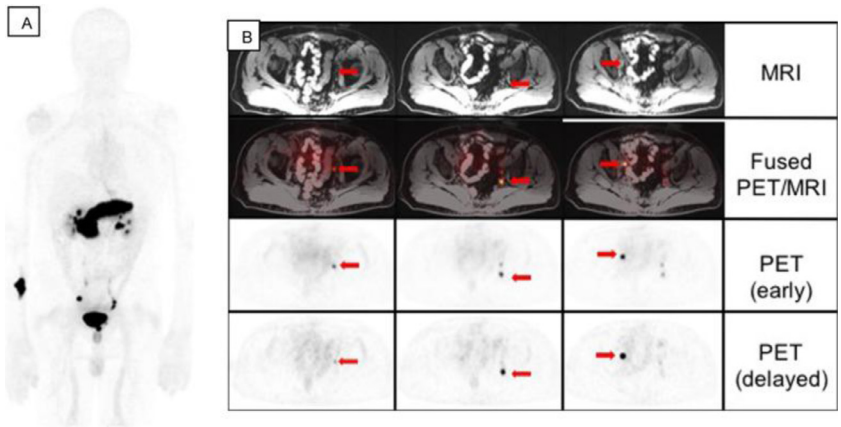

Fig. 3. ^{68}Ga-RM2-PET/MRI in a patient with treated prostate adenocarcinoma, now with biochemical recurrence (PSA = 3.25 ng/ml) and negative findings on CT and bone scan. (A) MIP image. (B) Early and delayed axial PET/MRI image demonstrates multiple subcentimeter pelvic lymph nodes with high uptake on the initial and delayed ^{68}Ga-RM2-PET acquisitions (arrows). (Image courtesy: Andrei Iagaru, MD, Stanford University). MIP, maximum intensity projection. From Schuster DM et al [38].

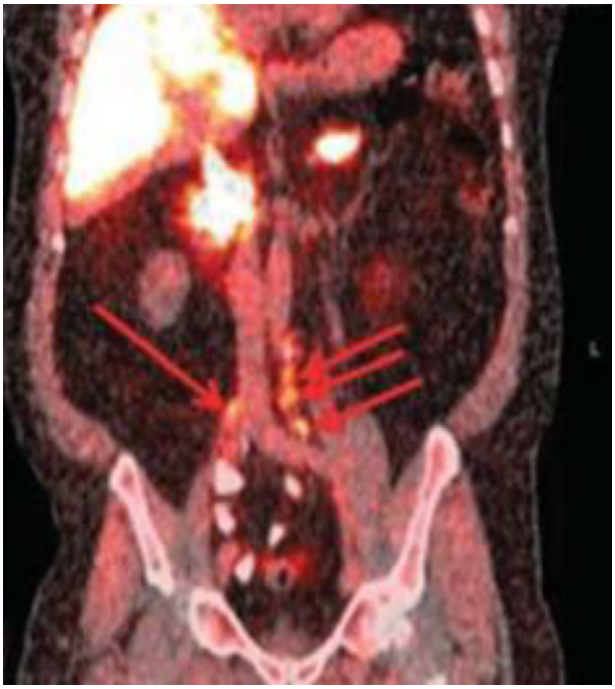

Fig. 4. Seventy two-year-old M with preradiotherapy PSA of 3.46 ng/ml. The initial plan was radiotherapy to the prostate bed plus pelvic lymph nodes. The fluciclovine (^{18}F) PET-CT scan showed uptake in the retroperitoneal nodes (arrows). Radiotherapy was thus aborted; the patient received hormone therapy alone, representing a decision change from radiotherapy to no radiotherapy (i.e., from local to systemic therapy). From Akin-Akintayo OO et al [33].

^{18}F-NaF PET-CT. However, since there is a limitation of detection rates and sensitivity at low PSA levels, there is less potential utility with detection and treatment of early recurrence. Future investigations and clinical trials are needed to address these issues.

References

1 Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin 2018;68(1):7–30. https://doi.org/10.3322/caac.21442. Epub 2018 Jan 4. PubMed PMID: 29313949.

2 Ost P, Jereczek-Fossa BA, As NV, et al. Progression-free survival following stereotactic body radiotherapy for oligometastatic prostate cancer treatment-naive recurrence: a multi-institutional analysis. Eur Urol 2016;69:9–12.

3 Conde Moreno AJ, Ferrer Albiach C, Muelas Soria R, et al. Oligometastases in prostate cancer: restaging stage IV cancers and new radiotherapy options. Radiat Oncol 2014;9:258.

4 Yang HL, Liu T, Wang XM, Xu Y, Deng SM. Diagnosis of bone metastases: a meta-analysis comparing (1)(8)FDG PET, CT, MRI and bone scintigraphy. Eur Radiol 2011;21(12):2604–17.

5 Lecouvet FE, El Mouedden J, Collette L, et al. Can whole-body magnetic resonance imaging with diffusion-weighted imaging replace Tc 99m bone scanning and computed tomography for singlestep detection of metastases in patients with high-risk prostate cancer? Eur Urol 2012;62(1):68–75.

6 Turkbey B, Mani H, Shah V, et al. Multiparametric 3T prostate magnetic resonance imaging to detect cancer: histopathological correlation using prostatectomy specimens processed in customized magnetic resonance imaging based molds. J Urol 2011;186:1818–24.

7 Faiena I, Salmasi A, Mendhiratta N, Markovic D, Ahuja P, Hsu W, et al. PI-RADS version 2 category on 3 tesla multiparametric prostate magnetic resonance imaging predicts oncologic outcomes in gleason 3 + 4 prostate cancer on biopsy. J Urol 2019;201(1):91–7. https://doi.org/10.1016/j.juro.2018.08.043. PubMed PMID: 30142318.

8 Cantiello F, Russo GI, Kaufmann S, Cacciamani G, Crocerossa F, Ferro M, et al. Role of multiparametric magnetic resonance imaging for patients under active surveillance for prostate cancer: a systematic review with diagnostic meta-analysis. Prostate Cancer Prostatic Dis 2018. https://doi.org/10.1038/s41391-018-0113-2. [Epub ahead of print] Review. PubMed PMID: 30487646.

9 Ward RD, Purysko AS. Multiparametric magnetic resonance imaging in the evaluation of prostate cancer recurrence. Semin Roentgenol. 2018 Jul;53(3):234–46. https://doi.org/10.1053/j.ro.2018.04.002. Epub 2018 Apr 5. PubMed PMID: 30031417.

10 Muller BG, Futterer JJ, Gupta RT, et al. The role of magnetic resonance imaging (MRI) in focal therapy for prostate cancer: recommendations from a consensus panel. BJU Int 2014;113:218–27.

11 Boesen L, Nørgaard N, Løgager V, et al. Assessment of the diagnostic accuracy of biparametric magnetic resonance imaging for prostate cancer in biopsy-naive menthe Biparametric MRI for Detection of Prostate Cancer (BIDOC) study. JAMA Network Open 2018;1(2):e180219. https://doi.org/10.1001/jamanetworkopen.2018.0219.

12 Kasivisvanathan V, Rannikko AS, Borghi M, Panebianco V, Mynderse LA, Vaarala MH, et al. MRI-targeted or standard biopsy for prostate-cancer diagnosis. N Engl J Med 2018;378(19):1767–77. https://doi.org/10.1056/NEJMoa1801993. Epub 2018 Mar 18. PubMed PMID: 29552975.

13 Ahmed HU, El-Shater Bosaily A, Brown LC, Gabe R, Kaplan R, Parmar MK. PROMIS study group. Diagnostic accuracy of multiparametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. Lancet 2017;389(10071):815–22. https://doi.org/10.1016/S0140-6736(16)32401-1. Epub 2017 Jan 20. PubMed PMID: 28110982.

14 Goldberg H, Hamilton RJ. Novel imaging in advanced prostate cancer. Curr Opin Support Palliat Care 2017;11(3):238–46. https://doi.org/10.1097/SPC.0000000000000275. Review. PubMed PMID: 28590314.

15 Spick C, Herrmann K, Czernin J. Evaluation of prostate cancer with 11C-Acetate PET/CT. J Nucl Med 2016;57(Suppl 3):30S–7S. Review. PubMed PMID: 27694168.

16 Kato T, Tsukamoto E, Kuge Y, et al. Accumulation of ^{11}C-acetate in normal prostate and benign prostatic hyperplasia: comparison with prostate cancer. Eur J Nucl Med Mol Imaging 2002;29:1492–5.

17 Mena E, Turkbey B, Mani H, et al. ^{11}C-acetate PET/CT in localized prostate cancer: a study with MRI and histopathologic correlation. J Nucl Med 2012;53:538–45.

18 Mohsen B, Giorgio T, Rasoul ZS, et al. Application of C-11-acetate positron-emission tomography (PET) imaging in prostate cancer: systematic review and meta-analysis of the literature. BJU Int 2013;112 (8):1062–72.

19 Simone G, Di Pierro GB, Papalia R, et al. Significant increase in detection of prostate cancer recurrence following radical prostatectomy with an early imaging acquisition protocol with (18)F-fluorocholine positron emission tomography/computed tomography. World J Urol 2015;33 (10):1511–8.

20 Kitajima K, Murphy RC, Nathan MA, et al. Detection of recurrent prostate cancer after radical prostatectomy: comparison of 11C-choline PET/CT with pelvic multiparametric MR imaging with endorectal coil. J Nucl Med 2014;55(2):223–32.

21 Kwee SA, Coel MN, Lim J. Detection of recurrent prostate cancer with 18F-fluorocholine PET/CT in relation to PSA level at the time of imaging. Ann Nucl Med 2012;26(6):501–7.

22 von Eyben FE, Kairemo K. Meta-analysis of (11)C-choline and (18)F-choline PET/CT for management of patients with prostate cancer. Nucl Med Commun 2014;35(3):221–30.
23 Buchegger F, Garibotto V, Zilli T, et al. First imaging results of an intraindividual comparison of (11)C-acetate and (18)F-fluorocholine PET/CT in patients with prostate cancer at early biochemical first or second relapse after prostatectomy or radiotherapy. Eur J Nucl Med Mol Imaging 2014;41(1):68–78.
24 Wondergem M, van der Zant FM, van der Ploeg T, Knol RJ. A literature review of 18F-fluoride PET/CT and 18F-choline or 11C-choline PET/CT for detection of bone metastases in patients with prostate cancer. Nucl Med Commun 2013;34:935–45.
25 Even-Sapir E, Metser U, Mishani E, et al. The detection of bone metastases in patients with high-risk prostate cancer: 99mTc-MDP Planar bone scintigraphy, single- and multifield-of-view SPECT, 18F-fluoride PET, and 18F-fluoride PET/CT. J Nucl Med 2006;47:287–97.
26 Shen CT, Qiu ZL, Han TT, Luo QY. Performance of 18F-fluoride PET or PET/CT for the detection of bone metastases: a meta-analysis. Clin Nucl Med 2015;40:103–10.
27 Abuzallouf S, Dayes I, Lukka H. Baseline staging of newly diagnosed prostate cancer: a summary of the literature. J Urol 2004;171:2122–7.
28 Farolfi A, Fendler W, Iravani A, Haberkorn U, Hicks R, Herrmann K, et al. Theranostics for advanced prostate cancer: Current indications and future developments. Eur Urol Oncol 2019. https://doi.org/10.1016/j.euo.2019.01.001.
29 Hijazi S, Meller B, Leitsmann C, et al. Pelvic lymph node dissection for nodal oligometastatic prostate cancer detected by 68Ga-PSMA-positron emission tomography/computerized tomography. Prostate 2015;75:1934–40.
30 Perera M, Papa N, Roberts M, Williams M, Udovicich C, Vela I, et al. Gallium-68 prostate-specific membrane antigen positron emission tomography in advanced prostate cancer-updated diagnostic utility, sensitivity, specificity, and distribution of prostate-specific membrane antigen-avid lesions: a systematic review and meta-analysis. Eur Urol 2019. https://doi.org/10.1016/j.eururo.2019.01.049. pii: S0302-2838(19)30095-8. [Epub ahead of print] Review. PubMed PMID: 30773328.
31 Van Leeuwen PJ, Stricker P, Hruby G, et al. (68) Ga-PSMA has a high detection rate of prostate cancer recurrence outside the prostatic fossa in patients being considered for salvage radiation treatment. BJU Int 2016;117:732–9.
32 Minamimoto R, Hancock S, Schneider B, Chin FT, Jamali M, Loening A, et al. Pilot comparison of ^{68}Ga-RM2 PET and ^{68}Ga-PSMA-11 PET in patients with biochemically recurrent prostate cancer. J Nucl Med 2016;57(4):557–62. https://doi.org/10.2967/jnumed.115.168393. Epub 2015 Dec 10. PubMed PMID: 26659347.
33 Akin-Akintayo OO, Jani AB, Odewole O, Tade FI, Nieh PT, Master VA, et al. Change in salvage radiotherapy management based on guidance with FACBC (Fluciclovine) PET/CT in post-prostatectomy recurrent prostate cancer. Clin Nucl Med 2017;42(1):e22–8. PubMed PMID: 27749412; PubMed Central PMCID: PMC5138124.
34 Akin-Akintayo O, Tade F, Mittal P, Moreno C, Nieh PT, Rossi P, et al. Prospective evaluation of fluciclovine (^{18}F) PET-CT and MRI in detection of recurrent prostate cancer in non-prostatectomy patients. Eur J Radiol 2018;102:1–8. https://doi.org/10.1016/j.ejrad.2018.02.006. Epub 2018 Feb 24. PubMed PMID: 29685521; PubMed Central PMCID: PMC5918427.
35 Schuster DM, Nieh PT, Jani AB, Amzat R, Bowman FD, Halkar RK, et al. Anti-3-[(18)F]FACBC positron emission tomography-computerized tomography and (111)In-capromab pendetide single photon emission computerized tomography-computerized tomography for recurrent prostate carcinoma: results of a prospective clinical trial. J Urol 2014;191(5):1446–53. https://doi.org/10.1016/j.juro.2013.10.065. Epub 2013 Oct 19. PubMed PMID: 24144687; PubMed Central PMCID: PMC4155751.
36 Jani AB, Schreibmann E, Rossi PJ, Shelton J, Godette K, Nieh P, et al. Impact of ^{18}F-Fluciclovine PET on target volume definition for postprostatectomy salvage radiotherapy: initial findings from a randomized trial. J Nucl Med 2017;58(3):412–8. https://doi.org/10.2967/jnumed.116.176057. Epub 2016 Sep 8. PubMed PMID: 27609792; PubMed Central PMCID: PMC5331938.
37 Schreibmann E, Schuster DM, Rossi PJ, Shelton J, Cooper S, Jani AB. Image guided planning for prostate carcinomas with incorporation of Anti-3-[18F]FACBC (Fluciclovine) positron emission tomography: workflow and initial findings from a randomized trial. Int J Radiat Oncol Biol Phys 2016;96(1):206–13. https://doi.org/10.1016/j.ijrobp.2016.04.023. Epub 2016 Apr 30.
38 Schuster DM, Nanni C, Fanti S. PET tracers beyond FDG in prostate cancer. Semin Nucl Med 2016;46(6):507–21. https://doi.org/10.1053/j.semnuclmed.2016.07.005. Epub 2016 Sep 7. Review. PubMed PMID: 27825431; PubMed Central PMCID: PMC5117950.
39 Bouchelouche K, Turkbey B, Choyke PL. PSMA PET and radionuclide therapy in prostate cancer. Semin Nucl Med 2016;46(6):522–35. https://doi.org/10.1053/j.semnuclmed.2016.07.006. Epub 2016 Sep 3. Review. PubMed PMID: 27825432; PubMed Central PMCID: PMC5123597.
40 Nanni C, Zanoni L, Pultrone C, Schiavina R, Brunocilla E, Lodi F, et al. 18F-FACBC (anti1-amino-3-18F-fluorocyclobutane-1-carboxylicacid) versus 11C-choline PET/CT in prostate cancer relapse: results of a prospective trial. Eur J Nucl Med Mol Imaging 2016;43(9):1601–10. PMID=26960562.